



The Pituitary Society presents the



*Immediately following the Endocrine Society's 2003 Meeting,
which is being held in Philadelphia June 19-22 2003*

Pituitary tumors: Back to basics

PROGRAM AND ABSTRACTS

WALDORF=ASTORIA • NEW YORK CITY



www.PituitaryCongress2003.com

The Pituitary Society

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Welcome

The 8th International Pituitary Congress will be held in New York City from June 22 through June 25, immediately following the ENDO 2003 meeting in Philadelphia. The meeting will be at New York City's prime location, the Waldorf=Astoria Hotel, which is conveniently located in the center of Manhattan.

The title of the program is Pituitary tumors: Back to basics. Apart from state-of-the-art presentations on the diagnosis and treatment of the most frequently occurring human pituitary tumors, many new recent developments in related aspects of their pathogenesis and pathology will be discussed.

Special sessions are dedicated to optional hormone replacement therapy and to novel pituitary ligands. There will also be interactive sessions during lunch in which eight different workshops will be presented covering the widest interests of the participants.

96 abstracts were submitted for the meeting, of which six were selected for the Hot Topics Session, and 90 for poster presentation. From the abstracts submitted by fellows-in-training, twenty were awarded travel awards to attend the conference.

The excellent social programs will also provide many opportunities for relaxation and congenial discussion.

We are pleased that you have been able to join us for the Congress for two days of excellent science and companionship.



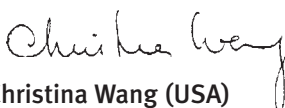
Steven Lamberts (The Netherlands)



Felipe Casanueva (Spain)



Paul Kelly (France)



Christina Wang (USA)

Program Committee for the 8th International Pituitary Congress

Symposia Schedule

SUNDAY, JUNE 22 2003

HOSPITALITY WELCOME DESK & REGISTRATION

6:00 PM – 11:00 PM Foyer, Waldorf=Astoria

MONDAY, JUNE 23 2003

SESSION 1: TUMOR PATHOGENESIS

08:05 AM - 09:45 AM The Grand Ballroom

Chairperson: D Clemmons (Chapel Hill, NC, USA)
& R Clayton (Stoke-on-Trent, UK)

- S1 08:05 AM Molecular pathogenesis
S Melmed (Los Angeles, CA, USA)
- S2 08:30 AM Feed-back tumors
SL Asa (Toronto, Canada)
- S3 08:55 AM Genetic syndromes associated with pituitary tumors: Carney complex, multiple endocrine neoplasias and related disorders
CA Stratakis (Rockville, MD, USA)
- S4 09:20 AM Surgical management of craniopharyngioma and other non-pituitary sellar lesions
ER Laws (Charlottesville, VA, USA)
& Jr JA Jane

COFFEE BREAK

9:45 AM – 10:45 AM East Foyer

POSTER VIEWING

9:45 AM – 10:45 AM John Jacob Astor Salon
(Even numbered posters will be attended)

SESSION 2: CUSHING'S DISEASE

10:45 AM - 12:25 PM The Grand Ballroom

Chairperson: S Webb (Barcelona, Spain)
& A Grossman (London, UK)

- S5 10:45 AM POMC-gene regulation
Y de Keyser (Paris, France)
- S6 11:10 AM The diagnosis of Cushing's disease
LK Nieman (Bethesda, MD, USA)
- S7 11:35 AM Characterization of ACTH-related peptides in ectopic Cushing's Syndrome
A White (Manchester, UK)
- S8 12:00 AM Management of recurrent Cushing's disease
R Fahlbusch (Erlangen, Germany)

LUNCH SEMINARS

12:20 PM – 1:50 PM

- Seminar 1: Is growth hormone replacement therapy in adults cost-effective?
(Starlight Terrace South)
- Seminar 2: The face of old problems
(Starlight Terrace North)
- Seminar 3: New aspects of prolactin in health and disease
(Starlight Terrace Center)
- Seminar 4: Do the results of the women's health initiative have impact on hormone replacement therapy for hypopituitarism?
(Metropolitan Suite)
- Seminar 5: New technologies
(Norse Suite)
- Seminar 6: Polymorphisms in pituitary hormone genes: the impact in the normal population
(Conrad Suite)
- Seminar 7: The pituitary in the frail elderly
(Park Avenue Center)
- Seminar 8: New aspects of growth hormone and PRL actions
(Basildon Room)

(See list on page 7 for full details)

SESSION 3: PROLACTINOMAS

1:55 PM - 3:35 PM

The Grand Ballroom

Chairperson: P Kelly (Paris, France)
& M Bronstien (Sao Paulo, Brazil)

- S9 1:55 PM Role of dopamine D2 receptors in pathogenesis of prolactinomas
ML Low (Portland, OR, USA),
ST Hentges, KG Schuff, N Binart,
PA Kelly, M Páez-Pereda, E Arzt &
SL Asa
- S10 2:20 PM Prolactin antagonists as an alternative to dopamine agonists?
V Goffin (Paris, France),
S Bernichtein, C Manhes,
C Kayser & PA Kelly
- S11 2:45 PM Prolactinomas: Gonadal dysfunction/treatment in menopause
KK Miller (Boston, MA, USA)
- S12 3:10 PM Treatment
DL Kleinberg (New York, NY, USA)

COFFEE BREAK

3:35 PM - 4:05 PM

East Foyer

SESSION 4: ACROMEGALY

4:05 PM - 5:45 PM

The Grand Ballroom

Chairperson: K Ho (Sydney, Australia)
& P Belchetz (Leeds, UK)

- S13 4:05 PM The pathogenesis of acromegaly
L Persani (Milan, Italy)
- S14 4:30 PM Acromegaly: diagnostic pitfalls
PU Freda (New York, NY, USA)
- S15 4:55 PM Medical treatment for acromegaly
JAH Wass (Oxford, UK)
- S16 5:20 PM Role of somatostatin receptor subtypes
LJ Hofland (Rotterdam,
The Netherlands)

STARLIGHT ROOF COCKTAIL RECEPTION

7:30 PM - 9:30 PM

Starlight Roof

TUESDAY, JUNE 24 2003

SESSION 5: NON-FUNCTIONING/ TSH-SECRETING TUMORS

08:00 AM - 09:40 AM **THE GRAND BALLROOM**

Chairperson: F Casanueva (Santiago Compostela, Spain) & R Gaillard (Lausanne, Switzerland)

- S17 08:00 AM Genetic syndromes of T3 resistance
P Beck-Peccoz (Rozzano, Italy)
- S18 08:25 AM Mechanisms of interaction of GnRH, activin, and androgen in regulation of the FSH beta gene in the pituitary gonadotrope
PL Mellon (La Jolla, CA, USA), D Coss, JS Bailey, TJ Spady, SBR Jacobs, SM McGillivray, VG Thackray & F Pernasetti
- S19 08:50 AM Evaluation of the patient with a non-functioning pituitary mass
ML Vance (Charlottesville, VA, USA)
- S20 09:15 AM Non-functioning tumors - recurrence - radiotherapy?
NJL Gittoes (Birmingham, UK)

COFFEE BREAK

9:40 AM - 10:40 AM **East Foyer**

POSTER VIEWING

9:40 AM - 10:40 AM **John Jacob Astor Salon**
(Odd numbered posters will be attended)

SESSION 6: REPLACEMENT THERAPY: DIAGNOSIS & TREATMENT

10:40 AM - 12:20 PM **THE GRAND BALLROOM**

Chairperson: C Wang (Torrance, CA, USA)

- S21 10:40 AM Thyroid
JA Franklyn (Edgbaston, UK)
- S22 11:05 AM Glucocorticoid replacement therapy: diagnosis and treatment
GP Chrousos (Bethesda, MD, USA)
- S23 11:30 AM Sex steroids
A Klibanski (Boston, MA, USA)
- S24 11:55 AM Diagnosis and management of growth hormone deficiency in adults
SM Shalet (Manchester, UK)

LUNCH SEMINARS

12:25 PM - 1:55 PM

- Seminar 1: Is growth hormone replacement therapy in adults cost-effective?
(Starlight Terrace South)
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(Basildon Room)

(See list on page 7 for full details)

SESSION 7: NOVEL PITUITARY LIGANDS

1:50 PM - 4:10 PM

THE GRAND BALLROOM

Chairperson: C Strassburger (Munich, Germany)

- S25 1:50 PM Somatostatin-dopamine chimeras
MD Culler (Milford, MA, USA) MD, JE Taylor, S Kim, JZ Dong & J-P Moreau
- S26 2:10 PM SOM230: A potent inhibitor of the GH / IGF-1 Axis
C Bruns (Basel, Switzerland), H Schmid, I Lewis & G Weckbecker
- S27 2:30 PM Radiolabeled somatostatin analogs
WW de Herder (Rotterdam, The Netherlands), DJ Kwekkeboom, R Valkema, SWJ Lamberts & EP Krenning
- S28 2:50 PM Ghrelin analogs
E Ghigo (Turin, Italy)
- S29 3:10 PM Growth hormone receptor antagonists
JJ Kopchick (Athens, Greece)
- S30 3:30 PM Mutant receptor rescuing ligands for the GnRH receptor: a new therapeutic approach based on receptor folding
PM Conn (Beaverton, OR, USA) & J Janovick
- S31 3:50 PM Novel pituitary ligands: PPAR-gamma ligands
AP Heaney (Los Angeles, CA, USA)

COFFEE BREAK

4:10 PM - 4:40 PM

East Foyer

SESSION 8: HOT TOPICS: PRESENTATIONS ON EXCITING LATE-BREAKING DEVELOPMENTS

4:40 PM - 6:10 PM

The Grand Ballroom

Chairperson: M Thorner (Charlottesville, VA, USA) & BA Bengtsson (Gothenberg, Sweden)

- OC1 4:40 PM Estrogen and selective estrogen receptor modulators (SERMs) exert divergent: Effects on growth hormone signaling through different mechanisms
KC Leung (Sydney, Australia), N Doyle, GM Leong, K Sjogren & KKY Ho

- OC2 4:55 PM A single dose comparison of the acute effects of the new somatostatin analog: SOM230 and octreotide in acromegalic patients
J van der Hoek (South-Holland, The Netherlands), AJ van der Lely, WW de Herder, RA Feelders, P Uitterlinden, V Boerlin, Ch Bruns, I Lewis, KW Poon, G Weckbecker, LJ Hofland & Lamberts SWJ
- OC3 5:10 PM The novel somatostatin analog SOM230 inhibits ACTH release by cultured human corticotroph tumors
LJ Hofland (Rotterdam, The Netherlands), J van der Hoek, PM van Koetsveld, C Bruns, G Weckbecker, D Sprij-Mooij, M Waaijers, MO van Aken, A Beckers & WW de Herder
- OC4 5:25 PM Endocytosis mechanism for the ghrelin-activated growth hormone secretagogue receptor type 1a (ghrelin/GHS-R1a)
JP Camiña (Santiago de Compostela, Spain), MC Carreira, S El Messari, C Llorens-Cortes, RG Smith, M Lage & FF Casanueva
- OC5 5:40 PM Gene expression profiling of pituitary adenomas in LHCTP mice reveals a role for p8 as a putative pituitary transforming gene
H Mohammad (Cleveland, OH, USA), DD Seachrist & JH Nilson
- OC6 5:55 PM Endoscopic endonasal pituitary surgery. Results on a series of 203 patients
P Cappabianca (Bologna, Italy), LM Cavallo, A Colao, E de Divitiis

NEW YORK CITY GALA DINNER

7:30 PM TIL LATE (tba)

The Grand Ballroom

Lunch Seminar Schedule

SEMINAR 1 Starlight Terrace South

*Chairs: A Attanasio (Agliano Terme, Italy),
EM Erfurth (Lund, Sweden)*

Is growth hormone replacement therapy in adults cost-effective?

NICE growth hormone - lessons from the UK
PM Stewart (Birmingham, UK)

The burden of neuroendocrine diseases in a low budget health-care system
J Marek (Praha, Czech Republic)

A debate about the effects of growth hormone replacement on quality of life
A Barkan (Ann Arbor, MI, USA) and S Shalet (Manchester, UK)

SEMINAR 2 Starlight Terrace North

Chairs: K Post (New York, NY, USA), A Beckers (Liege, Belgium)

The face of old problems

The re-emergence of Sheehan's syndrome in Western Europe
F Kelestimur (Kayseri, Turkey)

Traumatic brain injury: endocrine effects
G Aimaretti (Turin, Italy)

Primary pituitary lymphoma: An emerging clinical entity
A Giustina (Brescia, Italy)

SEMINAR 3 Starlight Terrace Center

*Chairs: H Turner (Oxford, UK),
V Bonert (Los Angeles, CA, USA)*

New aspects of prolactin in health and disease

Is a medical cure of prolactinomas possible?
A Colao (Naples, Italy)

Psychological stress and hyperprolactinemia
L Sobrinho (Lisbon, Portugal)

Dopamine resistance of prolactinomas
M Molitch (Chicago, IL, USA)

SEMINAR 4 Metropolitan Suite

*Chairs: J Schlechte (Iowa City, IA, USA),
Y Greenman (Tel Aviv, Israel)*

Do the results of the women's health initiative have impact on hormone replacement therapy for hypopituitarism?

Introduction to the theme
C Wang (Torrance, CA, USA)

Estrogen replacement therapy
S Berga (Pittsburgh, PA, USA)

Androgen deficiency in women with hypopituitarism
K Miller (Boston, MA, USA)

SEMINAR 5 Norse Suite

*Chairs: A Schonbrunn (Houston, TX, USA),
N Horseman (Cincinnati, OH, USA)*

New technologies

Mechanism of pituitary cell secretion (studies using atomic force microscopy)
B Jena (Detroit, MI, USA)

The use of BRET for detecting protein interactions in cellular functions
K Eidne (Perth, Australia)

Non-invasive imaging of small animals: contributions from MRI
N Beckmann (Basel, Switzerland)

SEMINAR 6 Conrad Suite

*Chairs: L Frohman (Chicago, IL, USA),
P Chanson (Kremlin-Bicetre, France)*

Polymorphisms in pituitary hormone genes: the impact in the normal population

Glucocorticoid receptor gene
E van Rossum (Rotterdam, The Netherlands)

Growth hormone receptor
K Chihara (Kobe, Japan)

LH/FSH and their receptors
I Huhtaniemi (London, UK)

SEMINAR 7 Park Avenue Center

*Chairs: S Ezzat (Toronto, Canada),
R Salvatori (Baltimore, MD, USA)*

The pituitary in the frail elderly

GH-IGF axis in frail elderly
A Hoffman (Palo Alto, CA, USA)

Testosterone
S Bhasin (Los Angeles, CA, USA)

DHEA
W Arlt (Birmingham, UK)

SEMINAR 8 Basildon Room

*Chairs: M Tschopf (Potsdam-Rehbrücke, Germany),
C Auernhammer (Munich, Germany)*

New aspects of growth hormone and PRL actions

Overview of growth hormone and IGF actions in the central nervous system
T Wood (Hershey, PA, USA)

Mechanisms for storing pituitary hormones: Implications for controlling hormone release
PS Dannies (New Haven, CT, USA)

GH effects on fat metabolism and obesity
D Flint (Ayr, Scotland, UK)

Course description

The 8th International Pituitary Congress is designed to further the knowledge of clinicians and scientists specializing in the pituitary. Single-session, non-overlapping lectures, symposia, workshops and discussions will address a broad range of pituitary research and clinical issues. The focus of this Congress is on current concepts, future strategies, and options for the investigation, diagnosis and treatment of pituitary diseases.

Who should attend

Pituitary Society members and other professionals interested in state-of-the-art clinical and basic advances in pituitary biology and disease.

Venue

The 8th International Pituitary Congress will take place from the evening of June 22 to the morning of June 25 at the Waldorf=Astoria, 301 Park Avenue, New York, NY 10022-6897, USA, tel: +212 355 3000, fax: +212 872 7272, Website: www.waldorfastoria.com.

As one of the first 'grand' hotels to combine luxurious elegance with a myriad of amenities and services, the Waldorf=Astoria has been renowned for over a century. With a reputation for unparalleled hospitality and service this Art Deco landmark beckons New Yorkers and visitors alike.

Registration

The program and abstract book will be given out at the meeting. Name badges will be issued at the registration desk. Please ensure that you wear your badge to all of the events, including the scientific and social program. No delegates will be admitted to sessions or social events without a badge.

NB: We will take out the section below if we reach 400 delegates

The charges for on-site registration are as follows:-

Congress fees including accommodation

All of the registration fees below (except for spouses/guests) include three nights accommodation at the Waldorf=Astoria from June 22 – June 24 inclusive of \$25 (tba) breakfast vouchers for both days, admission to the scientific meeting, program and abstract books, all coffee breaks, lunches, Starlight Roof Cocktail Reception, and the New York City Gala Dinner.

	<i>On-site registration</i>
Pituitary Society members:	\$1225
Non-members:	\$1375
Fellow-in-training:	\$1100
Spouses/Guests:*	\$600
Members/non-members sharing a two-bedded room:**	\$1075
Fellow-in-training sharing a two-bedded room:**	\$800

**Spouses/guest registrations will include accommodation in a room with a kingsize bed with the person named on the registration form, admission to The Starlight Roof Cocktail Reception and The New York City Gala Dinner. Spouses/guests will also receive \$25 breakfast vouchers if registered to stay at the Waldorf=Astoria.*

*** The number of rooms for sharing are limited. Please register as soon as possible if you wish to share a room.*

Two-bedded rooms have two double beds.

Congress fees not inclusive of accommodation

All of the registration fees below (except for spouses/guests) include admission to the scientific meeting, program and abstract books, all coffee breaks, lunches, Starlight Roof Cocktail Reception, and the New York City Gala Dinner.

	<i>On-site registration</i>
Pituitary Society members:	\$900
Non-members:	\$1050
Fellow-in-training:	\$775
Spouses/Guests:*	\$500

**Spouses/guest registrations will include admission to The Starlight Roof Cocktail Reception and The New York City Gala Dinner at the Waldorf=Astoria*

Contact number

The contact telephone number for the registration desk through the course of the meeting is TBA.

Room locations

Please note that all rooms will be well signed from the registration area.

Accommodation and breakfast vouchers

Accommodation for the 8th International Pituitary Congress will be at the meeting venue, the Waldorf=Astoria. Congress fees inclusive of accommodation include three nights accommodation at the Waldorf=Astoria from the 22 – 24 June inclusive (unless otherwise requested) plus \$25 (tba) breakfast vouchers for each day. The vouchers will be handed out on check-in.

The \$25 breakfast vouchers are redeemable at any outlet in the hotel (eg, room service, Bull and Bear and Sir Harry's Bar) excluding the gift shop and Inagiku Japanese restaurant which are not owned by the Waldorf=Astoria.

Please note that the breakfast vouchers are not redeemable for cash.

Tourist information

For information about attractions in New York please visit the website for NYC & Company on <http://www.nycvisit.com> or call them on +212 484 1222.

Wheelchair access

There is wheelchair access to all areas of the Waldorf=Astoria.

Lunch and refreshments

Tea and coffee will be available during scheduled breaks in the program in the East Foyer. A lunch on June 23 and June 24 is included in the registration fee for delegates registered for the scientific program, and will be served during the lunch seminars in the room where the lunch seminars are taking place.

Security

Please wear your badge at all times. Entrance to lecture theatres and social events will not be permitted to delegates who are not wearing their badges. Delegates are advised to look after their own belongings, as neither the Pituitary Society or The Waldorf=Astoria can be held responsible for any loss.

Business Meeting

We discussed welcoming new members at the gala dinner on Tuesday. Do you want us to mention this under this section?

Poster presentations

Posters will be on display throughout the meeting in the John Jacob Astor Salon and should be set-up by 8 am on June 23. Posters should be dismantled by 2 pm on June 24.

Travel awards

Twenty travel awards of \$500 have been awarded to the best abstracts submitted by Fellows-in-training. The winners of the travel awards have also received one-year of free membership to The Pituitary Society. The travel awards will be presented at The New York City Gala Dinner at the Waldorf=Astoria on June 24 in the Grand Ballroom.

Social events

In 1893 when William Waldorf Astor launched the grand hotel that would bear his name, The Waldorf became ensconced as the definitive New York social venue, a tradition that continues today. We hope you will join us for the excellent social programs included as a part of the 8th Pituitary Congress.

June 22 - Hospitality Welcome Desk

After you sign in at the registration desk, join your colleagues for soft drinks and snacks to refresh yourself following your journey.

June 23 - The Starlight Roof Cocktail Reception at the Waldorf=Astoria

Come and enjoy an evening of entertainment, lots of delicious hors d'oeuvres (enough for dinner!) and cocktails with your colleagues at the legendary Starlight Roof. This has been newly restored to its dazzling Art Deco grandeur and is the jewel in the hotel's crown, offering unrivalled elegance and grandeur from its lofty setting on the hotel's 18th floor. After this, the evening will be your own to enjoy the legendary sights and sounds of New York City. Attendance is included in the registration fee for the congress.

June 24 - The New York City Gala Dinner at the Waldorf=Astoria

The beautiful Grand Ballroom will be the venue for the Congress Gala Dinner, which will include a cocktail reception, three course seated dinner, exciting entertainment, music and dancing. Attendance is included in the registration fee for the Congress.

Additional social programs

In addition to the pre-arranged evening events, we can also offer you the option of booking your own social activities. These range from a variety of *sightseeing trips, theatre performances and recommended restaurants. A full listing of the social activities on offer throughout your stay will be available from the main conference registration desk.

To make a reservation please call 800-299-8587 in USA or (212)-944-8910 and ask for an agent, identifying yourself as calling for PITSOC, then continue with your request. You may also email a request to am@continentalguestservices.com indicating PITSOC as the code number.

*Please note that all activities are subject to availability.

Congress Secretariat

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Attended posters

Posters will be on display in the John Jacob Astor Salon. Please note that even-numbered posters will be attended on Monday, June 23 2003 at 9:45 am – 10:45 am and odd-numbered posters will be attended on Tuesday, June 24 2003 at 9:40 am – 10:40 am.

- P1 The role of radiation therapy after surgical resection of non-functional pituitary macroadenomas
WF Chandler, AL Barkan, P Park, JJ Orrego & JA Cowan
- P2 Acquired prolactin deficiency in patients with disease of the hypothalamic-pituitary (HP) axis
A Mukherjee, RD Murray, B Murray, HK Gleeson & SM Shalet
- P3 Radiotherapy for non-functioning pituitary adenomas: long-term results in a large cohort of patients followed in a single center
F Donadille, M Delannes, A Bennet & PH Caron
- P4 Determination of oxidative protein and lipid damage in adult hypopituitary patients with growth hormone deficiency
N Ozbey, A Telci, U Cakatay, A Yurci & S Molvalilar
- P5 'Primary empty sella' (PES): a review of 31 cases
MA Guitelman, ML Cunillé, M Zeller, L Fiszlejder & A Oneto
- P6 Pituitary GABA-B receptor (GABA-B-R) subunit expression: effect of testosterone (TP) and sexual differentiation
C Libertun, MS Bianchi, MO Fernandez, PN Catalano, B Bettler & VAR Lux-Lantos
- P7 Prolactinomas and pregnancy
MA Guitelman, N Rella, M Zeller, A Oneto & L Fiszlejder
- P8 Timing for the development of Addison syndrome in patients with Cushing disease cured by surgery who did not received peroperative steroid therapy
K Nogueira, B Liberman, J Goldman, ME Rossi-Silva, RS Jacob, L Frontana, F Marques, F Oliveira, A Cukiert & JA Burattini
- P9 Postoperative clinical remission of acromegaly in patients with invasive pituitary GH-secreting tumors
B Liberman, K Nogueira, J Goldman, ME Rossi-Silva, RS Jacob, L Frontana, F Marques, F Oliveira, A Cukiert & JA Burattini
- P10 Postoperative clinical remission of acromegaly with persistently high IGF1 plasma levels
A Cukiert, K Nogueira, J Goldman, ME Rossi-Silva, RS Jacob, L Frontana, F Marques, F Oliveira, B Liberman & JA Burattini
- P11 Trends in pituitary surgery: lessons from a series of 800 patients
A Cukiert, K Nogueira, J Goldman, ME Rossi-Silva, RS Jacob, L Frontana, F Marques, F Oliveira, B Liberman & JA Burattini
- P12 Long-term pituitary dysfunction after traumatic brain injury: occurrence and predictive factors
MR Ambrosio, L De Marinis, M Bondanelli, M Monesi, A Fusco, D Valle, A Bianchi, M Farneti & EC degli Uberti
- P13 Exacerbation of lymphocytic hypophysitis by growth hormone therapy: a case report
P Cohan, DF Kelly, DP Becker, F Pedouim, C Felix & SG Korenman
- P14 GH receptor expression and function in pituitary adenomas
LR Clausen, MT Kristiansen, LM Rasmussen, N Billestrup, O Blaabjerg, T Ledet & JOL Jorgensen
- P15 Determinants of neurosurgical outcome in pituitary adenomas
SM Webb, MJ Barahona, A Wagner, B Oliver & F Bartumeus F
- P16 Changes in serum thyroid hormones levels during two years of growth hormone replacement in deficient adults
DV Soares, LC Spina, RR Brasil, FL Conceição, PM Lobo, EM Silva & M Vaisman
- P17 Somatostatin receptor expression pattern in growth hormone secreting pituitary adenomas influences *in vitro* response to somatostatin
MC Zatelli, D Piccin, MR Ambrosio, A Margutti, F Tagliati, R Padovani, M Scanarini & EC degli Uberti
- P18 First experience in surgery of pituitary adenomas and craniopharyngeomas with high-field intraoperative magnetic resonance imaging
R Fahlbusch, CH Nimsky & O Ganslandt

- P19 'MacroLH': unsuspected high LH value in a patient with endogenous antibodies against LH
JG Vieira, SK Nishida, MT Lombardi, OM Hauache, RM Maciel & V Guimaraes
- P20 Short and long term effects of growth hormone replacement therapy on protein metabolism in growth hormone deficient adults
J Shi, RV Sekhar, A Balasubramanyam, K Ellis, PJ Reeds, F Jahoor & MD Sharma
- P21 The possibility of a bioinactive ACTH producing pituitary adenoma
A Matsuno, R Okazaki, Y Oki, H Katayama, M Nakashima, H Tanaka, M Murakami & T Nagashima
- P22 Treatment of TSH-secreting pituitary adenomas with iopanoic acid (Telepaque)
KS Dhillon, P Cohan, DF Kelly, C Darwin, KV Iyer & IJ Chopra
- P23 Diagnosis of adult growth hormone (GH) deficiency in normal subjects, obese and hypopituitary patients. Comparison between four different stimuli
F Cordido, P Álvarez-Castro, ML Isidro, A Leal-Cerro, O Vidal, C Diéguez & FF Casanueva
- P24 Chromatin derived acidic peptides stimulate anterior pituitary prolactin secretion *in vitro*
C Di Nisio, L Brunetti, G Orlando, L Recinella, B Michelotto & M Vacca
- P25 Men with acquired hypogonadotropic hypogonadism treated with testosterone may be spontaneously fertile
A Drincic, OK Arseven, E Sosa, M Mercado, P Kopp & ME Molitch
- P26 Correlation between mean intima-media thickness of carotid arteries and IGF-1 in acromegaly
CK Kramer, CM Dallago, RL Batista, D Hatem, E Rosa, I Castro, E Camargo Neto & MC Oliveira
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Abstracts

ABSTRACT S1

Molecular Pathogenesis

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Pituitary adenomas arise as monoclonal expansions of transformed differentiated cells which hypersecrete hormonal gene products. Although hypothalamic hormones promote pituitary DNA synthesis in addition to hormone regulation, compelling evidence points to intrinsic pituicyte genetic disruption leading to pituitary oncogenesis. Mutations of tumor suppressor genes, including p53, p27, p16 and Rb appear not to be consistently associated with human pituitary tumorigenesis but maybe implicated in tumor invasive phenotypes. Despite compelling evidence for multiple chromosomal LOH patterns in sporadic tumors, no loss of a specific suppressor gene has been identified. Activating ras and FGF family mutations have been detected in aggressive or malignant tumors. We isolated a potent transforming gene, PTTG, from rat GH-and PRL-secreting tumor cells. PTTG transfectants are highly transforming both in vitro and in vivo. The human PTTG family consists of at least 5 genes, 2 of which are located on chromosomes 5q33 and 4p12 respectively and each are also uniquely expressed in normal tissues. PTTG abundance in hormone-secreting pituitary tumors correlates with tumor invasiveness. In estrogen-induced rat prolactinomas, pituitary PTTG expression consistently precedes adenoma and new vessel formation. PTTG is the index mammalian securin protein, regulates sister-chromatid separation, and its overexpression results in dysregulated chromosome separation, cell cycle disruption and aneuploidy. Mice harboring an alpha GSU-driven PTTG transgene are fertile, develop focal pituitary hyperplasia with MRI evidence of early pituitary enlargement. PTTG-null mice, in contrast, exhibit small pituitary glands with decreased BrdU incorporation and decreased endocrine cell proliferation. These knockout mice also have beta cell hypoplasia with insulinopenia and diabetes. When crossed with Rb+/- mice, they rescue the pituitary tumor phenotype for 12 months. Conclusions: Pituitary tumorigenesis results from a spectrum of subcellular oncogenic lesions disrupting the non-transformed differentiated pituitary cell cycle leading to aneuploidy, with resultant hypertrophy, hyperplasia, focal adenoma and ultimately aggressive adenoma growth. Pituicyte chromosomal instability is an important initiating factor for pituitary tumorigenesis.

ABSTRACT S2

Pituitary Tumor Pathogenesis: Of Mice and Men

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Pituitary tumours are common and exhibit a range of hormonal and proliferative behaviors, providing an excellent model for the study of mechanisms of neoplasia. Mutations in classic oncogenes and tumour suppressor genes, however, are rarely associated with these tumours, however, epigenetic changes in cyclin-dependent kinase inhibitors have been associated with pituitary tumors. IN this tissue, tumour growth appears to be heavily orchestrated by a balance of signaling pathways implicated in normal pituitary development and/or feedback of hormone secretion. Several mouse models have validated the roles of these alterations. The striking differences in disease pathogenesis between mice and humans will be discussed.

ABSTRACT S3

Genetic syndromes associated with pituitary tumors: Carney complex, multiple endocrine neoplasias and related disorders

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The genetic background of pituitary tumors is little understood, despite some fascinating advances in the last 15 years: the association of GNAS1 mutations with growth hormone (GH) and prolactin (PRL) - producing tumors in the late 80's promised rapid advances in the elucidation of pituitary oncogenesis. However, discoveries did not continue with the same pace: despite advances in the understanding of oncogenesis in other tissues, there was little progress in pituitary tumors. Why pituitary cancer is so rare, when adenomas may be present in up to one fifth of the population? Why perturbations of the cAMP-dependent PKA signaling appear to be so strongly associated with GH- and PRL-producing tumors but not with tumors from other pituitary cells? And why mouse pituitary tumors do not seem to model human disease? Two recent discoveries, the MEN 1 gene (menin) and the Carney complex (CNC) gene (PRKAR1A) appear to provide us with some clues on the diversity of molecular signaling pathways that may be affected in at least some GH- and PRL-producing pituitary tumors; the former, a nuclear transcription factor interacting with JunD, NFkB, Smad3, perhaps TP53 and other proteins, and the latter one more crucial molecule of the cAMP-dependent protein kinase A signaling pathway. Interestingly, neither one is frequently mutated in sporadic GH- and PRL-secreting tumors; so far, the only gene associated with both a human genetic condition (McCune Albright syndrome) and frequent sporadic human pituitary tumors remains GNAS1. It is perhaps no co-incidence that even GNAS1 causes a genetic syndrome by somatic mutations; its epigenetic regulation also at the somatic level contributes to sporadic tumor formation. Do menin, PRKAR1A and/or GNAS1 interact? that seems possible in some tumors from patients with CNC or MEN1 Microarray technology in our laboratory has been employed to identify downstream effects of these germline mutations.

ABSTRACT S4

Surgical management of craniopharyngioma and other non-pituitary sellar lesions

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The rationale for the transsphenoidal approach in the microsurgical removal of craniopharyngioma lies in the pathological anatomy of those lesions which take origin below the diaphragma sellae. When a craniopharyngioma arises below the diaphragm, this membrane tends to remain an effective barrier, even though it may stretch dramatically as a tumor extends into the suprasellar compartment. Craniopharyngiomas associated with sellar enlargement rarely, if ever, have intimate attachments to the optic chiasm, hypothalamus, or other intracranial structures. This feature of the pathologic anatomy of infradiaphragmatic craniopharyngiomas theoretically permits 'total' removal of the lesion so long as the surgeon is willing to resect the diaphragm and create the potential for a large CSF leak.

The transsphenoidal approach may also be useful in the management of craniopharyngiomas which are predominantly suprasellar. In these cases, and in patients who have been operated upon previously by craniotomy, a 'total' removal usually cannot be accomplished safely, but the goal of palliation may be achieved by drainage of the cystic component of such tumors or by subtotal removal of tumor contents, decompressing the optic apparatus and other intracranial structures.

Surgical techniques are similar to those used for the transsphenoidal management of pituitary adenomas. New concepts and techniques that have been developed for the removal of craniopharyngiomas include: the extended trans-sphenoidal skull-base approach; intraoperative computerized neuronavigation; intraoperative MRI; the use of the operating endoscope; and novel methods of skull base repair.

ABSTRACT S5

POMC-gene regulation

Y de Keyzer

ABSTRACT S6

The Diagnosis of Cushing's Disease

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Having identified ACTH-dependent Cushing's syndrome (CS), the clinician must determine whether ACTH secretion derives from a corticotrope tumor (Cushing's disease, CD), ectopically from another tumor (EAS) or rarely because of tumoral CRH secretion. Recent onset and rapid progression, urine cortisol excretion \rightarrow 10-fold normal and hypokalemia suggest EAS from an overt malignancy. Occult EAS and CD have similar clinical and biochemical presentations. Various tests may distinguish EAS from CD. In studies that included about 20 patients with EAS and used criteria to exclude EAS, the sensitivity for CD of the 8-mg dexamethasone suppression test (DST) (~70%) was less than that of the CRH stimulation test (93%) but inferior petrosal sinus sampling (IPSS) had 100% diagnostic accuracy. Not surprisingly, further experience in ~80 patients with EAS and ~600 patients with CD showed worse test performance. Specifically, the DST and CRH tests gave a positive result in 8 and 10% of patients with surgically-confirmed EAS. However, \leftarrow 1% of patients with positive responses to both tests had EAS. IPSS was falsely negative in \leftarrow 1% of those with CD, usually associated with abnormal venous anatomy, and was falsely positive in 1/60 patients with EAS. Jugular venous sampling (JVS) identified 83% of patients with CD. Thus, IPSS is the best test for the identification of Cushing's disease. However as the technical expertise for this test is not widely available, an alternative approach is to perform the DST and CRH tests and/or JVS and assign a diagnosis of CD if the results are positive. Based on our experience, these strategies could correctly identify CD in 60 to 70 percent of patients; the remainder would need IPSS. Finally, testing should be done during sustained hypercortisolism, to ensure that the normal corticotrope responses are suppressed, and results close to any diagnostic criterion should be viewed with skepticism.

ABSTRACT S7

Characterisation of ACTH-related peptides in Ectopic Cushing's Syndrome

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Processing of pro-opiomelanocortin (POMC) to pro-ACTH and subsequently to ACTH requires specific cleavage by the prohormone convertase, PC1. This occurs within cells following transport through the Golgi stacks and targeting to regulated secretory granules. The extent of POMC processing is very tissue dependent such that in the pituitary, processing results in ACTH, but in the hypothalamus, additional enzymes process ACTH to alpha MSH (Pritchard et al. 2002). We and others have shown that defects in POMC processing can affect this pathway giving rise to obesity.

It is therefore important to understand what determines the extent of POMC processing in tumour cells, which give rise to Cushing's Syndrome. We have identified the precursors of ACTH (POMC and proACTH) in the circulation of normal subjects in the range 5-40pmol/l, which suggests that processing in the normal pituitary is incomplete. In 38 out of 39 patients with pituitary dependent Cushing's Syndrome, ACTH precursors were \leq 100pmol/l and the mean ratio of ACTH precursors and ACTH was 4.7 which indicates that these tumours do process POMC to ACTH relatively efficiently. After CRH stimulation, the proportion of mature ACTH to ACTH precursors increases in the inferior petrosal sinuses within 5-15 minutes, which provides evidence that release of ACTH is regulated independently of secretion of POMC.

In ectopic Cushing's Syndrome, it is unlikely that the extra-pituitary tumour cells, which originate from different tissues, have the same regulated secretory pathway for processing of POMC, as the anterior pituitary. Therefore increased prevalence of ACTH precursors in the circulation, would be expected. The presence of these high molecular weight forms of ACTH was first identified by gel chromatography. However, the advent of immunometric assays has made it possible to measure the large excess of ACTH precursors (106-18,000pmol/l) in the circulation of patients with the ectopic ACTH Syndrome. This offers a simple diagnostic test for the differential diagnosis of Cushing's Syndrome, which should be fully evaluated in relation to other more complex approaches.

ABSTRACT S8

Management of recurrent Cushing's disease

R Fahlbusch

ABSTRACT S9

Role of dopamine D2 receptors in pathogenesis of prolactinomas

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Hypophyseotropic dopamine exerts a tonic inhibitory tone on pituitary lactotrophs by the activation of dopamine D2 receptors (D2R). We generated a strain of D2R-deficient mice by targeted mutagenesis and found that the pituitary lactotrophs undergo a stereotyped response of prolonged hyperplasia followed inevitably by the development of multifocal prolactinomas. Recent studies have focused on the hypothesis that the loss of inhibitory D2R signaling promotes a cycle of increased lactotroph proliferation and apoptosis leading to the accumulation of additional somatic mutations in a few of the cells, which eventually give rise to adenomas. Ovariectomy markedly attenuated the proliferative response of lactotrophs in D2R-deficient mice, but estrogen alone did not reverse the growth inhibition suggesting the involvement of additional ovarian factors in the stimulation of lactotrophs. Prolactin apparently has a direct dopamine-independent inhibitory effect on lactotroph mitogenesis, possibly providing an autocrine or paracrine feedback signal to moderate tumor growth. Molecular analyses of the hyperplastic pituitary glands showed decreased phosphorylation of the mitogen-activated protein kinases (MAPK) ERK1/II, indicating that unlike many other cell types, the proliferation of lactotrophs is associated with decreased activity of the MAPK cascade. A differential display comparison of mRNA from normal pituitary glands and mouse prolactinomas identified a marked reduction in expression of noggin, an inhibitor of the bone morphogenetic (BMP) family of ligands for the transforming growth factor-beta receptor, in the adenomas. In contrast, BMP4 expression was increased in both mouse and human prolactinomas. Further studies suggested an important function of BMP4-mediated Smad4 signaling and estrogen receptor cross-talk in tumor pathogenesis. In conclusion, although spontaneous mutations in the human D2R are not a principal cause of prolactinomas, the experimental model of prolactinomas in D2R-deficient mice has provided new insights concerning the intracellular signaling pathways controlling lactotroph growth that may guide the discovery of more common genetic mutations.

ABSTRACT S10

Prolactin antagonists as an alternative to dopamine agonists ?

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There is a large body of literature arguing for a growth-promoting action of prolactin (PRL) in various in vitro and in vivo tumor models, as recently confirmed by the observations that PRL transgenic mice develop prostate hyperplasia (males) and mammary gland neoplasia (females). In addition, it has been proposed that extrapituitary PRL acts as an autocrine growth factor in various human cells. Since dopamine agonists do not regulate local production of PRL, alternative strategies need to be pursued to inhibit the proliferative effect of PRL in the context of tumor growth. Several years ago, we engineered the G129R-hPRL antagonist (Gly 129 substituted for Arg) which was shown to competitively inhibit hPRL activity when added in 10-50 fold molar excess in various in vitro bioassays, including proliferation of human mammary tumor cell lines. Unexpectedly, whereas abolition of PRL signaling in PRL receptor knockout mice induces total failure of reproduction and lactation functions, mice transgenic for G129R-hPRL reproduce well and lactate, which clearly indicates that over-expression of this analog fails to inhibit the effects of PRL in vivo. Using various in vitro bioassays with different sensitivities, some of which were developed in-house, we showed that G129R-hPRL maintain a significant level of residual agonistic activity in the most sensitive ones, clearly demonstrating that substitution of Gly 129 is not in itself sufficient to generate a full hPRL antagonist. We recently designed second generation antagonists by combining G129R substitution with various N-terminal tail deletions. Although these new analogs display binding affinities and antagonistic potencies similar to those of G129R-hPRL in the various in vitro bioassays, remarkably, they are devoid of the undesirable agonistic activity observed for the latter. This suggests that these analogs will act as pure hPRL antagonists in vivo. The biological potencies of these compounds are currently being investigated using various approaches, including the production of transgenic mice.

ABSTRACT S11

Prolactinomas: Gonadal dysfunction/treatment in menopause

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The natural history of untreated microprolactinomas through the menopause has not been determined, nor have the effects of estrogen replacement therapy. In pre-menopausal women, amenorrhea is an important indication for treatment because of its association with bone loss. Mean bone density of amenorrheic women is lower than that of eumenorrheic women with comparable serum levels of prolactin. Therefore, hypoestrogenemia is primarily responsible for bone loss in women with prolactinomas. Dopamine agonist therapy is generally prescribed to restore menses. When contraindicated in patients with microprolactinomas — e.g. in women with severe psychiatric disease — or for women who desire oral contraceptives for birth control, estrogen therapy can be considered to preserve bone. Although prolactin levels and MRI scans must be monitored carefully in such women, only a minority of women with microprolactinomas experience tumor growth over time.

Menopause might be expected to be associated with declining prolactin levels in women with microprolactinomas, due to the abrupt reduction of estrogen secretion by the ovaries. In contrast, estrogen replacement therapy might result in increases in prolactin levels. We therefore conducted a retrospective chart review to determine the natural history of untreated hyperprolactinemia at menopause and the effect of estrogen replacement therapy on prolactin levels in menopausal hyperprolactinemic women. We identified 20 women with untreated hyperprolactinemia before and after menopause and ten women followed before and after initiation of estrogen replacement therapy. In untreated patients, mean prolactin was significantly lower in the 5 years after menopause compared to the 5 years before menopause (25.9 plus/minus 5.9 vs. 56.4 plus/minus 5.9 nanograms per milliliter, $p < 0.001$). Moreover, there was a trend toward increased prolactin levels on vs. off HRT (62.4 plus/minus 27.1 vs. 42.0 plus/minus 24.9 nanograms per milliliter, $p = 0.096$). Further studies are needed to determine the optimal management of hyperprolactinemic menopausal women.

ABSTRACT S12

Treatment of Prolactinomas

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This talk will focus on various forms of therapy for prolactinomas. The current role of surgery, radiotherapy and dopamine agonist therapy will be reviewed. The clinical approach to challenging patients with resistance to dopamine agonist therapy will be discussed.

ABSTRACT S13

The pathogenesis of acromegaly

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Acromegaly is the consequence of an increased activity of GH-IGF1 axis. In more than 99% of the cases acromegaly is due to GH-secreting pituitary adenomas (GH-omas). GH-omas, as the other pituitary adenomas, provide an interesting model of tumorigenesis rarely progressing toward malignancy. GH-omas are generally sporadic tumors, though rare familial cases were reported either isolated or as part of MEN-1 or Carney syndromes. Causal molecular events have been found so far in almost half of the cases, and GH-omas are probably the category of pituitary tumors provided with the most documented information on their pathogenic mechanisms. Sporadic GH-omas represent the first of a long series of natural and experimental models showing that constitutive activation of cAMP-dependent pathway can be associated to tumor formation. Evidence has been now accumulated showing that around 40% of isolated GH-omas are bearing the *gsp* oncogene. Accordingly, GH-omas can also occur as part of McCune Albright syndrome due to germline mosaicism for *gsp* mutation or in patients with GHRH-secreting tumors. On these bases, several other elements belonging to cAMP-dependent pathway, from GHRH receptor till nuclear transcription factors, have been investigated with variable success. These candidate genes include the regulatory subunit (R1A) of PKA, which was indeed found to be mutated in a subset of patients with Carney syndrome who can be affected with endocrine overactivity, including acromegaly. Other mechanisms potentially involved in GH-oma formation include disruption of inhibitory somatostatin (SST) action. We described the first mutation in type 5 SST receptor that could have contributed to adenoma cell growth in one SST-resistant acromegalic patient. Following studies have indicated that SST receptor mutations are not frequent events in GH-omas. Future progress in this research field will receive important contribution by the careful biochemical characterization of GH-omas both in vivo and in vitro.

ABSTRACT S14

Acromegaly: Diagnostic Pitfalls

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When clinical manifestations of acromegaly are obvious, the biochemical diagnosis is also usually straightforward: IGF-I levels are high, GH is elevated and does not fall after oral glucose. Such clinical manifestations typically represent years of unrecognized active disease. Although the major hindrance to early disease recognition will likely remain the fact that acromegaly is not considered often enough, a current diagnostic challenge is to establish biochemical criteria that recognize early acromegaly. A major pitfall to early recognition of active acromegaly has been that the traditional criterion for excluding acromegaly, GH suppression to less than 2 micrograms per liter after oral glucose, did not detect all cases of acromegaly. The suppression criterion suggested for use with newer GH assays, GH less than 1 microgram per liter, may also still not necessarily exclude acromegaly. GH and IGF-I assessments are usually consistent, but discrepancies may exist that could be clinically important to recognize. Failure of normal GH suppression can occur in the setting of renal or liver disease, diabetes and malnutrition. In young women, in particular those on oral contraceptives, the cut off for normal GH suppression may need to be higher than for other groups. Also, measurement of glucose-suppressed GH may reveal subtleties of GH secretion not appreciated by IGF-I alone. Pitfalls to the diagnostic use of IGF-I also exist. An accurate, well-standardized IGF-I assay must be used, but not all clinically available assays meet this requirement. Also, in certain clinical settings, such as pregnancy that raises IGF-I and malnutrition and liver disease that can lower serum IGF-I, it is not a reliable marker for acromegaly. Thus, because caveats to the use of either GH or IGF-I assessments alone do exist, combined testing, especially for the detection of early acromegaly, is warranted.

ABSTRACT S15

Medical Treatment for Acromegaly

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The medical treatment of acromegaly has advanced greatly in the last few years with the availability of long acting analogues of somatostatin and the licensing and use of growth hormone receptor antagonists. Particularly with large pituitary tumours, primary therapy with medical treatment is suggested but the effects of pre-treatment with somatostatin analogues on surgical outcomes still need larger studies to assess the effects on surgical cure rate. New analogues of somatostatin which have wider somatostatin receptor specificity are being developed and offer the potential of a greater ability to suppress growth hormone in active acromegaly. They also have a number of other potential applications in the field not only of pituitary tumours but outside endocrinology.

Pegvisomant has recently been licensed in the United States and will be in Europe towards the end of this year. Its place in the medical treatment of acromegaly is probably in the those patients who are non somatostatin responsive. Further work needs to be done on IGF1 values on Pegvisomant because there are difficulties in monitoring patients with acromegaly on IGF1 alone for a number of reasons including lack of an IGF1 standard as well as high interassay variations. Epidemiological studies looking at IGF1 have shown disparate results and it is difficult to be sure that patients are not being over treated. This is in the light of the fact that a number of patients with growth hormone deficiency have a normal IGF1. Expense apart medical therapy has a very important future. Most particularly at the moment this is in the treatment of patients who have not been successfully treated surgically. Primary treatment of excessive growth hormone levels may well be the future and should already be considered in patients with tumours that cannot be cured surgically.

ABSTRACT S16

Role of somatostatin receptor subtypes

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Somatostatin (SS) receptors (sst) on GH-secreting pituitary adenomas form the molecular basis for the effectiveness of SS-analogs in lowering circulating GH and IGF-I levels in acromegalic patients. Treatment with SS-analogs such as octreotide and lanreotide, results in a clinical and biochemical cure in approximately two-third of the patients. Tachyphylaxis to treatment with SS-analogs, as well as mutations in sst receptor genes, have been reported in extremely rare cases only. Nevertheless, one-third of the patients is more or less resistant to current SS-analog therapy. The variable expression pattern of sst subtypes in GH-secreting pituitary adenomas could explain the variation in responsiveness to SS-analog treatment. Sst2 receptors, to which octreotide and lanreotide bind with high affinity, seem expressed at lower levels in the 'resistant' patients. Among the other sst subtypes, sst5 receptors are expressed at relatively high levels in GH-secreting pituitary adenomas. Previous in vitro studies demonstrated that sst5 receptors mediate a potent inhibitory effect on GH release by GH-secreting pituitary adenoma cells. Therefore, SS-analogs with high affinity to both sst2 and sst5 receptors may become a novel medical treatment modality in acromegalic patients 'resistant' to the current generation of octapeptide SS-analogs. Sst2-sst5 selective analogs, e.g. BIM-23244, as well as SS-analogs with a more universal sst binding profile, e.g. SOM230, have been recently introduced. Our studies show that SOM-230 and octreotide are equally effective in inhibiting GH-release in the majority of GH-secreting pituitary adenoma cultures in vitro, whereas selected cases with relative low sst2 and high sst5 expression, show a better response to SOM-230. In cultured normal rat anterior pituitary cells, octreotide transiently inhibits GH release, whereas tachyphylaxis to SOM-230 is delayed and only partial. These results could explain in part the potent and sustained inhibitory effects of SOM-230 on circulating IGF-I levels in rats, as was recently demonstrated. The clinical role of this new generation of SS-analogs needs to be further explored.

ABSTRACT S17

Genetic syndromes of T3 resistance

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The effects of thyroid hormones on physiological processes are mediated by two receptors (TR α and TR β), belonging to the nuclear receptor superfamily of ligand-inducible transcription factors. TR binds preferentially to promoter regulatory DNA sequences as a heterodimer with the RXR. In the absence of T₃, unliganded receptor recruits corepressors to 'silence' gene transcription. T₃ binding results in dissociation of corepressor and recruitment of coactivators with ligand-dependent transcriptional activation. Thyroid hormone resistance (RTH) is an uncommon disorder characterised by reduced responsiveness of target tissues to circulating thyroid hormone levels. The biochemical hallmark of RTH (elevated circulating levels of free thyroid hormones and non-suppressed TSH secretion) reflects resistance in the hypothalamic-pituitary-thyroid axis, and is accompanied by variable refractoriness in peripheral tissues. On the basis of clinical features, two major forms of RTH are recognised: generalized resistance (GRTH) and pituitary resistance (PRTH) where patients present with features of thyrotoxicosis. However, there is a wide overlap of clinical and biochemical features between GRTH or PRTH. Genetic analyses show that both disorders are associated with a number of different mutations in TR β gene which localize to three regions in the hormone binding domain. The mutant proteins are transcriptionally impaired but preserve the ability to bind DNA, dimerize and inhibit the function of their wild type counterparts in a dominant negative manner. Dominant negative effects of mutant receptors within the pituitary-thyroid feedback axis generates abnormal thyroid function tests characteristic of RTH. The variable peripheral resistance may be related to differences in tissue distribution of various receptor isoforms, variable dominant negative effects of mutant receptors on different target genes or other non-receptor-mutation related factors. Although GRTH and PRTH represent the variable phenotypic spectrum of a single genetic entity, this clinical distinction will remain useful as a guide to the appropriate approach to the treatment.

ABSTRACT S18

Mechanisms of Interaction of GnRH, Activin, and Androgen in Regulation of the FSH Beta Gene in the Pituitary Gonadotrope

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Reproduction is controlled by rhythms of GnRH acting at the pituitary to regulate transcription and secretion of LH and FSH from gonadotrope cells. Gonadal steroids, activin and follistatin modulate the function of the gonadotrope in coordination with GnRH. We have created a series of immortalized pituitary gonadotrope cell lines and their progenitors that have allowed the characterization of sequential stages of differentiation and identification of regulatory molecules responsible for specific developmental transitions. Basal expression of the LH and FSH beta-subunit genes is restricted to the most differentiated of the gonadotrope cell lines, as are GnRH and activin regulation. These cells express GnRH receptor, activin, follistatin, inhibin, ER, AR, PR, and GR, as well as FSH and LH. FSH beta induction by GnRH and androgen is dependent on these cells' activin autocrine loop and specific mechanisms involved in basal, cell-specific, and hormonal activation of the FSH beta gene will be presented. Thus, the more differentiated gonadotrope cell lines have allowed dissection of the molecular mechanisms of androgen, activin, and GnRH action and the interactions among these key modulators of reproductive function.

ABSTRACT S19

Evaluation of the Patient with a Non-Functioning Pituitary Mass

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Evaluation of the patient with a Non-Functioning Pituitary Mass. Mary Lee Vance, M.D.

Assessment of a patient with a non-functioning pituitary mass should include pituitary function and mass effect (visual field loss, diplopia, headache). Viewing the MRI is mandatory, the scan may indicate the type of lesion (e.g. cystic - craniopharyngioma, Rathke's cleft cyst; diffuse enlargement with stalk involvement - infiltrative disease). Evaluation for hormone deficiency should include a morning ACTH and cortisol, thyroxine, IGF-1, testosterone (men), estradiol and menstrual history (premenopausal women). A serum alpha subunit, LH and FSH may provide a tumor marker to follow after surgery. A serum prolactin is necessary to identify a prolactinoma or secondary hyperprolactinemia (prolactin less than 200, macroadenoma: not likely a prolactinoma). Diabetes insipidus (DI) suggests craniopharyngioma, lymphocytic hypophysitis or metastatic disease, preoperative DI is uncommon with a pituitary adenoma. Glucocorticoid and thyroid hormone should be replaced preoperatively; a dynamic test of ACTH reserve is performed after surgery.

Postoperatively, evaluation should determine the need for replacement therapies, including a dynamic test of ACTH reserve. The MRI is obtained 3 months after surgery. All patients are at risk for tumor recurrence (16% within 10 years) and should be monitored lifelong with regular MRI studies and appropriate endocrine studies.

ABSTRACT S20

Non-functioning tumours - Recurrence - Radiotherapy?

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The initial management of large clinically non-functioning pituitary adenomas (NFAs) is uncontroversial and involves effective surgical debulking. However, despite almost 100 years of experience of the use of conventionally fractionated external beam pituitary radiotherapy (RT), considerable controversy surrounds the application of this treatment modality to post-operative remnants of NFAs. In the absence of prognostic markers to predict the likelihood of NFA regrowth, some centres adopt a 'blanket' RT approach whilst others adopt a more conservative 'watchful waiting' policy using sequential MRI scanning to detect early evidence of tumor remnant regrowth. Our group observed a 7% rate of regrowth after 10 years in those treated with RT compared with 53% in those who did not receive post-operative RT. Nonetheless, despite these data, case selection for pituitary RT remains based on individual risk-benefit ratios, and thus is a contentious issue. Historically there have been concerns surrounding a number of potentially significant complications of pituitary RT. However, with careful modern planning and dosing regimens, many of the historical safety concerns relating to pituitary RT may be currently unfounded. For example, radiation damage to the chiasm, and brain necrosis are extremely rare. Furthermore, risks of secondary oncogenesis following pituitary RT are likely to have been exaggerated due to anomalies in case acquisition; any excess risk being small. Clearly, however, the risk of radiation-induced hypopituitarism is real. The relative sensitivities of anterior pituitary cells to RT are well documented, as is the 2-fold excess mortality associated with hypopituitarism. Interestingly, the mortality ratio is significantly higher in RT-induced hypopituitarism. In summary, conventionally fractionated external beam RT has a role in preventing regrowth of NFAs but careful patient selection is required to avoid unnecessary RT-induced hypopituitarism. Using modern methods for delivering pituitary RT, the risks of visual loss and second tumor formation may be less than originally estimated.

ABSTRACT S21

Replacement therapy: diagnosis and treatment. Thyroid

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Central hypothyroidism is an important component of hypothalamic pituitary disease and is likely to be one factor contributing to long-term morbidity and mortality in patients with these disorders. Hypothalamic pituitary disease is associated with changes in TRH secretion as well as changes in patterns of TSH secretion and bioactivity. Measurement of serum TSH may be unhelpful in the diagnosis of central hypothyroidism since values may be raised or normal rather than low in up to 50% of cases. Measurement of free T₄ is the most widely used marker of central hypothyroidism but there is some controversy regarding definition of the normal range and the need for adjunctive tests in making the diagnosis.

Treatment of central hypothyroidism is generally straightforward, namely with T₄ replacement in standard doses. Serum TSH is not, however, a reliable marker of adequacy of replacement, so circulating free T₄ is generally used as the best index of treatment. Studies of patients treated with T₄ for primary hypothyroidism are providing evidence for adverse long-term effects of over-treatment, and perhaps under-treatment. No such data, specific to T₄, exist for subjects with treated secondary hypothyroidism. It would seem important nonetheless to titrate T₄ doses carefully to achieve physiological replacement. One aim should be to develop better biochemical markers of thyroid status in patients with hypothalamic pituitary disease in order to improve both diagnosis and management of replacement therapy.

ABSTRACT S22

Glucocorticoid Replacement Therapy: Diagnosis and Treatment

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Daily glucocorticoid secretion is tightly regulated. In addition to the glucocorticoid effects that cortisol has by binding to the glucocorticoid receptor (GR), it also binds to the mineralocorticoid receptor (MR), although this binding is physiologically inhibited by conversion of cortisol to its inactive metabolite cortisone, by the enzyme 11 β -hydroxy-steroid dehydrogenase (11 β -OHSD2) which co-localizes with the MR in the kidney. The basal daily rate of cortisol secretion is approximately 6-8 mg/m² body surface area, although this may increase up to 10-fold in response to acute severe stress. Physiologic replacement of cortisol requires doses of 10-15 mg/m² because oral bioavailability is 50-60%. Other synthetic glucocorticoids are available, all of which have different relative potencies as glucocorticoids and mineralocorticoids due to their differing structures and affinities for the GR and MR, as well as 11 β -OHSD2. Since glucocorticoids began to be used for their anti-inflammatory and immunomodulatory effects in the late 1940s, much work has been done to maximize their beneficial and minimize their adverse effects. The pharmacologic differences between synthetic steroids result from alterations of their basic steroid nucleus and its side groups. These changes may affect the bioavailability of these compounds, - including their gastrointestinal or parenteral absorption, plasma half-life and metabolism in the liver, fat, or target tissues - and their ability to interact with the GR and MR and to modulate the transcription of glucocorticoid-responsive genes. In addition, structural modifications eliminate their undesirable salt-retaining activity. Other modifications increase their water solubility for parenteral administration, or decrease their water solubility to enhance topical potency. Most of the synthetic glucocorticoids are minimally bound to cortisol-binding globulin and circulate mostly bound to albumin, or in the free form. Glucocorticoids can be divided into short-, intermediate-, or long-acting, based their biologic effect half-life which is the duration of ACTH suppression after a single dose of the compound.

ABSTRACT S23

Sex Steroids

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The consequences of gonadal steroid deficiency are well established in both women and in men. Studies have clearly shown that hypogonadism in both women and men is associated with decreased bone density and an increased risk for osteoporosis. In addition, gonadal steroids have marked effects on body composition that may impact on a number of variables including truncal fat and cardiovascular events. Low testosterone in men is associated with obesity, decreased muscle mass and elevated total and low density lipoprotein cholesterol. Recent data have also focussed on the role of testosterone in both women and men on such endpoints as libido, depression and cognitive function. In women, hypopituitarism, either structural or functional, is associated with loss of estrogen, progesterone and testosterone. Although the benefits of estrogen replacement in postmenopausal women are controversial, data support the importance of physiologic estrogen/progesterone replacement in hypogonadal pre-menopausal women. A relatively recently defined syndrome of 'acquired androgen deficiency' in women is associated with loss of testosterone due to ovarian and/or adrenal function resulting in low total and free testosterone levels. An active area of research involves the definition of testosterone deficiency in both women and men using currently available assays. Although the availability of more physiologic androgen replacement regimens in men has facilitated the attainment of more physiologic testosterone levels, whether androgen replacement has a role in the treatment of hypogonadal women remains to be determined.

ABSTRACT S24

Diagnosis and management of growth hormone deficiency in adults

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Diagnosis and management of growth hormone deficiency in adults

Professor S M Shalet

Unlike pediatric practice, growth hormone replacement in adults is restricted to patients with severe growth hormone deficiency (GHD). Furthermore the natural evolution of pituitary hormone deficits from isolated deficiency to panhypopituitarism occurs in a predictable fashion from a number of different pathological insults; GHD being an early feature, usually the earliest deficit observed, and therefore predictable severe GHD being present in 90-95% of patients with 2 to 3 additional pituitary hormone deficits. In the latter situation only one diagnostic test of GH status is required whilst in those patients with potential isolated GHD or one additional deficit 2 tests are required. In adults with childhood-onset GHD IGF-I estimation is particularly discriminatory but this is not the case in middle and elderly adult-onset GHD patients. Thus the diagnosis remains dependent primarily on GH provocative tests to which equal weighting is given irrespective of the stimulus. Isolated GHD remains difficult to diagnose and the use of similar thresholds for diagnosing severe GHD in teenagers as in adults remains potentially unsatisfactory.

Strategies for treatment vary worldwide from GH replacement for all severe GHD patients, to restricting replacement only for those with a specific indication, such as severe impairment of quality of life. The 'all or some' dilemma is highlighted by our lack of sufficient data to inform the optimal approach to the GHD teenager in transition from pediatric care. In the meantime the next challenge will be partial GHD, in which the adverse effects on biological endpoints seen in severe GHD exist in an attenuated form, but no intervention studies have been performed. If benefit is established, then all the issues regarding diagnosis, and optimising GH dosing in GH insufficient children that have plagued the pediatrician, will rise up to torment the adult endocrinologist.

ABSTRACT S25

Somatostatin-Dopamine Chimeras

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Several clinical reports suggest that combined therapy with somatostatin (SS) and dopamine (DA) agonist analogs results in greater suppression of growth hormone (GH) secretion in acromegalic subjects than is achieved with either agent used alone. This observation may be partially explained by improved bioavailability of the DA agonist in the presence of SS; however, interactions at the cellular level may also contribute to the effect. Collaborative studies between our laboratory and those of S. Melmed (Cedars-Sinai, Los Angeles) and P. Jaquet (CNRS, Marseille) have demonstrated that combined treatment of either rat or human pituitary cells with SS and DA analogs produces synergistic interactions. As a result of these observations, we have created novel chimeric compounds that combine structural elements of both SS and DA within a single molecule. The first prototypes of these molecules retain potent affinity and selectivity for both the SS type-2 receptor (SSTR2) and the DA D2 receptor. In cells cultured from human GH- and prolactin-secreting adenomas, the SSTR2/D2 chimeras display comparable efficacy as the most potent SS or DA analogs, but with approximately 100-fold greater potency. Previous collaborative studies with these same investigators demonstrated that combined activation of SSTR2 and 5 results in enhanced suppression of GH secretion from human adenomas. We are now investigating chimeras that combine DA D2 and both SSTR2 and 5 activity within the same molecule. These new analogs retain the enhanced potency of the original SSTR2/D2 chimeras, but also demonstrate enhanced efficacy in suppressing GH secretion from human adenomas beyond that attained with individual SS and DA agonists. These results suggest that this novel class of chimeric SS/DA molecules may offer far greater efficacy than current therapeutic options for treating acromegaly, and may do so at greatly reduced dosages.

ABSTRACT S26

SOM230: A Potent Inhibitor of the GH / IGF-1 Axis

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The aim of this project was to identify small, metabolically stable SRIF analogs with a binding profile similar to that of somatostatin-14.

The incorporation of structural elements of SRIF-14 into a stable cyclohexapeptide template resulted in the identification of the novel cyclohexapeptide SOM230, a SRIF analog with improved pharmacological properties and hence potential for new therapeutic uses. SOM230 binds with high affinity to sst1-3 and sst5 and inhibits effectively GH and IGF-1 secretion in several species. Studies in rats demonstrated a long duration of action of SOM230 in vivo and a plasma half life of 23h. This increased metabolic stability of SOM230 was confirmed in monkeys and recently also in man. When rats were treated with SOM230 (25 microgram per kilogram bid), SOM230 suppressed the GHRH-induced GH release completely both on day 1 and day 4. SMS 201-995 inhibited to a lesser extent GH release on both days and was much less active on day 4 of treatment demonstrating signs of escape. Continuous treatment of rats with SOM230 at 10 micrograms per kilogram per hour decreased plasma IGF-1 levels on day 2 by 90% while under SMS 201-995 treatment IGF-1 levels decreased only by 49%. After a 2-week infusion of SOM230 the suppression of IGF-1 levels was still pronounced, while the response to SMS 201-995 was largely lost indicating escape of the inhibitory response. In cynomolgus monkeys SOM230 also very effectively lowered plasma GH and IGF-1 levels.

In summary, SOM230 binds almost universally to human sst's and inhibits potently the GH / IGF-1 axis in various species. Based on its high affinity for the different ssts, especially sst5, SOM230 may allow to identify new therapeutic uses for SRIF analog treatment.

ABSTRACT S27

Radiolabeled somatostatin analogs

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Presently, peptide receptor targeted radiotherapy of somatostatin receptor subtype 2 (sst2)- and sst5-positive metastatic carcinoids and pancreatic neuroendocrine tumors can be performed using alpha-, or beta-emitting isotopes coupled to somatostatin analogs. In patients with metastatic neuroendocrine tumors, therapy with ¹¹¹In-pentetreotide resulted in partial responses in 31-67% of patients, 0-31% of patients had stable disease, and progressive disease was observed in 33-38%. Therapy of patients with endocrine tumors of the digestive tract with [90Y-DOTA₀,Tyr₃]octreotide, (90Y-DOTATOC or 90Y-SMT487 / OctreoTher) has resulted in partial responses in 7-22%, stable disease in 49-83% and progressive disease in 10-32%. Therapy with [177Lu-DOTA₀,Tyr₃]octreotate in 33 patients with endocrine tumors of the gastrointestinal tract have shown partial remission in 11 patients (33%), 2 minor responses (6%), 13 patients with stable disease (39%), and 7 patients with progressive disease (21%). Major toxicity's observed in these peptide receptor targeted radiotherapy trials were hematological and renal toxicity. Until now there has been no evidence for pituitary toxicity, but there was evidence for transient gonadal toxicity in man with ¹¹¹In-pentetreotide. Only those patients with a high uptake in the tumor deposits as for instance shown by ¹¹¹In-pentetreotide scintigraphy are good candidates for these therapies and patients with scan-negative tumor deposits will not benefit. For patients with pituitary tumors, the uptake of the radiolabeled somatostatin analogs by these tumors is probably too low for peptide receptor targeted radiotherapy. Even in patients with acromegaly who were very sensitive to octreotide therapy, the pituitary uptake was less than 0.06%. The feasibility of this therapy for somatostatin receptor positive tumors in the peripituitary region (like meningiomas) has to be determined.

ABSTRACT S28

Grehlin analogs

E Ghigo

xx.

xx

ABSTRACT S29

Growth Hormone Receptor Antagonists

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A protein structure/function approach was used to understand the molecular topology of the growth hormone (GH) molecule. A result of those studies was our discovery that glycine (G) in the third alpha-helix of GH (G119 of bovine GH and G120 of human GH) was an important amino acid required for GH action. Substitution of this glycine residue with a variety of amino acids resulted in molecules that bound to the GH Receptor (R) but lacked growth-promoting activity. More importantly, these molecules inhibited the actions of GH both in vitro and in vivo. These results were obtained in the late 1980s and were the basis for the discovery of GH antagonists. Since that time, we have focused our efforts on determining whether GH antagonists can be efficacious in animal models of human disorders.

In vitro, GH antagonists (bGH-G119K or hGH-G120K) inhibit GH-mediated differentiation of α 3T3F422A preadipocytes to adipocytes. They will also inhibit both the insulin and anti-insulin actions of GH and can act as insulin sensitizers.

In vivo expression of GH antagonist genes in transgenic mice results in dwarf animals. The animals are fertile and possess no abnormal 'phenotypes.' These mice are protected against diabetes-induced glomerulosclerosis and ischemia-induced retinal neovascularization. Additionally, injection of GH antagonists into diabetic mice results in an inhibition of kidney enlargement, glomerular hypertrophy, and urinary albumin excretion. Finally, the GH antagonist confers resistance to DMBA induced mammary gland carcinomas in the transgenic mice.

Together, these results laid the foundation for the clinical use of GH antagonists when endogenous GH levels are elevated or when GH is known to be a factor in the progression of the disorder. Three such indications are acromegaly, diabetes induced end organ damage and certain types of cancer. Animal data concerning these types of disorders will be presented. An update of the results of the clinical trials using the GH antagonist, SOMAVERT™ (Pegvisomant for injection), for acromegaly also will be presented.

ABSTRACT S30

Mutant Receptor Rescuing Ligands for the GnRH Receptor: A New Therapeutic Approach Based on Receptor Folding

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Disease-causing receptor mutations are believed to damage function by precluding receptor-ligand or receptor-effector binding interactions. Recent observations challenge this view, supporting receptor misrouting as a primary means by which the damage due to mutation and subsequent misfolding is manifest. As a proof of principle, we have studied hypogonadotropic hypogonadism (HH). HH presents as a wide clinical spectrum, characterized by delayed sexual development and by inappropriately low or apulsatile gonadotropin and sex steroid levels, in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary axis. The reported mutations in GnRHR associated with HH are widely distributed across the entire sequence of the GnRHR. Patients with GnRHR mutations exhibit a broad spectrum of phenotypes, ranging from complete to partial hypogonadism, even among affected kindred. Expression in heterologous cell systems that express each naturally-occurring GnRHR mutant separately show that some mutants are totally non-functional (E90K, A129D, R139H, S168R, C200Y, S217R, L266R, C279Y, and L314X) while others retain a modest degree of function (N10K, T32I, Q106R, R262Q, and Y284C). We demonstrate rescue of eleven of the thirteen naturally occurring gonadotropin releasing hormone receptor (point) mutants by a small cell-permeant molecule, IN₃, originally designed as a non-peptide receptor antagonist, but is used here as a (removable) folding template, correcting the structural defects caused by the mutations and restoring function. In addition, rescue was accomplished for other deletion and Cys (removed) mutants indicating that misfolded receptors are a more common disease etiology than previously suspected and presenting a new approach for pharmacological intervention. Accordingly, therapeutic approaches based on restoration of the receptor to its correct cellular locus now present a novel means of disease treatment, potentially applicable to hypogonadotropic hypogonadism, cystic fibrosis, nephrogenic diabetes insipidus, hypercholesterolemia, retinitis pigmentosa, cataracts, Alzheimer's and other diseases. (These studies were supported by NIH grants HD-19899, RR-00163, HD-18185 and TW/HD-00668).

ABSTRACT S31

Novel Pituitary Ligands: PPAR-gamma Ligands

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Pituitary tumors account for ~15% of intracranial tumors, and are associated with significant morbidity due to local compressive effects, hormonal hypersecretion, or treatment-associated endocrine deficiency. Dopamine agonists and somatostatin analogs effectively suppress prolactin (PRL) and growth hormone (GH) hypersecretion respectively and control tumor growth or induce shrinkage in most PRL- and GH-secreting pituitary tumors. In contrast, there are no effective drug therapies for ACTH-secreting, or non-functioning pituitary tumors, and surgical excision with or without adjuvant radiotherapy is currently the only effective treatment. Peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a member of the nuclear receptor superfamily, is activated by thiazolidinedione synthetic PPAR-gamma ligands leading to adipocyte and glucose regulation, inhibition of macrophage and monocyte activation, and inhibition of prostate, and colon tumor cell growth. We examined PPAR-gamma expression in pituitary tumors, and in normal pituitary tissue, and examined effects of synthetic PPAR-gamma ligands on murine and human pituitary tumors in vitro and in vivo. PPAR-gamma was abundantly expressed in all of 54 human pituitary tumors examined compared to minimal PPAR-gamma expression in autopsy-derived normal pituitaries (~ 10-fold). PPAR-gamma activators (troglitazone, rosiglitazone) induced G₀-G₁ cell-cycle arrest, led to decreased number of cells in S-phase, and decreased phosphorylated Rb protein in human and murine pituitary tumor cells in vitro (~4-fold). FACS and TUNEL analysis of TZD-treated human and murine pituitary tumor cells demonstrated increased apoptosis, compared to controls, and TZD-treatment caused ~2-fold decrease in the proliferative marker, pituitary tumor transforming gene (PTTG) mRNA expression, confirming decreased pituitary tumor cell proliferative rates. In vivo, pituitary tumors, generated by s.c. injection of corticotroph, gonadotroph and somatolactotroph tumor cells, were considerably smaller in rosiglitazone-treated mice, compared to vehicle-treated tumor-bearing animals. Conclusions: PPAR-gamma is an important molecular target in pituitary adenoma cells and PPAR-gamma ligands inhibit tumor cell growth in vitro and in vivo. Based on these results, PPAR-gamma ligands proposed as a novel medical management of pituitary tumors.

ABSTRACT P1

Estrogen and Selective Estrogen Receptor Modulators (SERMs) Exert Divergent Effects on Growth Hormone Signaling Through Different Mechanisms

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Estrogen inhibits GH activation of JAK2/STAT5 signaling by suppressing JAK2 phosphorylation, an action mediated by SOCS-2 (Leung et al. (2003) PNAS 100:1016-1021). To determine whether SERMs exert similar effects on GH signaling, we have compared the effects of 17beta-estradiol (E2), 4-hydroxytamoxifen (4HT) and raloxifene (Ral) on the GH/JAK2/STAT5 cascade in HEK293 cells stably expressing human GHR. The cells were transiently transfected with an expression plasmid for human ERalpha and a luciferase reporter containing the STAT5 binding element, and treated with GH (500ng/ml) and E2 or SERMs (1, 10, 100nM) for 18h before measuring transcriptional activity. JAK2 phosphorylation was assessed by immunoprecipitation of JAK2 and Western blotting for tyrosine-phosphorylated proteins.

GH alone increased the reporter activity by 3.6 plus/minus 0.7 fold (mean plus/minus SE; $P < 0.02$). Co-treatment with E2 resulted in a dose-dependent reduction of the activity, to a maximum of 62 plus/minus 4% ($P < 0.02$) at 100nM. In contrast, 4HT and Ral increased the activity maximally by 58 plus/minus 5% and 43 plus/minus 5% ($P < 0.02$), respectively. GH-induced JAK2 phosphorylation was reduced by E2 to 57 plus/minus 4% of control, but increased by 4HT and Ral to 178 plus/minus 15% and 184 plus/minus 11%, respectively ($P < 0.01$). We next examined whether SOCS-2 or phosphotyrosine phosphatases played a role in mediating the enhancing action of SERMs on GH signaling. Quantitative RT-PCR study revealed that the SOCS-2 mRNA level was increased by E2 to 156 plus/minus 12% of control ($P < 0.05$), but unaffected by 4HT and Ral. Co-treatment with a phosphatase inhibitor (vanadate) did not alter the inhibitory effect of E2, but completely abrogated the enhancing effects of 4HT and Ral on GH-induced reporter activity. In summary, SERMs enhanced the transcriptional activity of GH by promoting JAK2 phosphorylation, an effect likely involving phosphatases. We conclude that estrogen and SERMs exert opposite effects on GH signaling through different mechanisms. (Supported by NHMRC and Eli Lilly Australia)

ABSTRACT P2

A single dose comparison of the acute effects of the new somatostatin analog SOM230 and octreotide in acromegalic patients

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Introduction: Treatment with the sst2 preferring analog octreotide (OCT), induces clinical and biochemical 'cure' in about 65% of acromegalic patients. GH secreting adenomas, which are not controlled, also express sst5. We compared the acute effects of OCT and SOM230 (SOM), a new somatostatin analog with high affinity for sst1-3 and exceptionally high affinity for sst5, on hormone release in patients with active acromegaly. Study protocol (approved by the local ethical committee): In a phase 2 double-blind, randomized, cross-over study, 100 microgram OCT, 100 and 250 microgram SOM were given sc at 0900 am to 12 patients. 24h profiles of GH and prolactin (PRL) were collected. Statistical analysis was performed by Student t-tests. Efficacy: 100 and 250 microgram SOM dose-dependently suppressed GH levels. Different subgroups were recognized for the effects on GH (mean plus/minus sem from 2-8h after drug administration compared to control). In 8 patients, GH levels were suppressed by OCT and 250 microgram SOM (-72 plus/minus 7 vs -65 plus/minus 6%: n.s.) to a similar extent. In 3 patients, the acute effect of 250 microgram SOM was superior to that of OCT (-70 plus/minus 2 vs -17 plus/minus 15%: $p < 0.006$). In another patient, the acute effect of OCT was better than that of SOM. Tolerability/Safety: Three patients experienced mild adverse drug reactions following one out of three treatments. Glucose levels were elevated after OCT and SOM compared to control day ($p < 0.05$) whereas insulin levels were only suppressed by OCT ($p < 0.01$). Conclusions: 250 microgram SOM and OCT exert a similar acute suppressive effect on GH secretion in 8 out of 12 patients, SOM was superior in 3, while OCT appeared more efficacious in 1 patient. SOM is well-tolerated and causes a slight increase in glucose levels, similar to OCT. SOM is an effective GH-lowering drug in acromegalic patients with the potential to increase the number of patients controlled during long-term medical treatment.

ABSTRACT P3

The novel somatostatin analog SOM230 inhibits ACTH release by cultured human corticotroph tumors

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Surgery is the first line treatment in patients with pituitary dependent Cushing's syndrome. This is related to the absence of an effective medical treatment in this type of patients. In most patients with untreated Cushing's disease, the long acting-, sst2-selective somatostatin (SS) analog octreotide (OCT), does not suppress ACTH release, a finding which is supported by in vitro studies. Recently, a novel SS-analog, named SOM-230, with high binding affinity to sst1, sst2, sst3, and sst5 receptors has been introduced. We compared the in vitro effects of OCT and SOM-230 on ACTH release in primary cultures of human corticotroph tumors, as well as in mouse AtT20 pituitary tumor cells. In a series of six immunohistochemically proven corticotroph adenomas sst expression levels were determined by real time quantitative PCR. In a 72 hr incubation with 10 nM SOM230 ACTH release was significantly inhibited in 3 out of 5 cultures (range -30, -34% to -40%). In contrast, OCT slightly inhibited ACTH release in 1 out of 5 cultures (-28%) only. In AtT20 cells, 10nM SOM230, but not OCT, induced a significant inhibition of ACTH production as well (-25% after 72 hr). RT-PCR analysis showed the presence of sst2, sst3 and sst5 receptors in AtT20 cells. In six human corticotroph adenoma tissues, a predominant expression of sst5 mRNA was found (relative copy number ranging between 109 and 433), whereas expression of sst2 mRNA was very low (relative copy number between 13 and 66).

On the basis of the more selective expression of sst5 receptors in corticotroph adenomas, the very high affinity of SOM230 for sst5 receptors, and the preferential inhibition of ACTH release by human corticotroph adenoma cells in vitro, it is hypothesized that the universal SS-analog SOM-230 may become a new medical treatment modality in a subgroup of patients with pituitary dependent Cushing's disease.

ABSTRACT P4

Endocytosis mechanism for the ghrelin-activated growth hormone secretagogue receptor type 1a (ghrelin/GHS-R1a)

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In this work, a sequential analysis of pathways involved in the regulation of GHS-R1a has been undertaken to characterize desensitization, endocytosis and down-regulation upon ghrelin binding. These parameters were evaluated on basis of [¹²⁵I]-ghrelin binding studies and measurement of intracellular calcium mobilization in stable clones of HEK-293 cells expressing the human GHS-R1a as well as confocal microscopy in CHO cells stably expressing the GHS-R1a-EGFP. The results indicate that GHS-R1a, mainly localized at the plasma membrane under unstimulated conditions, rapidly desensitizes after stimulation, as measured by ligand-induced intracellular calcium rise. The agonist-dependent desensitization is not mediated by protein kinase C (PKC) since phorbol ester, PMA, failed to block the ghrelin-induced calcium response. However, ghrelin-activated PKC might mediate the agonist-independent desensitization of other receptors and induce the heterologous desensitization, as it was observed for the cross-desensitization of LPA receptor(s). The ghrelin/GHS-R1a complex progressively disappears from the plasma membrane after 20 min after exposure to ghrelin and accumulates in the perinuclear region after 60 min. Colocalization of the internalized GHS-R1a with the early endosome marker (EEA1) after 20 min exposure to ghrelin indicates that endocytosis occurs via clathrin coated pits, which fit in well with the lack of internalization of this receptor observed after potassium depletion. Furthermore, these data indicate that GHS-R1a trafficking occurs through the endosomal recycling pathway. Inhibition of vacuolar H⁺-ATPases prevented recycling of the receptor, suggesting that the non-dissociation of the ligand/receptor complex is responsible for this effect. Sustained agonist treatment caused a reduction of GHS-R1a binding sites showing that the system is susceptible to be down regulated in a ligand dependent manner. Taken altogether these data suggest that GHS-R1a internalization play an important role in the physiology of ghrelin action.

ABSTRACT P5

Gene Expression Profiling of Pituitary Adenomas in LHCTP Mice Reveals a Role for p8 as a Putative Pituitary Transforming Gene

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Targeted and chronic overexpression of LH in transgenic mice (LHCTP) causes hyperproliferation of Pit-1 positive cells and culminates in the appearance of functional pituitary adenomas exhibiting focal to multifocal expansion of lactotropes, somatotropes, and thyrotropes. Tumors fail to develop in ovariectomized mice indicating that contributions from the ovary are necessary for development of adenomas. While the link between chronic ovarian hyperstimulation and PRL-secreting adenomas was expected, the involvement of somatotropes and thyrotropes was surprising and suggests that multiple ovarian hormones may contribute to this unusual pathological consequence. In support of this notion, we have found that ovariectomy followed by estrogen replacement results specifically in focal expansion of lactotropes, only in transgenic animals. In contrast, expansion of somatotropes or thyrotropes failed to occur. Therefore, estrogen appears to mediate transformation of lactotropes but is not sufficient for transformation of somatotropes or thyrotropes in our model. To characterize transcriptome changes associated with longitudinal development of the adenomas, we performed expression profiling with Affymetrix U74A microarrays. We identified a number of candidate genes with increased expression. One of these genes, p8, is a putative HMG-I/Y like transcription factor previously shown to be necessary for transformation of mouse embryonic fibroblasts. Increased expression of p8 was confirmed by RT-PCR. In addition, analysis by in situ hybridization demonstrated the presence of p8 in tumor foci containing lactotropes, suggesting that p8 may be important in the transformation of these cells. Currently, we are using several cell culture and transgenic paradigms to directly assess the tumorigenic potential of p8.

ABSTRACT P6

Endoscopic endonasal pituitary surgery. Results on a series of 203 patients

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A retrospective analysis on a 203 consecutive patient series, operated on by means of an endoscopic transsphenoidal approach to the sellar region for pituitary adenomas, from January 1997 to December 2002, has been conducted.

The surgical technique employed is an endoscopic endonasal unilateral approach to the sella, performed via an anterior sphenoidotomy, through the enlargement of the natural sphenoid ostium, with a rigid diagnostic endoscope as the sole visualizing tool, and without the use of a transsphenoidal retractor.

Tumor removal, as assessed by serial post-operative MRI, revealed complete removal of the lesion in 111 cases (64.1%), subtotal (more than 80%) in 42 cases (24.2%) and partial in 20 cases (11.5%), among the 173 macroadenomas, while in the 30 patients with pituitary microadenomas the removal was total in 26 cases (86.6%) and subtotal in 4 (13.3%).

Preoperative visual field defects were present in 92 cases of the sample. A full recovery of the visual field was achieved post-operatively in 48 patients (52.1%), and improvement occurred in 27 patients (29.3%), while vision remained unchanged in 17 patients (18.5%).

An overall decreased incidence of complications was observed, when compared to large historical series of traditional microsurgical transsphenoidal approach.

The procedure represents now a young established technique, well defined in its main aspects. The biology of pituitary adenomas demands time to draw definitive sentences about effectiveness of treatment, and the learning curve for the initial experience must be considered.

Anyway main advantages of the endoscopic procedure are its wider vision of the surgical field, close-up 'look' inside the anatomy, reduced incidence of complications, less traumatism to the nasal structures, easier treatment of the recurrences, and reduced hospital stay.

de Divitiis E, Cappabianca P: Endoscopic endonasal transsphenoidal surgery, in Pickard JD (ed): *Advances and Technical Standards in Neurosurgery*. Wien New York, Springer Verlag, 2002, vol 27, pp 137-177.

ABSTRACT P1

The Role of Radiation Therapy after Surgical Resection of Non-Functional Pituitary Macroadenomas

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Radiotherapy after aggressive surgical resection of a non-functional pituitary macroadenoma remains controversial. Historically, patients underwent post-operative radiotherapy to prevent recurrence. Due to potential side effects and availability of high-resolution imaging, most neurosurgeons now withhold radiation until a recurrence occurs. There is, however, relatively little evidence to support this practice. This study reviews the post-operative results of a large number of patients with non-functional pituitary macroadenomas, the majority of whom did not undergo prophylactic radiation.

One hundred seventy-six patients from 1979 to 1999 underwent surgery by a single neurosurgeon for non-functional pituitary macroadenoma. Forty-four patients were treated with prophylactic radiation after tumor resection with an average followup of 6.4 years. Another group of 132 patients were followed with serial imaging for an average of 4.4 years and were radiated only after a recurrence was documented on follow-up imaging. The radiated group of patients did not differ significantly from the non-radiated group in age or gender.

The recurrence rate of 19.7% in the non-radiated group at an average of 5.7 years was significantly higher than 2.3% in the radiated group ($P=0.007$). No patient in the non-radiated group, however, had a symptomatic recurrence and of the 19 that received radiation for recurrence, with an average followup of 3.9 years, tumors either remained stable or regressed.

Withholding radiotherapy after high percentage resection of non-functional pituitary macroadenoma leads to a higher recurrence rate. Deferring radiotherapy until recurrence, however, appears to be a safe and reasonable approach, since recurrences can be identified early with high-resolution imaging and treated effectively with radiation at the time of recurrence. Unnecessary radiation can thereby be avoided in up to 80% of patients.

ABSTRACT P2

Acquired Prolactin Deficiency In Patients With Disease Of The Hypothalamic-Pituitary (HP) Axis

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Adults with disease of the HP axis were studied to determine the prevalence of severe acquired prolactin deficiency (APD) and the pathophysiological characteristics associated with it. APD was defined as a serum prolactin level persistently below the detection limit of the assay i.e less than 1.8 ng/mL (normal range; male 3.0 to 16.0; female 3.0 to 19.0). Patients with a diagnosis of acromegaly, prolactinoma or congenital or drug induced prolactin deficiency were excluded.

Three hundred and sixty-nine patients (190 female, age range 17 to 79 years) with disease of the HP axis, meeting the specified criteria were identified. Twenty-two (13 female, age range 29 to 76 years), showed evidence of APD and, of these, 15 of 16 who underwent testing with TRH showed no prolactin response. Thirteen patients with APD had been treated for Cushing's disease. In all, 62 patients treated for Cushing's disease were identified, providing a prevalence of APD in treated Cushing's disease of 20.97 %. Excluding treated Cushing's disease, the prevalence of APD in the remainder of the cohort was 2.93 %.

No patient with isolated APD was identified. All patients with APD had evidence of severe growth hormone deficiency (GHD) with a peak GH response to provocative stimuli of <0.7 ng/ml and a median IGF-I standard deviation score (SDS) of -4.85 (quartiles -9.56 to -2.80). Of the 13 patients with APD and Cushing's disease, all were gonadotrophin and TSH deficient, 8 were ACTH deficient and 6 (46.1 %) had cranial diabetes insipidus (CDI). Of the remaining 9 patients with APD, total anterior pituitary failure was present in all and CDI in 2 (22.2 %).

APD in humans occurs late in the evolution of HP axis disease. It is universally associated with severe GHD. It has a low overall prevalence except in patients treated for Cushing's disease.

ABSTRACT P3

Radiotherapy for non-functioning pituitary adenomas: long-term results in a large cohort of patients followed in a single center

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Ninety-five patients with non-functioning pituitary adenomas from a single center were retrospectively studied with a mean follow-up of 9 ± 8 years. The patients were aged 52 ± 15 years with a male to female ratio at 1.9. At diagnosis, 70 % of the patients presented with a campimetric defect. Secondary hypogonadism was found in 65 % of them. Hypothyroidism and/or hypocortisolism and/or low IGF-1 level were present in half of the patients. Seventy-seven patients underwent surgery: 61 % were gonadotroph adenomas (beta-FSH, beta-LH, or alpha subunit immunostaining) and 39 % were non-secreting adenomas. A post-operative residual adenoma was present in 80 % of them. Forty-five subjects were treated by radiotherapy (RT) and 35 patients received a medical therapy (somatostatin analogues and/or dopamine agonists). Among 69 operated patients, 51 did not have early post-operative RT despite residual adenoma in 31/51. The other 18 patients had RT within the 12 months following surgery because of residual adenoma. For the all cohort, the regrowth rate was 43 % after an average period of 5.2 years (0.3-25 years). Probability of recurrence-free survival after 5 and 10 years is 94 % in patients treated by RT, versus 58 % after 5 years and 28 % after 10 years in patients who did not undergo RT (11 % vs 55 %, $p = 0.001$), implying that post-operative RT prevents tumor recurrence. Hypopituitarism appeared in 9 patients within 14 months (6-24 months). Visual field defect ($p=0.01$) and high plasma alpha subunit level ($p=0.04$) at diagnosis are predictive indicators of tumor regrowth. Age, sex, immunohistopathological findings or the dose of radiation did not affect significantly tumor recurrence. In conclusion, this retrospective study shows that post-operative RT is well tolerated and significantly reduces the risk of tumoral regrowth in patients with non-functioning pituitary adenomas.

ABSTRACT P4

Determination of oxidative protein and lipid damage in adult hypopituitary patients with growth hormone deficiency

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The aim of this study is to determine oxidative protein and lipid damage in adult hypopituitary growth hormone (GH) deficient patients. Eighteen hypopituitary GH deficient -otherwise healthy- adults on conventional replacement therapy other than GH (9 male, 9 female, age 41.8 plus/minus 16.4 years) and eighteen healthy subjects (6 male, 12 female, age 40.3 plus/minus 16.2 years) participated in the study. Plasma products of oxidative protein damage [protein carbonyl (PCO) and nitrotyroline (NT)], plasma oxidized LDL (oxLDL), plasma product of oxidative lipid damage [lipid hydroperoxide (LHP)] and antioxidant status of the plasma [total thiol (T-SH)] were measured. Body fat percent, total and LDL cholesterol concentrations were significantly higher in the hypopituitary group. Plasma PCO, NT, LHP and T-SH concentrations did not differ significantly between patients and controls. OxLDL concentration was significantly higher in the hypopituitary patients (62.4 plus/minus 17.8 vs 43.1 plus/minus 11.3 U/l, $p=0.001$). In the patients, oxLDL correlated significantly with the duration of hypopituitarism ($r=0.6323$, $p=0.01$). In the controls, oxLDL correlated significantly with blood pressure, total and VLDL cholesterol concentrations. Increased oxLDL concentration may indicate increased oxidative stress within the vascular compartment and may contribute to the proatherogenic state in GH deficient hypopituitary patients independent from conventional risk factors.

ABSTRACT P5

'Primary Empty sella'(PES): a review of 31 cases

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Introduction: The term PES makes reference to the herniation of cerebrospinal fluid filled into the sella turcica(ST) in patients with neither pituitary tumor, nor surgery or radiotherapy. It is more frequent in obese, hypertensive, middle aged women. Almost asymptomatic, it is usually not associated with endocrine abnormalities, although mild hyperprolactinemia , and deficient GH secretion (DGH) in children have been reported, as well as hypogonadotropic-hypogonadism .

Objective: To analyze clinical features, radiological findings and biochemical endocrine function in patients with PES.

Material and Method: 31 patients, age 22-78, 30 females and one male were evaluated retrospectively. All of them had radiological diagnosis of PES by pituitary imaging (MRI 27,TAC 4), asked for different reasons: abnormalities on the simple ST radiography indicated in a routine study (11); headaches (4); clinical and biochemical suspicion of pituitary deficiency (5) ; neurological symptoms (4); visual abnormalities (5); Hiperprolactinemia (2). Only pituitary basal hormones were made, except for the TRH test which was performed for primary hypothyroidism diagnosis.

Results: 97% of the patients were females, 65% had multiple pregnancies, 45% hypertension, and 55% reported headaches. Primary thyroid disease was found in 45%, obesity in 35%. Sixteen out of eighteen patients had an enlargement of ST shown in radiography. No visual field abnormalities were found. Pituitary dysfunction was found in 5 patients with different degree of hypopituitarism (16%) : Hypogonadotropic-hypogonadism (5) , Secondary Hypothyroidism (4), Adrenal deficiency (3), DGH (1). Adult GH deficiency should not be excluded, since ITT were not made in hypopituitary and normal patients.

Conclusions: PES seems to be more common in obese, middle aged women. Hypertension, headaches, and multiple pregnancies are usual, as previously reported. It is related to the enlargement of the ST, as an incidental finding. Pituitary dysfunction is not an infrequent feature in patients with PES.

ABSTRACT P6

Pituitary GABA-B Receptor (GABA-B-R) subunit expression: effect of testosterone (TP) and sexual differentiation

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A clear sexually dimorphic ontogenic expression of GABA-B-R subunits in rat pituitary membranes has been shown (*Neuropharmacology* 40:185-192:2001). Here we investigated the role of perinatal testosterone on GABA-B-R subunit expression.

Rat groups: 8 day-old females (8F); 8F treated with 1 micrograms per day of TP (days 1-4) or 100 micrograms on day 1 or flutamide (FL: 2.5 milligrams per 100g BW of pregnant mother, embryonic days 17-23); 8 day-old males intact (8M) or castrated on day 1; 8M treated with FL as above, intact or castrated on day 1; 15 day-old females (15F); 15F treated with 100 micrograms TP on day 1; 15 day-old males intact (15M) or castrated on day 1. Rats were decapitated on day 8 or 15; blood and pituitaries collected and frozen. GABA-B-R subunit expression was determined on pituitary membranes by Western Blot with antiserum Ab 174.1 which detects GABA-B1a/b-R subunits, using alpha-syntaxin expression to ensure comparable protein load. Hormones were determined by RIA. GABA-B1a-R and GABA-B1b-R expression was higher in 8F than in 15F or 8M (GABA-B1a-R (AU): 8F: 0.98 plus/minus 0.08 vs. 15F: 0.46 plus/minus 0.06 vs. 8M: 0.56 plus/minus 0.02, $p < 0.01$). One hundred micrograms of TP in 8F, but not in 15F, decreased GABA-B-R subunit expression to male levels ($p < 0.05$). One microgram TP, or FL, in 8F did not alter expression. In 8M, FL treatment, alone or with castration, increased subunit expression to 8F levels, though castration alone was not effective (GABA-B1a-R : 8M-castration: 0.67 plus/minus 0.06, 8M-FL: 0.81 plus/minus 0.05, 8M-FL-castration: 0.97 plus/minus 0.03). One hundred, but not 1, micrograms TP, profoundly altered serum gonadotropins at 8 days of life, though both treatments effectively androgenized animals, as evidenced by lack of cycling and LH surge in animals reaching adulthood.

We conclude that androgens, pre- and post-natally, decrease pituitary GABA-B-R subunit expression.

ABSTRACT P7

Prolactinomas and pregnancy

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Introduction : There is less than a 2% risk of microprolactinoma enlargement during pregnancy but a higher than a 15% risk of symptomatic enlargement of a macroprolactinoma, which should be carefully followed up so as to prevent complication during pregnancy

Objectives : to analyze the effects of pregnancy on prolactinoma size and the postpartum follow up. To determine the incidence of embryo-fetal development in relation with the exposure to the dopamine agonist.

Material and Methods : 51 women with prolactinomas (42 microadenomas, 9 Macroadenomas) were studied during the course of 77 pregnancies. Five patients have had previous surgery, three of them became pregnant without dopamine agonist. Sixty two pregnancies were achieved with Bromocriptine 2,5- 25 mg/day, 13 with cabergoline 0,25 - 3 mg/week. The patients were followed with PRL levels, computerized visual field and clinical exams.

Results : Eighty two percent of the pregnancies were full term, 1,3 % preterm and 15% of spontaneous abortion (9% without justified cause). In eight pregnancies, women developed headaches, tumor enlargement was documented by MRI in two patients, one of them with visual field defects. Forty three of the cases breastfed postpartum without complication. Postpartum MRI did not change in 75%, and some degree of tumor size decrease was seen in the remaining. In 30% of the cases postpartum PRL levels were lower than those taken before pregnancy. Fetal malformation were found in 3 cases.

Conclusions: postpartum tumor enlargement did not occur in any patient with prolactinoma, even in those with tumor growing during pregnancy. Agonist dopamine proves safe given at the early stage of pregnancy, considering the low incidence of mother and fetal complications

ABSTRACT P8

Timing for the development of Addison syndrome in patients with Cushing disease cured by surgery who did not received peroperative steroid therapy

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Rationale: The fear for developing Addison syndrome (AS) after successful transphenoidal surgery (TS) for Cushing disease (CD) led many centers to use immediate postoperative steroid replacement therapy. Recent data suggested the corticotrophic blockage is not complete in patients with CD and that the stress response to surgery would be able to sustain vascular responsiveness for many hours postoperatively. We studied the timing for the first symptoms of AS after successful TS for CD in patients who did not receive postoperative steroid therapy.

Methods: Twenty consecutive patients with documented CD who were considered under remission after TS were studied. Age ranged from 16 to 47 years and mean follow-up time was 1,8 years (8 months-4 years). All patients were submitted to TS and pathological examination showed ACTH-secreting tumor. All patients were under clinical remission at the last follow-up. Cortisol levels were measured at least every 12 hours postoperatively.

Results: Eighteen patients disclosed symptoms of AS correlated to low cortisol plasma levels postoperatively. Mean time for initiation of symptoms was 43 hours (20-96 hours) and mean cortisol levels at this point was 1,5 micrograms per deciliter (0,5-4,7). Two patients who were subsequently considered under remission did not exhibit symptoms of AS (lower cortisol levels of 5 and 5,6 micrograms per deciliter, respectively).

Discussion: It is safe not to administer steroids during the immediate postoperative period in patients with CD submitted to TS as far as they are kept under clinical surveillance for the first 2 days postoperatively. Ninety percent of the patients who will go into remission postoperatively will develop AS although 10% of them may come into remission without any AS symptom. Immediate (24-48 hours) postoperative cortisol levels lower than 2,0 micrograms per deciliter are highly suggestive of future clinical remission of the hypercortisolism.

ABSTRACT P9

Postoperative clinical remission of acromegaly in patients with invasive pituitary GH-secreting tumors

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Rationale: The endocrinological results expected from transesphenoidal microsurgery in patients bearing invasive pituitary tumors are much worse than those obtained in patients with non-invasive lesions. Cavernous sinus invasion as demonstrated preoperatively by high resolution MRI is correlated to very high surgical failure rates.

Methods: Eighty-six consecutive adult acromegalic patients submitted to surgery were studied. All patients were submitted to transesphenoidal surgery and had pre and postoperative MRI, GTT and sequential GH and IGF1 plasma level determination. Mean follow up time was 12,4 months (3-28). Forty-one patients had cavernous sinus invasion as determined by preoperative MRI and invasion was confirmed intraoperatively in all. Patients with invasive tumors that were considered under remission (basal GH lower than 2,5 nanogram per milliliter and GH lower than 1 nanogram per milliliter after GTT) were studied.

Results: Six patients with invasive tumors went into clinical remission of acromegaly. In 5, clinical remission was obtained immediately after surgery and in 1, sub acute (40 days postoperatively) remission was noted. Residual tumor was seen on postoperative MRI in 1 patient. Preoperative mean GH and IGF1 levels were 19,5 nanogram per milliliter and 902 nanogram per milliliter, respectively; postoperative mean GH level was 1,6 nanogram per milliliter and IGF1 level 360 nanogram per milliliter. Two patients still had abnormally high IGF1 levels at last follow-up (mean follow-up time = 14 months).

Discussion: Cavernous sinus invasion is usually associated to bad endocrinological surgical outcome in patients with acromegaly. On the other hand, remission could be seen in some patients; prolonged follow-up would be needed to rule out recurrence in such patient's population. IGF1 might remain high in patients under remission with either invasive or non-invasive tumors. As in a population with non-invasive tumors, patients in the present selected series has normal or slightly increased IGF1 plasma levels. Sub acute remission might be associated to additional postoperative intracavernous necrosis of remaining tumor.

ABSTRACT P10

Postoperative clinical remission of acromegaly with persistently high IGF1 plasma levels

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Rationale: Standard criteria for remission of acromegaly include low (lower than 2,5 nanogram per milliliter) basal GH plasma level and GH lower than 1 nanogram per milliliter after GTT. This paper analyses patients with acromegaly who were submitted to surgery and disclosed low GH level, normal GH after GTT and persistently abnormal IGF1 level.

Methods: Eighty-six consecutive adult acromegalic patients submitted to surgery were studied. All patients were operated through the transesphenoidal route and had pre and postoperative high resolution MRI, GTT and sequential GH and IGF1 plasma level determinations. Mean follow-up time was 12,4 months (3-28) for the whole series.

Results: Overall, 56% of the patients went into clinical remission of acromegaly (93% of the non-invasive microadenoma, 60% of the non-invasive macroadenoma and 7% of the invasive micro or macroadenoma). Twelve patients were considered under remission (GH lower than 2 nanogram per milliliter and normal GTT), but disclosed persistently high IGF1 level during follow-up (mean follow-up time = 7,4 months). Mean preoperative GH level was 18 nanogram per milliliter (7-80) and mean IGF1 level was 820 nanogram per milliliter (390-1920); mean postoperative levels were 0,7 nanogram per milliliter (0,08-1,5) and 409 nanogram per milliliter (330-490), respectively. All patients had postoperative MR scans showing no residual tumors, except for 1 patient. In 2 of the patients, cavernous sinus invasion was documented intraoperatively; all the others had non-invasive tumors.

Discussion: Some acromegalic patients might be considered under remission but have persistently high IGF1 level. Our patients had IGF1 levels that, despite being abnormal (mean= 409 nanogram per milliliter; mean upper normal limit approximately 320 nanogram per milliliter), were not extremely high. One patient has been followed up for 19 months and still has abnormal IGF1 level. The pathophysiological role of these abnormal IGF1 levels remains unknown. So far, it is probably reasonable to keep following up these patients without further treatment, until we could better understand the long term IGF1 level dynamics.

ABSTRACT P11

Trends in pituitary surgery: lessons from a series of 800 patients

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Rationale: Surgical procedures for the treatment of pituitary lesions have sequentially incorporated new technology over the years. The introduction of the surgical microscope and intraoperative fluoroscopy had a major technical impact at the early days of pituitary surgery. More recently, neuroendoscopy, intraoperative neuroimaging and neuronavigation come into place and their relative role is now being investigated.

Material: Eight hundred patients with sellar lesions submitted to surgery from 1994 to 2002 were studied. Ninety-six percent of the patients were treated through the transesphenoidal route and 4% through craniotomy. The surgical mortality was 0,4%.

Results: The sub labial approach has been used from the beginning of this series. Transnasal procedures has been carried out in patients with small tumors or big nostrils, but the sub labial approach is still preferred in patients with larger lesions. Neuroendoscopy has been used as an adjunctive technique in selected patients only. Intraoperative fluoroscopy and neuronavigation has been used over the years but are actually not needed most of the time if the surgeon has adequate anatomical knowledge. Intraoperative imaging has only recently been introduced and is still under investigation. Closure of the sellar floor has become simpler: there has been no need for any type of reconstruction if there is no CSF leakage. CSF leakage sealing has benefited from the use of fibrin glue without autologous graft.

Discussion: It is unlikely that new technology such as neuroendoscopy, neuronavigation or intraoperative imaging would impact on our ability to remove invasive tumors using microsurgery alone, although they might impact on our ability to adequately remove non-invasive tumor. Neuroendoscopy would become a more useful technique with the development of endoscope's holders that would free the surgeon's second hand, and especially if '3D endoscopes' could be developed. Intraoperative imaging would help but there is already enough cumulated experience with early (immediate postoperative) MRI showing that we would certainly face difficulties while interpreting intraoperative imaging findings of the sellar region.

ABSTRACT P12

Long-term pituitary dysfunction after traumatic brain injury: occurrence and predictive factors

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Traumatic brain injury (TBI) may be associated with hypothalamo-pituitary impairment in hormone secretion, which may contribute to long-term physical, cognitive, and psychological disability. We studied the occurrence and risk factors of pituitary dysfunction in 66 patients (52 M, age 20-87 yrs) with TBI over the last 5 years. Skull or facial fractures were documented in 16, and neurosurgery was performed in 18 cases. According to Glasgow Coma Scale (GCS), 29 patients had suffered from severe, 8 moderate, and 29 mild TBI. Glasgow outcome score indicated good recovery in 48, moderate disability in 12, and severe disability in 6 cases. Hormonal evaluation showed: hypogonadotropic hypogonadism in 7 (10.6%), central hypothyroidism in 5 cases (7.6%), low PRL levels in 4, and high PRL levels in 4 cases. All subjects had normal corticotroph and posterior pituitary function. Seven patients showed low IGF-I levels for age and sex. GHRH plus arginine test, performed in 50 subjects, indicated partial GH deficiency (GHD) in 10 (20%) and complete in 4 cases (8%). MRI abnormalities were seen in 3 cases (2 empty sella; 1 stalk dislocation). The percentage of pituitary dysfunction was 62.0%, 37.5%, and 24.1% in the patients with severe, moderate, and mild TBI, respectively. GSC was significantly ($p < 0.005$) lower in patients with pituitary dysfunction (8.4 ± 0.7 vs. 11.4 ± 0.6). No relationship was detected between overall pituitary dysfunction and years from trauma, type of injury and outcome. In conclusion, our study shows that subjects with a history of TBI may frequently develop pituitary dysfunction (42.4%), especially GHD. Evaluation of pituitary function should, therefore, be included in the long-term follow up of patients with TBI, in order to detect the occurrence of post-traumatic hypopituitarism so that adequate hormonal replacement therapy may be initiated.

ABSTRACT P13

Exacerbation of Lymphocytic Hypophysitis by Growth Hormone Therapy: A Case Report

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Lymphocytic Hypophysitis (LH) is an increasingly appreciated cause of hypopituitarism in adults. We report a case of an older gentleman with LH, in whom recombinant human growth hormone (GH) replacement therapy induced significant enlargement of the sellar mass lesion.

The patient was found to have panhypopituitarism at age 62 during an evaluation for sexual dysfunction and headaches. MRI revealed a large intrasellar and suprasellar mass with optic chiasmal compression. The mass was debulked via a transsphenoidal approach. Morphological examination revealed extensive lymphoplasmacytic infiltrate. One year later, he required craniotomy due to enlargement of the sellar lesion. Postoperative MRI indicated residual suprasellar disease, which remained stable in size over the ensuing year. At that time, therapy with GH was initiated as part of a clinical research study. Over a 2-month period, the GH dose was increased to 1 microgram SC daily. Repeat MRI after 4 months of GH therapy showed increase in the size of the mass. GH therapy was withheld for 2-months and follow-up imaging indicated interval reduction in the size of the sellar lesion. A subsequent 6-month trial of GH replacement therapy again resulted in enlargement of the mass, prompting fractionated stereotactic radiation therapy. No further growth has since occurred over the past 9-months.

Although it is generally accepted that LH results from autoimmunity, the precise immunopathogenic mechanisms underlying this disorder remain unclear. It is conceivable that the anterior pituitary hormones themselves serve as auto-antigens that trigger the immune reaction. In contrast to other anterior pituitary hormone deficiencies in which therapy involves replacement of the end-organ hormone, GH deficiency is treated by administration of the actual hormone synthesized by the pituitary gland. An immune reaction against GH can potentially explain the exacerbations experienced by our patient each time he was challenged with GH.

ABSTRACT P14

GH Receptor Expression and Function in Pituitary Adenomas

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Growth hormone (GH) replacement is used in patients rendered hypopituitary due to a non-functioning pituitary adenoma (NFPA), which makes it relevant to study the effects of GH on the biology of NFPA.

In NFPA tissue from 14 patients we evaluated 1)GH receptor (GHR) expression and signal transduction 2)the effect of GH exposure on cell proliferation and hormone secretion in vitro. Expression of GHR was assessed by RT-PCR, and in cell culture STAT5 was measured by WLB. Cell proliferation was assayed by [³H]-thymidine incorporation.

All adenomas expressed GHR but it was not possible to detect STAT5. Overall GH did not significantly affect cell proliferation, although stimulation was observed in 30 % of adenomas. GH did not significantly stimulate in vitro hormone secretion.

CONCLUSION: 1)GH receptors are expressed in NFPA but their functional role is uncertain 2)GH does not consistently stimulate proliferation of NFPA cells in vitro

ABSTRACT P15

Determinants of neurosurgical outcome in pituitary adenomas

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Our aim was to review neurosurgical outcome (hormonal + radiological cure) in 289 pituitary adenomas operated between 1982 and 2001 by the same 2 neurosurgeons, in order to identify predictors of cure. Thirty-eight % were males and median age was 40.8 years; patients were classified depending on operation date (before 1991 $n=1991$: 48.1%, and since 1992 $n=1992$: 51.9%), route (transsphenoidal 92% vs. craniotomy 8%), size (microadenomas 28% vs. macroadenomas MA), and secretory nature (NF 28%, Prol 27%, GH 26%, ACTH 17%, Gn and TSH 1%). In order to investigate determinants of neurosurgical outcome, a stepwise, forward logistic regression analysis was performed (SPSS 10.0 statistical package for Windows) including cure as dependent variable and age, size, operation date and secretory type as independent variables. Radiologically, size predicted 63% of cure (Odds ratio 0.16: cure of macroadenomas -MA- 16% compared to microadenomas 100%, $p < 0.0001$); hormonally, Prol-secreting versus GH- and ACTH-secreting adenomas predicted 67% of cure (OR 3.29: cure rate for Prolactinomas 3.29 less than other secreting adenomas, $p < 0.0001$), and MA had a probability of cure of 45% vs. microadenomas, $p < 0.001$. Considering simultaneous radiological and hormonal cure, size predicted cure in 65% (OR 0.35, i.e. MA cure 35% vs. microadenomas 100%, $p < 0.0001$), as did operation date (OR 0.4, indicating that operation $n=1991$ had 40% cure probability compared to operation $n=1992$ (100%, $p < 0.0001$). We conclude that both characteristics of the pituitary tumors and greater neurosurgical experience are determinants of postsurgical outcome.

ABSTRACT P16

Changes in serum thyroid hormones levels during two years of growth hormone replacement in deficient adults

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To evaluate the effect of recombinant growth hormone (GH) therapy on thyroid function, we studied 21 adults with GH deficiency (12 females and 9 males, mean age 41.1 ± 10.3 yr). Eighteen patients had central hypothyroidism and were adequately treated with LT_4 (mean dosage: 132.3 ± 26.1 μ g/day) and 3 were euthyroid. Serum IGF-1, TSH, free T_4 (FT_4) and total T_3 and T_4 were measured at baseline and after 3, 6, 12 and 24 months of therapy. During the first six months of GH therapy, 6 patients (28.5%), two of them euthyroid, had a reduction in FT_4 to near or below the normal range with concomitant increase in T_3 to near or above the normal range. In only one patient the LT_4 dose was increased because low serum levels of FT_4 were maintained. No patient had any clinical symptoms or changes in lipids compatible with hypothyroidism. There was no significant reduction in the FT_4 means ($p=0.24$) neither in the means of T_4 and TSH at any time. The increase in T_3 was significant at 3 and 6 months ($p=0.001$ and $p=0.003$, respectively). After 12 and 24 months there were no difference in thyroid hormones levels comparing to the baseline ($p=1$). There was a negative correlation between FT_4 and T_3 levels ($p=0.021$). We did not find any correlation between IGF-1 and thyroid hormones levels.

In conclusion, GH replacement causes a transient change in thyroid function. Thyroid hormones levels return to pre-treatment values after 6 months of continued GH replacement in most of the patients. So, to change the LT_4 dosage during this time, we must consider clinical symptoms of hypothyroidism or a persistent decline in FT_4 levels below the normal range.

ABSTRACT P17

Somatostatin receptor expression pattern in growth hormone secreting pituitary adenomas influences in vitro response to somatostatin

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Somatostatin (SRIF) analogs have been widely employed in the clinical practice to reduce growth hormone (GH) secretion by GH producing pituitary adenomas in vivo, and, recently, the functional dimerization between SRIF receptors (SSTRs) has been demonstrated in vitro. In order to evaluate whether SSTR expression pattern could influence SRIF effects on pituitary adenomas, we investigated SSTR subtypes (1 to 5) expression by RT-PCR and tested in primary cultures the effects of SRIF on GH secretion and cell viability in 18 GH-secreting adenomas. All adenomas expressed SSTR2, while SSTR5 was expressed in 12, SSTR1 and SSTR3 in 9, and SSTR4 in 2 adenomas. Treatment with 10 nM SRIF significantly reduced GH secretion in all adenomas (22.6% inhibition). This effect was much more pronounced in adenomas expressing SSTR1 (SSTR1+) vs. adenomas not expressing SSTR1 (SSTR1-) (30% vs. 2% inhibition, $P < 0.01$). A similar effect was apparent in SSTR5+ vs. SSTR5- adenomas (35% vs. 5.5% inhibition, $P < 0.01$). On the contrary, SRIF was less potent in inhibiting GH secretion in SSTR3+ than in SSTR3- adenomas (1% vs. 26% inhibition, $P < 0.01$). Treatment with SRIF also significantly reduced cell viability in all adenomas (13% inhibition). This effect was much more pronounced in SSTR1+ vs. SSTR1- (26% vs. 10% inhibition, $P < 0.01$), but not in SSTR5+ vs. SSTR5- adenomas (15% vs. 10% inhibition, $P = 0.5$). Moreover, SRIF was less potent in reducing cell viability in SSTR3+ than in SSTR3- adenomas (5% vs. 20% inhibition, $P < 0.01$). These results suggest that different SSTRs mediate the inhibitory effects of SRIF on cell survival and on hormone secretion in pituitary adenomas. Our data indicate that SSTR expression pattern influences the inhibitory effects of SRIF on GH secretion and cell viability in pituitary adenomas, suggesting that SSTRs differently contribute in mediating SRIF effects on pituitary tumors.

ABSTRACT P18

First experience in surgery of pituitary adenomas and craniopharyngeomas with high-field intraoperative magnetic resonance imaging

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Objective: To evaluate whether intraoperative magnetic resonance (MR) imaging can improve management and resection of pituitary adenomas and craniopharyngeomas using an intraoperative 1.5 Tesla scanner

Material & Methods: Since April 2002 we performed surgery in 58 patients with pituitary adenomas or large craniopharyngeomas. The patient was placed in supine position on a rotating MR tray, the head placed during surgery at the 5G line. A standard flexible coil was placed around the forehead in transphenoidal surgery. For transcranial approaches a MR compatible head coil and fixation device was used. The pituitary imaging protocol consisted of a scout, T1W and T2W sequences without contrast agent and fast HASTE-sequences, which last only 25 seconds. These protocol was used prior to surgery and for resection control. In craniopharyngeomas we performed T1W, T2W sequences without and with contrast agent, as well as FLAIR and gradient echo sequences for 3D volume rendering.

Results: In all patients MR imaging allowed an ultra-early evaluation of tumor resection, which is normally only possible 2-3 months after surgery. In the pituitary cases (N=45) imaging revealed a primary complete removal in 50%. A complete tumor removal after second look could be achieved in 11 additional patients (74%). 12 patients (26%) of the pituitary series could not be resected completely because of tumor invasion to the cavernous sinus. Among 13 craniopharyngeomas 6 patients were treated by stereotactic cystoventricular shunting in the scanner documenting correct catheter placement. In 5 of 7 patients with giant craniopharyngeomas a complete resection could be achieved. In one patient remnants of the capsula had to remain, in one other patient the suprasellar tumor was resected completely.

Conclusion: Intraoperative MR imaging serves as ultra-early quality control in transphenoidal pituitary surgery as well as in craniopharyngeoma surgery. Since anatomical structures in the hypothalamic-pituitary area, including the cavernous sinus, can be visualized convincingly in the majority of the cases resection can be performed more radical and gentle.

ABSTRACT P19

'MacroLH': unsuspected high LH value in a patient with endogenous antibodies against LH

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Interference in immunoassay results due to endogenous antibodies directed against peptide hormones is a well documented phenomenon. It is known to occur for insulin, GH, and especially Prolactin, being responsible for most of the cases of 'macroprolactin'. However, it has never been described for LH. We present the case of a female patient, 23 years old, with diagnosis of congenital adrenal hyperplasia (late onset 21OH defect) and Hashimoto's thyroiditis, both conditions under treatment. Laboratory evaluation showed high LH levels (206,0 IU/L) with normal FSH levels (4,0 IU/L). Serum hCG was undetectable (<2,0 UI/L) and alpha subunit levels were normal (553 ng/L; normal range: 80 to 604 ng/L). The patient was not using any LH stimulating drug, nor had ever received LH or hCG injections. LH was measured by an immunofluorometric assay (in house) and result confirmed by an electrochemiluminescent assay (Roche). Serum was submitted to gel filtration chromatography on a 1.5x30 cm Superdex 200 column (Pharmacia) and the elution profile showed that almost all immunoreactive LH eluted as a high molecular weight form (MW ~250 kDa). PEG precipitation led to a recovery in the supernatant of only 7%, and application to a protein G sepharose column (Pharmacia) showed complete binding of the LH immunoreactivity, that could be eluted by lowering the pH to 2.8. Gel filtration (Superdex 200) in dissociating conditions (Glycine-HCl 0.1M, pH 2.8) shifted the LH peak to the expected molecular size. In conclusion, we describe a patient with unexpectedly high LH values due to the presence of endogenous antibodies against LH. This finding has never been described and its etiology and frequency remains to be investigated.

ABSTRACT P20

Short and long term effects of growth hormone replacement therapy on protein metabolism in growth hormone deficient adults

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OBJECTIVE: To investigate the effect of GH replacement therapy on protein kinetics and body composition in hypopituitary patients with growth hormone deficiency (GHD).

METHODS: The study was approved by the Institutional Review Board of Baylor College of Medicine, and written informed consent was obtained from all subjects prior to their entry into the study. Splanchnic and whole body protein kinetics were measured in 8 adults with GHD and 8 matched healthy controls in the fasted and fed states using intravenous ((³H)leucine) and oral ((¹³C)leucine) infusions. Measurements were repeated in the GHD subjects after 2 weeks and 6 months of GH treatment. Body composition (fat free mass FFM and fat mass) were measured by DEXA before and after 6 months of GH. Student's non-paired t-test was used to compare baseline data between GHD patients and controls and one-way ANOVA was used to compare the data obtained at baseline, 2 weeks, and 6 months.

RESULTS: There was no significant difference in leucine kinetics (micromol/kg FFM/hour) between GHD subjects and controls. After 2 weeks of GH, leucine oxidation decreased (fasted: 41±5 versus 30±6, P < 0.05; fed: 49±3 versus 41±3.6, P < 0.05) and leucine balance improved (fasted: minus14±4 versus minus3.5±3, P < 0.05; fed: 65±13 versus 72±7, P = 0.07), because of increased protein synthesis. After 6 months of GH, these changes were maintained in the fasted but not in the fed state. Splanchnic leucine uptake was not affected by GH therapy. GH caused a modest increase in FFM in 5 GHD subjects who had decreased FFM at baseline.

CONCLUSIONS: GH replacement in GHD patients causes an acute improvement in protein balance due to an increase in synthesis and a decrease in catabolism. After 6 months of GH treatment, protein kinetics return to pre-treatment homeostasis.

ABSTRACT P21

The possibility of a bioinactive ACTH producing pituitary adenoma

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We present a case of 34-year-old man with an ACTH producing pituitary adenoma, lacking in the Cushing signs in spite of superfluous secretion of ACTH. The patient visited our hospital complaining headache, and a CT scan detected by chance a pituitary macroadenoma. Although the Cushing signs including center obesity and high blood pressure were not evident, the plasma ACTH concentration was elevated to be 107pg/ml (Big size ACTH was excluded in the measurement of ACTH), while the other pituitary hormones were within normal values. His ACTH and cortisol were not suppressed by oral administration of 1 mg and 8mg dexamethazon. His ACTH level increased from 105 pg/ml to 137 pg/ml at 15 minutes after intravenous CRH administration. MRI revealed a pituitary tumor with suprasellar extension. The transsphenoidal surgery was conducted and the tumor was extensively excised. The postoperative plasma ACTH decreased to 50.9 pg/ml, and his ACTH and cortisol were suppressed by oral administration of 1 mg and 8mg dexamethazon. Immunohistochemical stainings revealed the ACTH-immunopositive cells in adenoma. Thus, the patient was diagnosed to have ACTH-producing adenoma without Cushing signs. Although the reason for having lacked the Cushing signs was not clear in spite of superfluous secretion of ACTH in this patient, this patient's ACTH was interpreted to have low bioactivity.

ABSTRACT P22

Treatment of TSH-Secreting Pituitary Adenomas with Iopanoic Acid (Telepaque)

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TSH secreting tumors comprise less than 2% of all pituitary adenomas. All patients present with hyperthyroxinemia with a detectable TSH level, and the majority have macroadenomas. Telepaque (iopanoic acid) potently inhibits the conversion of T₄ to T₃. Although used successfully to treat primary hyperthyroidism, it has not been employed in central hyperthyroidism. We report two patients with thyrotropinomas, in whom telepaque was used perioperatively to rapidly achieve euthyroidism.

In case 1, a 38-year-old male presented with severe hyperthyroidism. Serum TSH, FT₄, FT₃, and alpha subunit/TSH molar ratio were all elevated. MRI confirmed a 0.7-cm sellar mass. He remained hyperthyroid despite the use of methimazole (45 mg/day) for approximately four weeks. Telepaque 500 mg BID was started. After 5 doses, serum T₃ level normalized and patient underwent surgery. On postoperative day 1, serum TSH became subnormal. Telepaque was discontinued on post-operative day four after near normalization of FT₄ and FT₃. TSH remains suppressed (with normal FT₄ and FT₃) five months after surgery. In case 2, a 32-year-old female presented with hyperthyroidism. TSH level was normal, but FT₄, FT₃, and alpha subunit/TSH molar ratio were all elevated. She remained hyperthyroid despite the use of methimazole 10 mg/day for six months. Pituitary MRI revealed a macroadenoma. Propylthiouracil (150 mg TID) and telepaque (500 mg BID) was substituted for methimazole. Euthyroidism was achieved within 7 days and the patient underwent surgery. On postoperative day 1, serum TSH became subnormal. Telepaque was continued and the TSH normalized on post-operative day twenty-four. Telepaque was discontinued two months after surgery when FT₄ and FT₃ normalized. The patient continues to be euthyroid three months after surgery. These two cases exemplify the efficacy of telepaque in rapidly restoring euthyroidism in patients with thyrotropinomas, particularly those resistant to thionamides.

ABSTRACT P23

Diagnosis of adult growth hormone (GH) deficiency in normal subjects, obese and hypopituitary patients. Comparison between four different stimuli

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The biochemical diagnosis of adult GH deficiency is established by provocative testing of GH secretion, the insulin-tolerance test (ITT) is the best validated. The aim of the present study was to evaluate the diagnostic capability of four different stimuli of GH secretion, ITT, GHRH, GHRH plus acipimox and GHRH plus GHRP-6, in two situations, hypopituitarism (Hy) and obesity (Ob), and normal subjects (N).

Eight adults with Hy (4F, 4M, 48.8±1.4 yr), ten patients with Ob (5F, 5M, 48.1±2.5 yr), with a BMI of 34.2±1.2 kg/m², and ten N subjects (5F, 5M, 48.1±2.8 yr) were studied. Four tests were done to each patient or normal: ITT (0.1 U/kg, iv, 0 min), GHRH (100 ug, iv, 0 min), GHRH (100 ug, iv, 0 min), preceded by acipimox (250 mg, orally, at -270 min and -60 min) (GHRH+Ac). GHRH (100 ug, iv, 0 min) plus GHRP-6 (100 ug, iv, 0 min) (GHRH+GHRP-6).

After the ITT the mean peak GH (mcg/l) secretion was 1.5±0.3 for Hy, 10.1±1.7 ($p < 0.05$ vs Hy) for Ob and 17.8±2.0 ($p < 0.05$ vs Hy) for N. GHRH-induced GH secretion was 2±0.7 for Hy, 3.9±1.2 ($p = NS$ vs Hy) for Ob and 22.2±3.8 ($p < 0.05$ vs Hy) for N. After GHRH+Ac was 3.3±1.4 for Hy, 14.2±2.7 ($p < 0.05$ vs Hy) for Ob and 35.1±5.2 ($p < 0.05$ vs Hy) for N. After GHRH+GHRP-6 was 4.1±0.9 for Hy, 38.5±6.5 ($p < 0.05$ vs Hy) for Ob and 68.1±5.5 ($p < 0.05$ vs Hy) for N. The differential between N and Hy for GHRH+GHRP-6 (64) was higher ($p < 0.05$) than for the ITT (16.3), GHRH (20.2) or GHRP+Ac (31.8). The differential between Ob and Hy for GHRH+GHRP-6 was (34.4) higher ($p < 0.05$) than for the ITT (8.6), GHRH (1.9) or GHRP+Ac (10.9).

In conclusion, although both acipimox and GHRP-6 partially reverse the functional hyposomatotropism of obesity after GHRH, while are unable to reverse the organic hyposomatotropism of hypopituitarism, the combined test GHRH+GHRP-6 most accurately distinguishes both situations, without the side effects of ITT.

ABSTRACT P24

Chromatin derived acidic peptides stimulate anterior pituitary prolactin secretion in vitro

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Low molecular weight acidic peptides (ACPs) have been isolated in the chromatin of eukaryotic cells, but they are also able to modulate neurotransmitter function, possibly through homophilic interaction with neural cell adhesion molecules (N-CAMs). In order to evaluate the possible neuroendocrine activities of ACPs, we have studied in vitro the prolactin (PRL) modulatory effects of ACP-1, a synthetic acidic peptide corresponding to the C-terminal fragment of the largest subunit of eukaryotic RNA polymerase II. Rat anterior pituitary cells were plated into multiwell dishes and incubated for 1 hour with graded concentrations (10 nM-10 µM) of ACP-1; the incubation medium was collected and assayed for PRL by RIA. We have also tested the effect of ACP-1 on dopamine release from perfused rat hypothalamic synaptosomes, which were loaded with [³H]dopamine and perfused with ACP-1 in Krebs-Ringer buffer, both basally and during K⁺(15 mM)-induced depolarization. Perfusate was collected in 2 min. fractions and beta-emission corresponding to [³H]dopamine was detected by liquid scintillation scanning.

We found that in vitro ACP-1 increases PRL secretion from pituitary cells, and inhibits dopamine release from hypothalamic synaptosomes. As ACP-1 shares 60-80% sequence homology with the IgIII domain of the 140 kDa isoform of rat neural cell adhesion molecule (NCAM), we speculated that the membrane effects of ACP-1 could result from an interaction with the homologue domain of NCAM. In order to evaluate whether polysialylation of NCAM could affect the acute synaptic activity of ACP-1, we have studied ACP-modulated dopamine release after pretreatment of synaptosomes with neuraminidase, which partially cleaves sialic acid residues from NCAM. We found that neuraminidase pre-treatment completely abolishes the inhibitory effect of ACP-1 on dopamine release. Our results suggest that ACP-1 could exert PRL stimulatory activities at both hypothalamic and anterior pituitary levels, with possible involvement of polysialylated N-CAM signaling.

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Men With Acquired Hypogonadotropic Hypogonadism Treated With Testosterone May Be Spontaneously Fertile

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Men with acquired hypogonadotropic hypogonadism treated with testosterone are generally assumed to be infertile. The finding of three such patients with unexpected fertility and normal sperm counts prompted an evaluation of spermatogenesis in additional men with this condition. Case records were initially searched and one similar case with fertility was found. Subsequently, 12 consecutive men with acquired hypogonadotropic hypogonadism were evaluated for gonadal function and sperm production while receiving testosterone. In five of the cases with proven spermatogenesis, exon 10 of the FSH receptor was sequenced to look for activation mutations.

The original three cases and four of the subsequent 12 men had sperm counts greater than or equal to 15 million per mL. Two additional men had counts of 1 million per mL and six were azoospermic. Residual LH and FSH levels were slightly higher in those with maintained spermatogenesis prior to testosterone replacement, although only the difference in LH levels was statistically significant (3.0 plus/minus 1.0 vs. 1.4 plus/minus 1.8 mIU per mL, $p = 0.0339$). No activating mutations were found in exon 10 of the FSH receptor in the five cases studied.

We conclude that men with acquired hypogonadotropic hypogonadism being treated with testosterone should not be assumed to be sterile, as we have found that more than half have been shown to have persistent spermatogenesis with more than one-third having sperm concentrations greater than or equal to 15 million per mL. This may be related to the fact that gonadotropin levels in such patients are present, albeit low. Semen analyses in such men should be routinely carried out so that they can be appropriately counseled regarding potential fertility.

ABSTRACT P26

Correlation between mean intima-media thickness of carotid arteries and IGF-1 in acromegaly

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Acromegaly is associated with increase in the prevalence of atherosclerosis as well as cardiovascular and cerebrovascular disease. The aim of this study was to relate IGF-1 levels to intima-media thickness (IMT) of the common carotid arteries in acromegalic patients. The sample was composed of 20 acromegalic patients, 4 of whom with GH < 1 nanograms per deciliter (Kramer, 2002). Our previous results showed that IMT was significantly higher in acromegalics than in controls. IGF-1 (IRMA, DSL 2800) in the acromegalics ranged between 11.7 to 2577.0 nanograms per milliliter, showing high values in 9 cases, reduced levels in 5, and normal levels in the other patients. While IGF-1 was normal or decreased in all cases with GH < 1 nanograms per deciliter, 5 patients with GH between 1.5 and 7.1 showed a normal or decreased IGF-1. Spearman's correlation test did not show a significant correlation between IMT and GH ($r_s = -0.56$) or between IMT and IGF-1 ($r_s = -0.92$). Although an atherogenic action of chronic excessive IGF-1 was suggested, our results do not support this hypothesis and, quite to the contrary, are in agreement with a possible protective value of IGF-1 at endothelial level (Walsh, 1996; Otsuki, 2001). The findings point to another factor involved in the increased IMT in acromegaly.

ABSTRACT P27

Preferential expression of somatostatin receptor subtypes 1,5 and 2B in gonadotropinomas and null cell adenomas; an immunocytochemical study

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The cloning of five different subtypes of somatostatin receptors (sst 1-5) allows the immunocytochemical detection of each of them in pituitary adenomas. We studied 18 pituitary tumors diagnosed before surgery as 'non-functioning'. After surgery the excised tissues were immunostained to reveal the pituitary hormones and/or their subunits as well as the somatostatin receptor subtypes 1-5. The primary antibodies were detected using the anti-rabbit IgG biotinylated goat antibody, streptavidin complex and 3, 3'-diaminobenzidine. Twelve adenomas were immunopositive for FSH, LH or alpha subunit and were classified as gonadotropinomas. The remaining six adenomas were immunonegative for all the examined pituitary hormones and were diagnosed as null cell adenomas. All the adenomas from both groups expressed at least three somatostatin receptor subtypes. In both groups the strongest immunopositivity concerned subtypes 1 and 5. Moreover, especially in gonadotropinomas, sst 2B receptor variant was more abundant in comparison to sst 2A. The main difference between gonadotropinomas and null cell adenomas concerned the sst 4 receptor subtype, which was absent in gonadotropinomas but present in all null cell adenomas. These findings suggest that 'non-functioning' pituitary adenomas are potential candidates for the therapy with somatostatin analogs targeted to the receptor subtypes 1 and 5. Moreover, the prevalence of sst 2B variant may be also relevant since this variant has been found to mediate the opposite effects on cell proliferation in comparison to sst 2A.

ABSTRACT P28

Treatment of Acromegaly with Oral Estrogen

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Oral estrogen reduces circulating IGF-I and attenuates the metabolic effects of GH. To assess its therapeutic potential in acromegaly, we undertook an open label, two period study of oral estrogen treatment in 13 women (age 48 ± 3 y; mean \pm SE) with persistent disease after surgical treatment. Either ethinyl estradiol (30-50 μ g/d) or conjugated estrogens (0.625-1.25 mg/d) was used with the dose titrated until IGF-I fell into normal range. Biochemical (GH, IGF-I, GHBP, glucose), body composition (fat mass [FM], lean body mass [LBM], extracellular water [ECW], total body nitrogen [TBN]) and metabolic (fat oxidation [Fox]) during a GTT measurements were performed before, after 4 months of estrogen and of control (no estrogen) treatments. Four were studied in the reverse sequence. Body composition was measured by DEXA, ECW by bromide dilution and TBN by neutron activation.

IGF-I levels fell (22 ± 3 to 46 ± 3 nmol/L, $p < 0.001$) into the normal range in all subjects. Estrogen increased GHBP ($p < 0.001$) but had no effect on GH levels. Body weight did not change. FM (32.5 ± 5.1 vs 30.8 ± 4.5 kg) was higher while LBM (44.1 ± 2.2 vs 45.9 ± 2.3 kg) and ECW (19.1 ± 2.5 vs 21.1 ± 2.5 L) were lower ($p < 0.02$) during the estrogen phase. Although TBN was lower during estrogen (1707 ± 215 vs 1811 ± 216 g) the difference did not achieve statistical significance. Glucose tolerance profiles were not different between the two periods. Fox in response to oral glucose was suppressed to a greater degree during the estrogen phase. Changes in IGF-I, GHBP, LBM and ECW were significant ($p < 0.05$) between treatments while TBN and Fox showed strong trends. No major side effects were encountered. In the doses used, oral estrogen normalised IGF without affecting GH levels and induced significant body composition and metabolic changes consistent with reduced GH action. Oral estrogen is potentially an economic, effective and safe form of adjunctive treatment for acromegaly in women. (Approved by SVH Research Ethics Committee, supported by NHMRC)

ABSTRACT P29

Expression of Ghrelin and Its Receptor According to Feeding State in Rats

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Ghrelin is a newly discovered gut peptide, produced mainly in the stomach, which is secreted into the circulation and acts on the hypothalamus and the pituitary gland. Although ghrelin was originally identified as an endogenous growth hormone secretagogue, recent studies have suggested its role is in the regulation of food intake and energy homeostasis. The aim of this study was to investigate changes in the expression of ghrelin in the stomach, and of its receptors in the hypothalamus and the pituitary gland in relation to the feeding state. Sprague Dawley male rats, divided into 3 groups, freely fed, fasted for 48hrs and fasted for 48hrs followed by feeding for 24hrs, were investigated. The gastric fundus, the hypothalamus and the pituitary glands were collected. The gastric ghrelin mRNA expression was determined by Northern blot analysis and the ghrelin protein by immunohistochemistry. The ghrelin receptor mRNA levels in the hypothalamus and anterior pituitary gland were determined by RT-PCR.

The ghrelin mRNA levels in the stomach were increased by fasting but reduced again by allowing feeding. The number of ghrelin-immunoreactive gastric epithelial cells tended to increase with fasting. Moreover, ghrelin receptor mRNA levels increased about 8 fold in the hypothalamus, and about 3 fold in the anterior pituitary gland harvested from the rats that had fasted for 48hrs compared to those that were fed.

Our data demonstrate that expression of both ghrelin in stomach and its receptor in target organs increase in the fasted state, which might be helpful in magnifying the orexinogenic effect of ghrelin in the negative energy balances state. Dynamic changes in ghrelin levels and ghrelin receptors relating to the altered metabolic state may suggest the physiologic role of ghrelin in the regulation of energy homeostasis.

ABSTRACT P30

Cognitive function, selective attention, event-related potentials and 1H magnetic resonance spectroscopy in childhood-onset growth hormone deficiency

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Aims: Cognitive deficits have been reported in adults with childhood-onset growth hormone (GH) deficiency. We performed a cross-sectional study in these patients with the objective to relate cognitive deficits to neurophysiological and metabolic changes.

Methods/Patients: We studied 11 adults with childhood-onset GH deficiency who had been treated with GH during childhood. All subjects were evaluated after interruption of GH supplementation for at least three months. We performed neuropsychological assessment (NPA) using different tests evaluating fluid and crystallised intelligence. Selective attention was assessed by visual stimuli with a specific conjunction of two non-spatial features (spatial frequency and orientation). During this task, event-related potentials (ERPs) were recorded to assess the attentional modulation of electrocortical responses to stimuli (selection potentials). 1H Magnetic resonance spectroscopy (MRS) of the brain was used to assess n-acetylaspartate (NAA)/choline ratios, which reflect neuronal viability. Data were compared to an age-, sex- and education-matched control group (n=9). The study was approved by our Ethics Committee, and all subjects gave informed consent.

Results: NPA demonstrated attenuated performance of the patients in the delayed recall score ($p < 0.05$) and the trail making A test ($p < 0.05$), which both reflect fluid intelligence. Other tests for fluid and crystallised intelligence showed no differences between the groups. During the selective attention task, GH deficiency was associated with normal reaction speed, but reduced target detection ($p < 0.05$). ERP data showed an almost absent N2b in comparison with the controls ($p < 0.01$), presumably reflecting affected frontal cortical areas. MRS data showed significantly attenuated NAA/choline ratios in GH deficient subjects ($p < 0.01$), suggesting attenuated neuronal activity and/or neuronal damage.

Conclusions: Specific cognitive defects reflecting affected fluid intelligence can be found in patients with childhood-onset GH deficiency. These defects occur simultaneously with alterations in selective attention and N2b (reflecting affected frontal-cortical areas) during ERP and coincide with altered cortical neuronal metabolism and neuronal damage.

ABSTRACT P31

Male hypogonadism caused by isolated LH deficiency: from pathology to gene, from gene to physiology

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The elucidation of the phenotype of naturally occurring isolated LH deficiency may provide intriguing information to understand the role of this gonadotrophin. We report the first description of a male hypogonadism caused by an immunologically and biologically inactive LH.

The patient was a 30 yr-old man with a normal 46, XY karyotype who was evaluated in Liege University center for sexual infantilism. He was 191 cm tall with a span of 205 cm and 100 kg. He presented gynecomastia, normal pubic hair, juvenile voice, a micropenis and testes about 8 ml. LH was <0.2 mIU/ml by IRMA and undetectable by RIA assays, FSH 23 mIU/L (1-8), alphasubunit <0.1 mIU/ml, betaHCG <2 U/L (0-5), inhibin B 156 ng/L (<400), testosterone 0.3 microg/L (2.5-10), DHEAS 851 µg/L (900-3700), progesterone 0.1 µg/L (0.1-0.7), oestradiol 26 ng/L (10-70). The remaining axis and pituitary MRI were normal. Testicular biopsy demonstrated immature Leydig and Sertoli cells and rare spermatogenic cells. LH pulsatility studies, acute and chronic LHRH stimulation failed to detect LH. Both Testosterone and hCG normalised FSH. Testosterone allowed azoospermic ejaculation whereas results of hCG are in evaluation. A G36D mutation was found in exon 2 of beta LH gene. Treatment with hLH, functional studies including alpha and beta heterodimerization and LH receptor in vitro binding to further characterize this mutation are ongoing (University of Lausanne). Only one homozygous betaLH mutation in exon 3 has been described by Weiss & al (New Engl J 1992) in a man with pubertal delay and increased LH. Two other mutations were related to immunologically active variants of LH with some degree of biological action. This single point mutation is a novel cause for congenital male hypogonadism. Furthermore, it helps to confirm the maternal role of betaHCG in testicular genesis as well as the role of LH in fertility.

ABSTRACT P32

Ghrelin stimulates gh discharge by acting at hypothalamic structures

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It has been postulated that ghrelin, a recently isolated hormone, participates in the physiological regulation of GH secretion. Plasmatic ghrelin is able to activate specific receptors at pituitary level as well as to cross the blood brain barrier and activate hypothalamic structures. Exogenous ghrelin administered iv is able to stimulate GH discharge, in all species so far tested including man, but whether such action is exerted at pituitary or alternatively at hypothalamic level is not known at present.

To understand the point of ghrelin action a group of patients with organic lesion in the hypothalamic area and matched controls were studied. Patients were selected by having a severe GH deficiency after hypothalamic stimulation (ITT), but partial response after GHRH administration, then suggesting hypothalamic disruption and partially preserved somatotrope reserve. Cases and controls were tested on three separate days by either ghrelin, GHRH; and ghrelin plus GHRH, always at 1 µg/Kg iv.

The mean GH peak after stimulation in the patients were 0.4 ± 0.1 µg/L by ITT; 3.1 ± 0.5 µg/L after GHRH; 2.0 ± 0.8 µg/L after ghrelin and 9.6 ± 2.9 µg/L after the combination of GHRH plus ghrelin. In the controls GHRH induced a GH peak of 26.6 ± 8.7 µg/L, and 92.0 ± 16.7 µg/L after ghrelin with a peak after GHRH+ghrelin of 133.5 ± 24.1 µg/L. These data suggest that when hypothalamic structures are not operative either ghrelin alone, or in combination with GHRH is not longer able to significantly release GH.

In addition to postulate mainly a hypothalamic point of action for the ghrelin-induced GH secretion, these results suggest that ghrelin will not have clinical utility in patients with GH deficiency due to organic lesion.

ABSTRACT P33

The GHRH+GHRP-6 test in healthy elderly and obese: Implications for the diagnosis of growth hormone deficiency

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Aim: Aging and obesity lead to decreased activity of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis. Therefore, we determined the validity of the GH cut-off value of 15.0 µg/L in the GH releasing hormone (GHRH) + GH releasing peptide-6 (GHRP-6) test for the diagnosis of GH deficiency in elderly and obese subjects.

Methods/Patients: We performed a combined GHRH+GHRP-6 test in 10 elderly men (age 74+/-1.4y (mean+/-SEM); BMI 24.6+/-0.8 kg/m²), 9 obese men (age 47+/-3.8; BMI 40.6+/-1.7), and 7 healthy controls (age 51+/-2.3; BMI 24.3+/-1.0). After assessment of fasting plasma GH, IGF-I, and IGF binding protein-3 (IGFBP-3), GHRH (100µg) and GHRP-6 (93µg) were administered iv. GH response was measured during 120 min. For data evaluation we used non-parametric analysis. The protocol was approved by our Ethics Committee. Subjects gave informed consent.

Results: Both peak GH levels and areas under the curve (AUC) were significantly lower in the obese group than in controls (13.2+/-2.3 vs. 53.4+/-11.7 µg/L; P=0.001 and 707+/-145 vs. 3250+/-651 µg/L/120 min; P=0.001). GH response in the elderly was lower than in controls (peak 35.0+/-7.0, AUC 2274+/-443). Although this difference was not statistically significant, it was significantly higher than in the obese. GH peak levels in seven obese subjects remained below the cut-off level of 15.0 µg/L, which is associated with severe GH deficiency. All other subjects had GH peak levels exceeding 15.0 µg/L. IGFBP-3 levels were significantly lower in the elderly than in controls (1.35+/-0.12 vs. 2.05+/-0.067 mg/L; P=0.001). Basal GH or IGF-I did not differ significantly between groups.

Conclusion: GH responses following GHRH+GHRP-6 administration are significantly reduced in severe obesity. GH response in elderly was not significantly reduced, although there was a negative trend. Our data indicate that the cut-off GH level after GHRH+GHRP-6 administration of 15.0 µg/L for the diagnosis of severe GH deficiency can not be used in morbid obesity.

ABSTRACT P34

Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing (OGTT) and measurement of (free) insulin-like growth factor 1, acid-labile subunit (ALS) and growth hormone binding protein (GHBP) levels

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Background. We prospectively examined 17 patients with acromegaly after transsphenoidal hypophysectomy (TH) by sequential OGTT's and measurement of the GH-dependent parameters total and free IGF-1, ALS and GHBP to define the optimal timing of postoperative evaluation.

Methods. After TH, OGTT's were performed at 1, 2, 3, 8 and 12 weeks, whereas GH, (free) IGF-1, ALS and GHBP levels were measured weekly until 12 weeks. Cure was defined by a GH nadir after an oral glucose load \leq 1 microg/l and normalization of IGF-1 levels.

Results. 8 patients were cured (group 1), 3 patients had a GH nadir \leq 1 microg/l but not normalized IGF-1 levels (group 2) and 6 patients were not cured (group 3). In all patients with a GH nadir \leq 1 microg/l this GH suppression was observed already from 1 week after TH. Postoperative stabilization of IGF-1 levels was reached at 1 to 9 weeks in group 1, at 7 to 11 weeks in group 2 and at 7 to 11 weeks in group 3. Free IGF-1 levels were elevated at baseline and decreased in all patients. In all cured patients free IGF-1 levels rapidly normalized and preceded normalization of total IGF-1 levels. Preoperative ALS levels were elevated in all patients. After TH, ALS levels slowly decreased and normalized in 5/8 patients in group 1, but remained elevated in group 2 and 3. GHBP levels were low before treatment and started to rise within 2 weeks after TH in all patients.

Conclusions. Patients with acromegaly can postoperatively be evaluated by measurement of OGTT-suppressed GH levels at 1 week and IGF-1 levels at at least 10 weeks after TH. Free IGF-1 and ALS levels are increased in active acromegaly and decrease rapidly respectively slowly after TH. GHBP levels are low in untreated acromegaly and increase after TH.

ABSTRACT P35

Hypoprolactinemia and Reduced Anterior Pituitary Weight in Transgenic Mice with Over-Expression of a Hyperpolarizing K Channel in Pituitary Lactotropes

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Dopamine (DA) acts on pituitary lactotropes to inhibit a variety of cell functions, including exocytotic release of prolactin (PRL), PRL transcription, and cell proliferation. These actions are mediated by the D₂ subtype of receptors on lactotropes which can regulate multiple effectors including cAMP, K channels and Ca channels. In an effort to identify the relative role(s) of each of these effector systems in the various actions of DA, we have created a 'gain of function' transgenic mouse model in which lactotropes express a constitutively active K channel that has the same biophysical properties as the endogenous K channel usually activated by DA. Expression of the transgene for the inwardly rectifying K (IRK) channel, Kir2.1 tagged with EGFP, was directed to lactotropes using the 3 kb PRL promoter. Expression of the mRNA is restricted to the anterior pituitary and is not detectable by RT-PCR in a variety of extrapituitary tissues, including those that have been reported to express endogenous PRL (mammary and prostate). The Kir2.1 protein is also expressed in pituitary cells as evidenced by EGFP fluorescence in a subpopulation of dissociated pituitary cells. The Kir2.1 transgene is functional and chronically active in untreated cells as determined in patch clamp experiments. Fluorescing cells from transgenic mice exhibit an IRK current that is sensitive to block by barium. Wild type lactotropes do not express a constitutively active IRK.

Anterior pituitaries of F₁ generation transgenic female mice are slightly but significantly smaller than wild type (2.40 +/- 0.19 v. 2.87 +/- 0.38 mg). These mice also are substantially hypoprolactinemic with basal circulating PRL at 4.19 +/- 0.82 ng/ml compared to wild type females at 22.79 +/- 6.74 ng/ml. Further analysis of this model should reveal the importance of K channel activity and membrane excitability in the pleiotropic actions of DA in lactotropes.

ABSTRACT P36

Differential in vivo response of embryonic zebrafish corticotrophs to glucocorticoid and antagonist

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Despite evolutionary divergence, zebrafish share similarity with higher vertebrate in hypothalamus-pituitary axis. We recently reported generation of a germline transgenic zebrafish expressing green fluorescent protein (GFP) driven by a pro-opiomelanocortin (POMC) gene promoter. Pituitary specific GFP expression in transparent embryos allows dynamic monitoring of corticotroph ontogeny in live zebrafish. Zebrafish corticotroph differentiation initiates at 18-20 hours post fertilization (hpf). Between 48 hpf to 10 days post fertilization (dpf), corticotrophs are organized as distinct anterior and posterior zones, and gradually become more diffusely distributed in the pituitary gland during later stages. To study in vivo responses of zebrafish embryonic corticotrophs to regulators, such as glucocorticoid and its antagonist, live POMC-GFP transgenic zebrafish embryos were treated with dexamethasone or mifepristone and monitored for corticotroph GFP expression. Dexamethasone was added to fish-medium culturing live homozygous POMC-GFP transgenic embryos immediately after fertilization. Corticotroph GFP expression in live transgenic embryos was monitored by fluorescent microscopy. Fluorescence intensity and area size of POMC-GFP expressing cells within the anterior and posterior pituitary zone were measured by the Area Of Interest function of Openlab software (Improvision). At 5 - 7 dpf, dexamethasone selectively suppressed POMC-GFP expression within the anterior corticotroph zone in a dose responsive pattern. Mifepristone, a potent antagonist of glucocorticoid receptor that blocks glucocorticoid negative feedback at the hypothalamus-pituitary level, increased both the fluorescent intensity and area size of POMC-GFP expressing corticotrophs within the anterior zone, without significantly altering corticotrophs in the posterior zone. Conclusions: 1) Zebrafish embryonic corticotrophs possess functional regulatory mechanisms soon after the initiation of their differentiation. 2) Embryonic corticotrophs within the anterior zone are more sensitive to glucocorticoid specific negative feedback than those in the posterior zone, reflecting a functional distinction of these POMC-expressing regions. 3) Zebrafish expressing a POMC-GFP pituitary corticotroph transgene offers a powerful genetic system for in vivo study of vertebrate pituitary lineage development.

ABSTRACT P37

Expression of the Protein Kinase A (PKA) Subunits in Normal Pituitary Tissue Compared to Pituitary Tumors using Real-Time Quantitative PCR and Immunohistochemistry

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Aberrations of the cAMP-dependent protein kinase A (PKA) pathway are associated with tumors of the somato- and/or mammatrophs, and infrequently seen in other pituitary adenomas. In familial pituitary tumors associated with Carney complex (CNC), mutations of PRKAR1A encoding the PKA type I-A regulatory subunit (R1A), underlie GH- and/or PRL-producing hyperplasia and tumors; sporadic tumors do not appear to frequently have PRKAR1A mutations. We investigated the expression of the 4 regulatory PKA subunits (R1A, R1B, R2A, R2B) and the main catalytic (CA) subunit in 17 adenomas, GH- and/or PRL- (N=6), ACTH-producing (N=4), and non-functioning (NF) (N=7) compared to 10 normal pituitaries. Quantitative RT-PCR (qRT-PCR) was used for amplification of mRNA and immunohistochemistry (IHC) was performed in 22 paraffin-embedded available specimens. The qRT-PCR showed R1A, R1B, R2A, R2B, and CA mRNA expression in tumors that was (mean±SE) plus 0.18±0.42, minus 0.84±0.69, plus 0.27±0.48, minus 0.48±0.66, and plus 0.036±0.54 fold different from that in normal tissue, respectively. There were no differences between the various types of tumors ($P > 0.1$); within GH-/PRL-tumors R2B was downregulated in the most invasive ones (minus 2.6 ± 0.42) but not in others (1.63 ± 0.37) ($P = 0.0015$). IHC showed the following significant changes: 65% of the specimens showed strong expression of R1A relative to normal pituitary ($P < 0.05$) and R2B showed stronger expression in 4 of 6 tumors. We conclude that 1) all PKA subunits, with the exception of R1B, are expressed in normal anterior pituitary tissue; 2) R2B down-regulation may be associated with aggressive behavior in GH- and/or PRL-producing tumors; and 3) R1A is the predominant PKA subunit in both normal and tumorous pituitary tissue.

ABSTRACT P38

The Utility of The High Dose Dexamethasone Suppression Test In Confirming The Diagnosis of Cushing's Disease

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The high dose dexamethasone (HDD) suppression test is widely used for the differential diagnosis of ACTH dependent Cushing's syndrome. It is generally accepted that HDD administration suppresses cortisol in patients with Cushing's disease in contrast to patients with the ectopic ACTH Syndrome where it does not. In 220 adult patients with pituitary Cushing's disease, with a proven microadenoma or a negative MRI, 138 underwent a HDD test. A positive inferior petrosal sinus sampling study, clinical remission or an ACTH-staining tumor on the surgical specimen confirmed pituitary dependent Cushing's disease. In 138 patients, 75 (54%) underwent the 8 mg overnight HDD test and 63 (46%) underwent a two day HDD test. (2 mg every 6 hours, 48 hours).

With the 8 mg overnight test, 71 of 75 (95%) had $\geq 50\%$ and 47 of 75 (63%) had $\geq 80\%$ suppression of the morning serum cortisol. Of these 75 patients, 56 (75%) had an 8 am serum cortisol ≤ 5 ug/dl. With the 2 day HDD test, only 41 of 63 (65%) had $\geq 90\%$ suppression of 24-hour urinary free cortisol.

We conclude that the overnight 8 mg HDD accurately confirmed the diagnosis of Cushing's disease with a high sensitivity of 95% with a criterion of $\geq 50\%$ suppression, with a much lower sensitivity of 65% with the 2 day HDD with a criterion of $\geq 90\%$ suppression. The sensitivity of the 8 mg overnight HDD was marginal, decreasing from 95% to 63% when the stricter criterion of $\geq 80\%$ suppression of serum cortisol was applied. These results are similar to previously published studies and confirm the limited precision of the HDD test.

ABSTRACT P39

Ectopic Intracavernous Sinus ACTH Secreting Microadenoma Confirmed by Negative Sellar Exploration and at Autopsy

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Despite diagnostic advances, it remains difficult to identify intrasellar and ectopic parasellar adrenocorticotropin hormone (ACTH)-secreting microadenomas.

The authors present a case of a 61 year-old woman with Cushing's disease that demonstrated significant right-sided ACTH gradient on inferior petrosal sinus sampling (IPSS) and no discernible abnormality on MRI. She underwent transnasal, transsphenoidal surgery. Sellar exploration was negative, a total hypophysectomy was performed, yet her hypercortisolemia persisted. The patient died 17 days postoperatively from cardiac events.

Autopsy revealed an isolated, right-sided, intracavernous ACTH-secreting adenoma with no intrasellar communication. This represents the first case of transsphenoidal surgery failure for Cushing's disease with postmortem confirmation of a suspected intracavernous sinus lesion.

The authors propose that Cushing's disease with negative imaging studies, strong ACTH-gradient on venogram, and negative sellar exploration is suspicious for ectopic intracavernous ACTH-secreting adenoma that might benefit from intracavernous exploration and/or unilateral stereotactic radiosurgery.

ABSTRACT P40

Symptomatic Lactotroph Hyperplasia in Pregnancy Mimicking Pituitary Adenoma

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History: A 25 y/o female G10P05455 presented with severe bifrontal headaches and blurred vision during her fourth month of gestation. An MRI performed at that time revealed a pituitary mass measuring 12 mm in maximal dimension, containing a 4 mm area of central lucency and creating mass effect on the optic chiasm. On physical exam, BP was 133/86 without orthostatic changes, HR 80, temp. 98.6 F and respirations 14. The remainder of her initial exam was normal including confrontational visual fields, pupils, extra ocular movements, skin, thyroid, cranial nerves and reflexes.

Hormone levels during fifth gestational month:

PRL=374 nanograms/dL (Nml 1.2-29.9)

FT4=0.9 nanograms/dL (Nml .8-1.8)

TSH=1.39 micrograms/ml (Nml .2-4.7)

One month later, the patient developed worsening headaches and visual changes. Automated perimetry (Humphrey) testing at this time revealed generalized depression without focal defect. She subsequently underwent transphenoidal hypophysectomy with complete resolution of her headaches and subjective improvement in vision.

Pathology specimens revealed abundant prolactin-immunoreactive cells with preserved nesting architecture and persistence of intermixed cell populations consistent with lactotroph hyperplasia.

Discussion: Due to physiologic lactotroph hyperplasia, the pituitary size increases at least 136 percent during pregnancy, reaching its maximum dimensions one week post partum. Upon review of the literature, it has been determined that the pituitary should not exceed 10 mm in size during pregnancy. Our patient's pituitary exceeded this limit and caused significant mass effect symptoms, which are highly atypical for physiologic lactotroph hyperplasia. In addition, her enlarged pituitary closely resembled a distinct mass on MRI, leading to the preoperative differential diagnosis of non-secreting pituitary adenoma versus lymphocytic hypophysitis.

Conclusion: We have described a case of physiologic lactotroph hyperplasia causing mass effect on the optic chiasm and cephalgia severe enough to warrant narcotic analgesia and surgery in the second trimester of pregnancy.

ABSTRACT P41

The relative risk of malignant disease and cardiovascular morbidity in hypopituitary adults with and without growth hormone replacement therapy

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(i)Background(/i) The effects of growth hormone (GH) replacement therapy in adults on overall mortality, cardiovascular morbidity, and the rate of malignancies are unknown. (i)Methods(/i) First, a retrospective comparison was performed between 1411 hypopituitary adults without GH replacement therapy and the normal population in terms of fatal and non-fatal morbidity. Secondly, a prospective comparison was made between 289 hypopituitary patients on long-term GH replacement (mean treatment duration 60 months, 1443 patient years) and the background population. Patients with a history of previous Cushings disease or acromegaly were excluded from both studies. (i)Findings(/i) In the 1411 hypopituitary patients without GH replacement, overall mortality (RR 3.80, 95% confidence interval 3.43-4.19), and the rates of cerebrovascular events and malignancies, were increased as compared with the normal population. Cancer in colon and rectum was the most common malignancy reported in this cohort (RR 4.81, 95% CI 3.27-6.83). In hypopituitary women without GH therapy, the rate of myocardial infarctions was increased (RR 1.87, 95% CI 1.27-2.65). In the 289 hypopituitary patients on GH replacement, overall mortality and the rate of malignancies were similar as in the normal population. In hypopituitary women on GH therapy, the rate of myocardial infarctions was even lower, and there was a tendency towards increased rate of cerebrovascular events in the hypopituitary adults on GH therapy, as compared with the normal population (RR 1.95, 95% CI 0.78-4.02). (i)Interpretation(i/) Hypopituitary patients without GH replacement had increased rate of malignancies with a dominance of colorectal cancer. The risk ratio of myocardial infarction was increased in hypopituitary women without GH therapy, and reduced in hypopituitary women who were receiving GH replacement. The increased rate of cerebrovascular events in hypopituitary adults was not normalised by long-term GH replacement therapy demonstrating that factors other than GH in the overall treatment are of importance for the outcome.

ABSTRACT P42

Intracranial aggressive fibromatosis presenting as panhypopituitarism and diabetes insipidus

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Fibromatosis is a rare locally aggressive, proliferative fibroblastic lesion affecting musculoaponeurotic structures, most often in the limbs and trunk, rarely metastasises or undergoes spontaneous malignant transformation. Intracranial fibromatosis is extremely rare and requires aggressive treatment to prevent recurrence. We present a 34 year-old male with aggressive skull base and intracranial fibromatosis. The patient was admitted to hospital because of polyuria, polydipsia, loss of libido, impotence, hearing loss, and gait disturbance. On cranial magnetic resonance imaging, the lesion extended through sphenoid sinus, into both pterygoid recesses, destroying left lateral wall of the sphenoid sinus and invading the retroorbital area. There was also involvement of the left infratemporal fossa and hypothalamic area. The MR images showed a multilobulated lesion of homogenous signal intensity. The tumor was markedly isointense on both T2- and T1-weighted images relative to brain tissue, enhanced strongly after administration of gadolinium. The patient underwent partial resection of the lesion via a trans-cranial approach. The pathology of the mass was reported as aggressive fibromatosis. No other site was found in thorax and abdominal CT. Endocrine assessment showed panhypopituitarism with central diabetes insipidus. Replacement therapy was instituted. Standard treatment of surgical resection with wide-field resection was impossible. Chemotherapy and hormonal treatment of non-resectable tumours has been described without convincing results. That's why, patient referred for radiotherapy.

ABSTRACT P43

Eosinophilic granuloma presenting as panhypopituitarism and diabetes insipidus

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Solitary eosinophilic granuloma that involves the CNS is an uncommon lesion which most frequently affects the hypothalamus. We hereby report a case of solitary eosinophilic granuloma of the hypothalamus in a patient without systemic involvement. A 22-year-old man was admitted to our hospital complaining of a few months onset of decrease in testicular volume, loss of libido, impotans, thirst, polydipsia, and polyuria. On magnetic resonance imaging, T1-weighted images demonstrated a 2 cm mass in the hypothalamus. Histological examination of two consecutive stereotactic biopsy specimen had revealed eosinophilic granuloma. Search for pulmonoray and bony involvement yield no suspicious lesion. Endocrine assessment showed panhypopituitarism with central diabetes insipitus. Replacement therapy was instituted. These patients have been difficult at all since no prospective study has absolutely shown that any spesific therapy is effective. A chemotherapy regimen consisting of velban 6mg/m2 weekly for six weeks followed by once every 3 weeks at the same dose for a total of 6 months were planned. Also prednisone 40mg/m2 daily for 6 weeks then every three weeks for 5 days at the same time as the velban were given. The patient is still on regular follow up.

This was an unusual presentation of the diabetes insipidus in an adult. Solitary focal eosinophilic granuloma is one element in the spectrum of diseases associated with Langerhans' cell histiocytosis. This report documents the occurrence of a primary isolated hypothalamic eosinophilic granuloma in a man who presented with diabetes insipidus and panhypopituitarism.

ABSTRACT P44

Somatostatin receptor subtype 2 in MCF-7 human breast cancer cells is associated with an intracellular network

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Although somatostatin receptor 2 (SSTR2) is considered a membranal receptor, several tissues exhibit intracytoplasmic SSTR2 by immunohistochemistry that is explained as receptor trafficking. Recently, cytoskeletal association of SSTR2 with anchoring proteins was suggested. We examined localization of human SSTR2 in MCF-7 human breast cancer cells, which are non-responsive to SSTR2 agonists even though they abundantly express the receptor. We used immunofluorescent cytochemisry and confocal microscopy (CM) to detect a highly purified, anti-human/rat SSTR2 antibody directed against the second extracellular loop. By Western blot a non-glycosylated 55-kDa protein was detected in MCF-7 cells, which was enhanced by membranal extraction and immunoprecipitation, a 70-kDa-protein in MDA human breast cancer and HEK-293 kidney cells, and both forms in GH3 cells. Co-incubation with both antibody and synthetic ligand eliminates immunostaining and dissipates the protein band. In SSTR2a transiently transfected HEK-293 cells, membranal immunoreactivity was observed as expected. CM of MCF-7 cells revealed a fiber-like distribution of hSSTR2, mainly in the cytoplasm. The receptor is arranged in a fine, submembranal spherical network that becomes more prominent with 1-hour incubation at 4C prior to fixation. Receptor internalization was not observed with either SRIF-14 or selective SSTR2 agonist treatment. By CM, SSTR2 co-localizes with intermediate filament cytokeratin-18 (CK18), but not with tubulin or actin. Cytoskeleton disassembly during mitosis, apoptosis, and vinblastin treatment, results in receptor re-localization to the membrane that is distinct from CK18. Western blot analysis of membranal extract revealed abundant CK18, compared with whole cell and cytoplasm lysate, indicating the presence of cytoskeletal elements in the membranal fraction. In conclusion, MCF-7 cells exhibit intra-cytoplasmic localization of hSSTR2 associated with CK18 that may function as a receptor-storage element. Intracellular hSSTR2 may explain the non-responsiveness of these breast cancer cells, as well as other tumors to SSTR2 agonists even though they express SSTR2 abundantly.

ABSTRACT P45

Cyclin D1 genotype and allele frequencies in sporadic pituitary tumors

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Cyclin dependent kinases (CDKs) are playing critical role in the transition through the G1 to S phase of the cell cycle. The cyclin D1 gene (CDK1) is a proto-oncogene, which is overexpressed in many tumors. It has been suggested that G/A polymorphism (G870A) at exon4/intron 4 splicing region of CDK1 gene leads to impaired protein turnover. Thus, DNA damage may pass the G1/S checkpoint and cells may damage more easily in individuals with an allele. The objective of this study is to examine the allele and genotype frequencies of CDK1 in pituitary tumors and healthy controls. For this purpose 84 (28 male, 56 female, mean age: 39,29±12,57 SD years) sporadic pituitary adenomas of various histologies (27 prolactinomas, 32 acromegaly, 13 ACTH-secreting, 11 non-functioning, 1 TSH-secreting tumor) and 101 healthy controls were included in the study. Peripheral blood samples were collected in EDTA and the DNA samples were extracted from peripheral blood by using the proteinase K/salting out method. PCR amplification was performed by using specific oligonucleotides and variant alleles were detected by restriction enzyme analysis. The chi-square test was used for comparing the data. Although the genotype distribution in sporadic pituitary adenomas (AA= 21%, AG= 57%, GG= 6%) was statistically different from healthy population (AA= 34 %, AG= 46%, GG= 18%, p=0.02), we could not determine any significant difference in CDK1 genotype distribution between individual tumor subtypes (p=0.92) and tumor invasion (p=0.96). The CDK1 allele frequencies were similar in tumor group (A= 0.59, G=0.41) with healthy population (A=0.58, G=0.42, p= 0.45). No statistical significance was observed in allele frequencies between tumor types (p= 0.81) or invasion (p= 0.25). In conclusion, CDK1 genotype distribution is important for tumor development, but the allele and genotype frequencies of CDK1 are not related to invasion.

ABSTRACT P46

Giant pituitary adenoma presenting as a nasopharyngeal mass: case report

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We present a giant pituitary adenoma case invading both cavernous sinuses and sphenoid sinus, extending into nasopharynx with the transverse diameter of 110mm (Grade IVE according to Hardy-Vezina Classification).

The patient was a 28 year-old man, who was married with 3 children and did not complain of sexual disturbance, referred to our clinic due to the intracranial mass revealed on cranial CT scanning. He had a complaint of postnasal discharge first appeared two years ago. A nasal biopsy was made in a different medical center and diagnosed as invasive planocellulare carcinoma two months before his admission. He showed no abnormalities on physical or neurological examination. Visual examination revealed bilateral papilledema. Endocrinological examinations were in normal limits except for prolactin as 190 nanograms per millilitre. It was thought to be due to stalk effect of the tumor.

The patient was operated by frontotemporal approach. An extraaxial, lobulated right temporal mass was totally resected. Tumor parts invading both cavernous sinuses and sellar area were left unresected. No complication was observed postoperatively. Cabergoline therapy was started after pathological examination revealed prolactin secreting pituitary adenoma, and he was discharged without any neurological deficit.

ABSTRACT P47

Free thyroid hormone levels in central hypothyroidism

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Standard treatment for hypothyroidism -central and primary-, consists on thyroxine (T₄) administration, assuming that conversion to triiodothyronine (T₃) proportionates adequate thyroid hormone concentrations and action at the tissue level.

Objective: To determine free T₃ (FT₃) and free T₄ (FT₄) serum levels in patients with central hypothyroidism compared to patients with primary hypothyroidism and healthy controls.

Methods: We studied 78 subjects: 32 with central hypothyroidism, 18 with primary hypothyroidism and 28 healthy controls. Patients had been stable in their T₄ dose for at least 3 months. A clinical history and exam were done. TSH, total T₄ (TT₄), total T₃ (TT₃), FT₄ and FT₃ were measured in fasting serum samples. Informed consent and Ethics Committee approval were obtained. ANOVA and Pearson correlation were used for analysis.

Results: All subjects had free T₄ levels within the normal range; healthy controls and patients with primary hypothyroidism had TSH levels within the normal range. FT₃/FT₄ ratio was significantly lower in patients with central and primary hypothyroidism than in healthy controls (0,223 ± 0,036, 0,220 ± 0,040, 0,260 ± 0,033 respectively, p=0,0002); no differences were found between patients with central and primary hypothyroidism. TT₃/TT₄ ratio was significantly lower in patients with central and primary hypothyroidism than in controls (0,013 ± 0,002, 0,012 ± 0,002, 0,015 ± 0,003, p=0,0001). There was a negative correlation between FT₃/FT₄ and dose of T₄ used in the treatment of hypothyroidism (r²= -0,26, p=0,0001). No correlation was found between FT₃/FT₄ ratio and age, sex or BMI.

Conclusion: Patients with central hypothyroidism have a FT₃/FT₄ ratio that is 85% that of healthy controls and is similar to patients with primary hypothyroidism. Treatment of hypothyroidism with T₄ does not reproduce serum levels of free thyroid hormones. Future studies are warranted to investigate whether T₃+T₄ combinations are a better choice for the treatment of hypothyroidism.

ABSTRACT P48

Acromegaly complicated with diabetic ketoacidosis: an autopsy case

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Abnormalities of glucose metabolism are a common feature of acromegaly. We report an usual case of acromegaly complicated with diabetic ketoacidosis (DKA) with fatal outcome. A 21-year-old man was diagnosed as having acromegaly nine months before admission and underwent trans-sphenoidal surgery without success. He had a family history of type 2 diabetes mellitus. One month before admission, he drank soft drinks much and general malaise with nausea developed. He was admitted to the hospital and was found to have high glucose levels (600mg/dl). He developed impaired consciousness. Plasma glucose and bicarbonate levels were 630mg/dl and 1.6mmol/l. He was transferred to our hospital for further treatment of DKA. His height was 182cm and weight was 120kg. There were multiple subcutaneous abscesses over chest wall and back. He required more than 100U/hour insulin infusion in order to overcome high glucose levels. He became unresponsive and CT scans revealed marked brain edema. His urine output gradually decreased and he was expired two days after. Plasma growth hormone (GH) and insulin-like growth factor-1 levels were 84.7ng/ml and 1770ng/ml, respectively. Autopsy showed that he suffered from residual GH secreting pituitary adenoma, uncus and tonsillar herniation of the cerebrum, and acute on chronic fibrous pancreatitis. He showed marked insulin resistance because of obesity, GH excess, skin infection and glucose toxicity. Concurrent acute on chronic pancreatitis may trigger the development of DKA. Only nine other cases of DKA associated with acromegaly were found in the medical literature. Although DKA is rarely diagnosed in conjunction with acromegaly, the association was confirmed in the current patient.

ABSTRACT P49

Lipopolysaccharide and interleukin-1-beta stimulate isoprostane production in rat anterior pituitary cells in vitro

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Isoprostanes are prostaglandin (PG) F and E isomers first described as products of noncyclooxygenase oxidative modifications of arachidonic acid that have resulted from free-radical attack of membrane phospholipids. In contrast to classic prostaglandins, isoprostanes are formed in situ from the fatty acid backbone esterified in membrane phospholipids and released in response to cellular activation. Inflammatory stimuli are known to modulate endocrine function and the oxidant signaling pathways may contribute to this effects. We have previously characterized 8-iso-PGF₂alpha release from rat anterior pituitary cells in vitro, by a radioimmunoassay (RIA) validated by comparison with gas chromatography mass spectrometry. We have now evaluated the effects of lipopolysaccharide (LPS) and interleukin (IL)-1-beta on rat anterior pituitary. Cells were plated into 24-multiwell dishes at a density of 300.000 cells/well and after 48 hour preincubation in DMEM, treated with LPS (10-1000 ng/ml), IL-1-beta (1-100 pM) or LPS + IL-1-beta. After either 1 or 24 hour incubation, incubation medium was collected and 8-iso-PGF₂alpha levels measured by RIA.

We have found that after either for 1 hour or 24 hours incubations with LPS and IL-1-beta, either when administered alone or in association, 8-iso-PGF₂alpha release was significantly increased in a dose-dependent manner.

These data support a role for isoprostanes as markers of oxidative stress in the pituitary and suggest their possible involvement in inflammatory-mediated pituitary hormone secretion.

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ABSTRACT P50

Cushing Disease, report of an unusual presentation

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Objectives:

Presentation of a patient with an oligosymptomatic corticotroph pituitary macroadenoma .

Case report:

A 58-yr old man presented for evaluation of a mass in the sella. Four years before admission, the patient developed tremor. Three years later he complained of diplopia and obtained the advice of a neurologist who performed a MRI, CSF puncture and visual evoked response and believed that the most likely diagnosis was multiple sclerosis and essential tremor, so he prescribed propranolol. One year later the patient complained of weakness and reduction of muscle mass; his physician obtained another MRI of the brain which demonstrated a mixed cystic and solid sellar and suprasellar mass compressing the optic chiasm.

On physical examination the patient was a healthy-appearing man but presented some mental disturbances. His visual field defects were not attributable to chiasmatic involvement.

Routine blood chemistry was normal. Endocrine studies showed normal thyroid function and prolactin levels. The morning cortisol level was 27.8 mcg/dl (normal range, 7-25), the cortisol level after the overnight 1-mg dexametason test was 12.4 mcg/dl, UFC was 103.2 mcg/day (normal range, 20-90), and ACTH level was 126 pg/ml(normal range, 0-54).

The patient underwent transsphenoidal surgery and the diagnosis of Cushing disease was confirmed by immunohistochemistry.

On follow-up 4 months later, UFC was 60 mcg/day and MRI showed an empty sella.

Conclusions:

Our findings are consistent with those described by Ikeda and col.¹

The case history we are presenting here shows an unusual presentation of Cushing disease, not only because of the low frequency of macroadenomas causing ACTH excess but also because of the clinical features.

The different clinical characteristics of patients with Cushing disease with large pituitary adenomas could be the result of a lower hormonal activity suggested by the sparsely granularity histologically founded in this tumors.

Ikeda and col. Clin. Endocrinol (Ox) 1997 June; 46 (6: 669-79).

ABSTRACT P51

The effect of pre-operative octreotide treatment on p27 expression in somatotroph adenomas

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The inhibitory effect of somatostatin on cell proliferation may occur indirectly via inhibition of growth factors or angiogenesis, as well as by direct pathways including the cell cycle inhibitor p27. However, only a small proportion of pituitary somatotroph tumours respond with a significant (>20%) decrease in tumour size to somatostatin analog therapy. We have previously shown that pituitary adenoma cells contain less p27 protein (40%) than normal pituitary somatotroph cells (75%). In the current study we therefore investigated the effect of preoperative octreotide treatment on p27 staining in somatotroph adenomas. Thirty-nine patients with acromegaly were treated for 12 months (range 2-62) with octreotide before transsphenoidal surgery, while 39 untreated patients were matched for sex, age, tumor size, extension and invasiveness and served as controls. Clinical characteristics, proliferative (Ki-67) and apoptotic indices in this cohort have been described previously (Losa, JCEM, 2001). The presence of nuclear p27 immunostaining of the adenoma samples in the pre-treated group and the control group was compared. We found no significant difference in p27 staining between the two groups; however, p27 showed a significant negative correlation with the proliferative index Ki-67 and there was a weak positive correlation between strong p27 staining and the length of octreotide treatment. Of the 25 patients treated with octreotide who had pre- and post-treatment MRI images, 5 showed >20% tumour shrinkage. All these samples showed high p27 and a low Ki-67 staining. In conclusion, (1) Ki-67 staining is inversely correlated with p27 staining, (2) octreotide does not significantly increase p27 staining in somatotroph tumours, although longer treatment shows a positive effect, and (3) tumours which show marked shrinkage with octreotide demonstrate an increase in p27. It seems therefore that upregulation of p27 may play a role in the long-term somatostatin induced shrinkage in acromegaly, although further studies in a larger group of patients with positive effect are needed.

ABSTRACT P52

Are the reproductive system disorders after successful kidney transplantation gender related(?)

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Forty consecutive patients (20 F) with fully functioning allograft for at least 15 months after RT were included in the study. Their age at RT ranged from 23 to 44 years and their post-RT follow-up lasted 15-86 months. FSH, LH, prolactin (PRL), estradiol/testosterone were determined in all subjects and pelvic ultrasonography was performed in patients. Testosterone was under the lower limit of the normal range in 70% patients and within the lower tertile in all remaining patients. LH was high only in 3 men, while FSH was increased in 4, suggesting a spermatogenesis damage. Prostate volume was decreased when compared to healthy controls and 9 men (45%) reported reduced libido. Ten of the women (50%) had menstrual cycles abnormalities after RT, six of them had amenorrhea (3 transient and 3 persistent). In four women (20%) the gonadotropin and estradiol values were in the menopausal range. Hirsutism was detected in 25% of women, all assuming cyclosporin A (CsA). Increased PRL was found in 4 women (20%) (25-75 ng/ml), while it resulted within normal range in all men. Testosterone tended to be higher in men transplanted from longer period and was significantly lower in males treated with CsA and/or tacrolimus than in those on other immunosuppressants. Conversely, no relationship was found between female reproductive disorders, age, period of uremia, time from transplant and treatments. Prolactin was lower in patients on CsA and/or tacrolimus treatment and in men than in women. While inhibition of the reproductive axis to a variable extent was found in male patients, more various disorders were revealed in females, with menstrual irregularities and PRL increase being the most frequent findings. In conclusion, the reproductive axis function after RT is not related to previous renal insufficiency, but seems to be profoundly influenced by immunosuppressive life-long treatments, with a gender-specific effects.

ABSTRACT P53

Is the severity of GH deficiency (GHD) correlated with impairment of cardiac performance in adult patients with hypopituitarism(?)

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To investigate whether the severity of GHD was correlated with the degree of cardiac impairment, we evaluated cardiac performance in 105 patients with adulthood-onset GHD and in 36 sex- and age-matched controls. On the basis of the GH response to ARG+GHRH, patients were subdivided into 4 groups: group 1, 50 patients with a very severe GHD (GH peak below 3 ng/mL); group 2, 26 patients with severe GHD (GH peak 3.1-9 ng/mL); group 3, 14 patients with partial GHD (GH peak 9.1-16.5 ng/mL); group 4, 15 patients with normal GH response (GH peak above 16.5 ng/mL). In patients of groups 1 and 2, circulating IGF-I, were lower than those in group 3, 4, and 5 which were not different from each other. While in both groups 1 and 2 the ejection fraction at exercise and peak ejection rate at exercise were significantly lower than those of groups 4 and 5. The other parameters of cardiac function were not significantly different among the different subgroups of patients. The heart rate and ejection fraction at exercise and exercise induced changes in LVEF were significantly lower in patients of groups 1, 2 and 3 than in controls. While the exercise duration was significantly lower in all different patients' groups than in controls. A significant correlation was found between the GH peak after ARG+GHRH, and IGF-I, diastolic blood pressure, ejection fraction, peak filling rate and peak ejection rate at rest, diastolic blood pressure, peak ejection rate and ejection fraction at exercise. Multiple correlation analysis revealed that the most relevant parameter associated with GH peak after ARG+GHRH and IGF-I was the diastolic blood pressure at exercise.

In conclusion, patients with very severe or severe GHD showed a significant impairment of cardiac performance, whereas non GHD hypopituitary patients had normal cardiac parameter.

ABSTRACT P54

Four times 0.5mg is 'more' than two times 1mg: A 'hyperfractionation' effect in Cabergoline pharmacokinetics in the treatment of non-functioning pituitary tumours

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Long term (6 months minimum) Cabergoline therapy either on its own or in combination with octreotide has been shown recently (Lohmann et. al. 2001, M. Andersen et. al.2001) to reduce in some cases non-functioning pituitary tumours. We prove here using Cabergoline pharmacokinetics that a regimen of four times 0.5mg Cabergoline per week achieves a 46% higher minimum steady state plasma concentration of Cabergoline than a regimen of twice 1mg per week. This is important in increasing the steady state plasma concentration and the tolerability in the long term treatment of non-functioning adenomas. Our 'hyperfractionation' effect is a new result in theoretical pharmacokinetics in general and represents a sort of reverse analogue of the 'hypofractionation' effect known in radiation dosimetry. It has to do with the exponential nature of both linear kinetics of drugs and biological effect of radiation. Cabergoline kinetics was shown to be linear for doses from 0.5mg to 7mg. It was shown that for single oral doses of 0.5mg to 1.5mg, maximum initial plasma levels of 30 to 70 pg/ml were observed within 2 to 3 hours. Elimination half life of Cabergoline was estimated in the range of 60-100 hours. Using these basic Cabergoline kinetic parameters we consider two 2mg/week multiple dose long term regimens: one in which 4 times 0.5 mg weekly are given at equal intervals and other one where 2 times 1 mg weekly are given at equal intervals. We calculated the linear kinetics formulas for the maximum and minimum steady state plasma concentrations for the two regimens :

$C1_{max} = 30 / (1 - \exp(-0.364))$, $C1_{min} = 30 \exp(-0.364) / (1 - \exp(-0.364))$

$C2_{max} = 50 / (1 - \exp(-0.728))$, $C2_{min} = 50 \exp(-0.728) / (1 - \exp(-0.728))$

That gives a 46% higher minimum steady state plasma concentration of Cabergoline, $C1_{min}$ than $C2_{min}$ ('hyperfractionation').

ABSTRACT P55

Immunocytochemical Study of Spatial Distribution Pattern and Number of Secretory Vesicles of Somatotrophs in Porcine Anterior Pituitary

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Anterior pituitary cells secrete growth hormone (GH) that plays a critical role in muscle accretion, lipolysis and lean growth in the pig. Somatotrophs characterized as specific topographical localizations in the gland store GH in 350-500 nm in diameter membrane-bounded secretory vesicles that dock and transiently fuse at the plasma membrane fusion pores [POROSOMES] to secrete GH as we revealed by atomic force microscopy. Objectives using light microscopy (LM) and transmission electron microscopy (TEM) were to (1) identify the spatial distribution patterns of somatotrophs during rapid growth, and (2) determine the fate of secretory vesicles after secretion. Immunoreactive somatotrophs were counted under LM, and total number of filled, empty, and partly empty vesicles before and after stimulation of GH secretion was determined in TEM. Data were subjected to analysis of variance (ANOVA) and Student's ttest. Somatotrophs were densely distributed in lateral wings of anterior lobe from proximal to distal (43.8 plus/minus SD 1.2 per 30,495 micrometer², Mean plus/minus SD SEM), whereas rarely distributed in shoulder regions (21.8 plus/minus SD 1.4 per 30,495 micrometer²) on day 1, day 42, and day 100. However, an increase in distal median region was observed in all groups (55.2%, P < 0.05). TEM and immunogold pGH antibody labeling showed that control cells contained more than twice as many filled vesicles than stimulated cells, whereas stimulated cells contained twice as many empty vesicles and 2.5 times more partly empty vesicles than control cells. Empty vesicles were devoid of immunogold label. There was no significant difference in total number of vesicles between the control and stimulated cells. Our investigations reveal (1) a regional/spatial specificity of cellular differentiation and transformation to facilitate GH secretion in porcine pituitary, and (2) GH containing vesicles in pituitary transiently fuse at the POROSOME and secrete GH without loss of secretory vesicles. Supported by NIH; USDA, NRI.

ABSTRACT P56

Extracoronary atherosclerosis and Cushing's disease

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Patients with Cushing's disease (CD) show increased cardiovascular mortality even after successful treatment; mortality risk in treated subjects has been calculated to be 4-5 times higher than in the normal population.

The aim of this work is to evaluate extension of atherosclerotic disease in a group of patients with CD compared to controls matched for age, sex and risk factors for atherosclerosis.

20 patients with CD were studied and compared to 20 sex-, age-, body mass index- and blood pressure levels-, low and high density lipoprotein cholesterol levels- and triglycerides levels- matched controls. Lipoprotein(a), basal insulin and glucose levels were measured in patients and in controls. In order to evaluate the intimal thickness, all the subjects have been checked for echo-doppler of common carotid, femoral and pre-renal arteries. The examination was performed by two different operators in order to obtain a correct validation.

Mean age of patients with CD (18 F, 2 M) was 54.0 plus/minus SD 5.2 years (range 24-65) and mean age of control group was 51 plus/minus SD 7.61 years (range 25-65). No significant difference in metabolic parameters between patients with CD and controls was demonstrated, except for insulin (13.5 plus/minus SD 4.5 and 6.4 plus/minus SD 0.7 in CD and controls respectively, p < 0.05) and lipoprotein(a) levels (60 plus/minus SD 12 and 27.5 plus/minus SD 0.2 in CD and controls respectively, p < 0.05).

A significantly increased intimal thickness at the carotid (1.055 plus/minus SD 0.59 vs 0.7 plus/minus SD 0.17 mm, p < 0.05) and femoral (0.965 plus/minus SD 0.4 vs 0.65 plus/minus SD 0.2 mm, p < 0.05) levels was demonstrated in patients with Cushing's disease compared to controls.

These preliminary data show that patients with Cushing's disease have a higher cardiovascular damage compared to a population with a similar cardiovascular risk probably due to hypercortisolism mediated by hyperinsulinism and they should be candidate to a specific treatment, combined with the standard therapy for hypercortisolism, to reduce cardiovascular risk.

ABSTRACT P57

pRb Protein Expression in Somatotropinomas has Inverse Correlation with GH levels

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RB1 is a tumor suppressor gene (TSG) involved in the pathogenesis of several tumor types, but its role in pituitary tumors is not completely understood. Previous studies suggest association between allelic loss at chromosome 13q, where this TSG is located, and pituitary tumor progression.

The aim of our study is to investigate if there is correlation between expression of the Retinoblastoma Protein (pRb) in somatotropinomas and parameters of biological aggressiveness of the tumor: (1) GH levels at diagnosis; (2) tumoral invasiveness.

The Ethical Committee approved our protocol and every patient signed an informed consent form before entering the study. We selected 40 acromegalic patients treated by surgical resection of the pituitary tumor. GH was measured by chemoluminescence. Tumoral invasiveness was assessed through magnetic resonance and/or computed tomography and was defined according to modified Hardy classification (grades 1 to 4). Immunocytochemical analysis (ICC) of pRb (NCL-RB-358 primary antibody, Novocastra Labs) was evaluated on an arbitrary scale as absent (-), isolated cells (+), sparse (++) , moderate (+++) and strong (++++). The relationship between ICC and parameters of tumoral aggressive behavior were assessed by Pearson Correlation Method (level of significance $p < 0.05$).

Median GH level at diagnosis was 64 nanograms per milliliter (range 6.15 to 1180 nanograms per milliliter). Forty eight percent of the tumors (16 of 33) were noninvasive (grades 1 and 2) and 52 percent were invasive (grades 3 and 4). Most of the adenomas (90%) were positive for pRb, with 4 '+' (10%), 12 '++' (30%), 14 '+++' (35%) and 6 '++++' (15%). The level of expression of pRb inversely correlated with GH levels at diagnosis ($p=0.039$), but not with the radiological grade of the tumors ($p=0.937$).

Our results suggest association between low expression of pRb in somatotropinomas and increment of its secretory activity

(This work was supported by FAPERJ).

ABSTRACT P58

Lanreotide 60 mg, a new long-acting formulation: effectiveness in the chronic treatment of acromegaly. A multicenter Italian study

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Lanreotide (LAN) 60 mg (LAN60), alleged to suppress GH/IGF-I hypersecretion for 28 days, was administered in a prospective open multicenter study to 92 patients with active acromegaly (61 F, 20-79 yrs). LAN60 was given as adjuvant treatment (AT) in 62 patients previously treated by neurosurgery, radiotherapy or both (no=31, 27, 4, respectively); the other 30 patients (PT) were naive or previously treated only by pharmacotherapy (no=20, 10, respectively). LAN60 was im started q 28 days for 3 injections; the dose was then individually tailored, aiming at achieving normal age-matched IGF-I levels and mean GH \leq 2.5 microg/L. After a median follow-up of 24 months (range 6-48), IGF-I normalized in 65%, decreasing from 199 (% of the Upper Limit of Normal Range, %ULNR) plus/minus 8% (mean plus/minus SE) to 87 plus/minus 4% ($P < 0.0001$). GH fell to \leq 2.5 microg/L in 63% and to \leq 1 microg/L in 25%, decreasing from 20 plus/minus 3 microg/l to 3 plus/minus 0.4 microg/l ($P < 0.0001$). The rate of GH/IGF-I normalization progressively increased and reached 72% at 36 months by Kaplan-Meier analysis. No tachyphylaxis was observed. Shortening interval between LAN60 injections to 21 days in 16 patients induced a higher suppression of GH/IGF-I levels. PT and AT patients achieved similar final GH/IGF-I levels and rate of hormonal normalization. Tumor shrank in 39% of assessable patients, and in 50% of PT. Plasma glucose levels did not change, HDL-cholesterol significantly increased. Gallstones appeared or worsened in 13% of patients. LAN60 is a new very effective and long-lasting formulation for the treatment of acromegaly. The powerful suppression of GH/IGF-I levels, without tachyphylaxis, the progressive increase in the rate of IGF-I normalization and the similar efficacy in PT and AT patients point to a role for LAN60 in the primary treatment of acromegaly.

ABSTRACT P59

The effect of octreotide on necrosis and CD95 expression in acromegaly

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The Fas/Fas ligand system is an important mediator of apoptosis. Fas (APO-1/CD95), a death receptor, is widely expressed in human tissues including the pituitary. The effect of octreotide in tumor volume reduction in GH secreting pituitary tumors is obvious in clinical studies. This effect can be related to death of tumor cells. The objective of this study is to examine the effect of octreotide on necrosis and apoptosis in acromegaly.

Formalin-fixed and paraffin-embedded tumor tissues from 15 acromegalic patients (8 females, 7 males, mean age: 36.21±12.24 SD years) were selected for this study. Octreotide were used in 8 patients before operation (median duration: 120 days [IQR: 16.25-450]), whereas 7 of them were operated without any medical treatment.

To screen the expression of Fas, immunohistochemistry was performed using CD95(Fas)Ab-3. Mann-Whitney U test was used for statistical comparisons. We could not determine any difference in necrosis ($p=0.07$), but CD95 expression was statistically significant higher in octreotide group ($p=0.02$). On the other hand, the duration of octreotide therapy was not correlated either with necrosis ($p=0.94$, $r=0.03$) or CD95 expression ($p=0.86$, $r=0.05$).

In conclusion, octreotide may cause an increase in Fas expression on GH secreting tumors, as shown in our study.

ABSTRACT P60

Non Functioning Pituitary Adenoma Transforming into Frank Prolactinoma 5 years after Initial Presentation

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The majority of pituitary adenomas are solitary and they either produce only one hormone or are non-secreting. Double or multiple producing hormone adenomas are rare, as is the transformation of one type of adenoma into another secreting pattern. We describe a case of a non-functioning adenoma that turned into prolactin secreting after an interval of five years.

A 47-year-old man with bi-temporal hemianopsia was found to have on MRI a 5x3 cm sellar/suprasellar mass that involved the left cavernous sinus. Besides the visual field defects his clinical evaluation was unremarkable. Initial laboratory data: IGF1: 227 ng/L (123-463), FSH: 5.9 mIU/mL (1.3-19.3), LH: 2.4 mIU/mL (1.2-8.6), free testosterone: 7.7 pg/mL (16-33), prolactin: less than 10 ng/mL (0-20), free thyroxine index: 2.7 (1.9-5.6), random cortisol: 1.8 microg/dL (2.0-9.0), alpha-subunit: <0.1 ng/mL (<0.1 -0.8). A diagnosis of a non-secreting macroadenoma was made. As surgical intervention resulted only in partial resection, the patient also received radiation therapy. Panhypopituitarism requiring full replacement therapy persisted. The tumor stained strongly for prolactin but was negative for other pituitary hormones. Post intervention, MRI and hormone requirement remained stable for five years. At 5 years, however, prolactin level sharply increased to 1,536 ng/mL and alpha-subunit to 1.6ng/mL. The mildly elevated alpha-subunit is compatible with that described in 7-10 percent of prolactinomas.

One could postulate that the high dose 'hook effect' may have complicated the initial diagnosis but, to our knowledge this is not previously described when the initial prolactin level is within the normal range. Due to the lack of biochemically obvious hormone secretion, this prolactin immuno-reactive adenoma was initially correctly classified as non-functioning.

This is the first documented case of a non-functioning pituitary adenoma with a positive immunohistochemical stain for prolactin that transformed into a frank prolactinoma many years later without apparent growth of the tumor.

ABSTRACT P61

Control of systemic ghrelin levels by various feedback mechanisms in healthy human

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Background: Ghrelin is a potent stimulator of growth hormone (GH) secretion. Furthermore, it is involved in energy homeostasis. Octanoylation of the peptide at serine-3 is necessary for biological activity. We investigated changes in active ghrelin plasma levels due to two different putative feedback mechanisms. Methods: Twelve healthy humans were tested by intravenous administration of the synthetic ghrelin analogue GHRP6 (1 microgram per kg), possibly activating a short feedback loop. On a different day, GH levels were increased by intravenous administration of growth hormone-releasing hormone (GHRH, 100 microgram iv) plus Arginine (30g iv over 30') to test for a GH-dependent feedback mechanism. Blood samples were taken for measurement of ghrelin and GH. Active ghrelin-levels were determined by a specific radioimmunoassay that exclusively detects the octanoylated form of ghrelin. Results: Basal active ghrelin levels demonstrated significant inter-individual differences, but very little intra-individual variation ($r=0.93$, $p<0.005$). Administration of GHRP6 resulted in a 11-fold increase in GH levels. However, no significant changes of active ghrelin levels were observed over a 90' period. Application of GHRH+Arginine led to an even higher 17-fold increase of GH levels, again without any significant change in levels of active ghrelin over a period of 120'. Conclusions: Acute increases in GH levels either by GHRP6 or by GHRH+Arginine did not feedback on systemic concentrations of active ghrelin. Furthermore, a ghrelin analogue had no short loop feedback effects on systemic active ghrelin levels. Due to its metabolic role, systemic ghrelin levels may be more dependent on energy homeostasis.

ABSTRACT P62

An audit of quality of life in patients who have undergone treatment for pituitary tumours at a single clinical neuroscience centre over a fifteen-year period

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Adults with brain tumours experience changes in multiple aspects of quality of life and this is associated with their medical condition and its treatment. We investigated within our cohort of pituitary tumour patients, whether there are differences in psychological wellbeing and psychosocial functioning, dependent on endocrine pathology and treatment variables.

We carried out a detailed assessment of 110 patients with benign pituitary tumours in relation to mode of treatment and primary diagnosis. Psychological rating scales used were: the Hospital Anxiety and Depression Scale (HADS-UK), World Health Organisation Quality of Life Scale (WHOQOL-BREF), General Health Questionnaire 28, and the Social Adjustment Scale (completed by a: the patient and b: another person who knows the patient well).

Psychological well-being and psychosocial functioning were consistently impaired across domains in subjects with Cushing's disease compared with all other pituitary tumours, where scores were similar. For Cushing's disease GHQ total 33.4 (95% CI 22.2-44.6) vs 20.2 (16.0-24.3), $F=4.7$, $p=0.03$; HADS-depression 9.2 (5.6-12.8) vs 4.7 (3.3-6.0), $F=5.3$, $p=0.02$; HADS-anxiety 10.6 (6.2-15.0) vs 5.9 (4.3-7.5), $F=3.8$, $p=0.05$; SAS patient 2.5 (2.1-2.9) vs 2.1 (1.9-2.2), $F=4.3$, $p=0.04$; SAS informant 2.3 (2.0-2.6) vs 1.9 (1.8-2.1), $F=3.0$, $p=0.05$. Similar statistically significant differences were also observed between these patient groups for WHO psychological health and WHO environment scales.

For the whole group, GHQ and HADS ratings differed by treatment with higher scores for patients who had undergone pituitary surgery (transsphenoidal or transfrontal): GHQ 24.3 (19.9-28.6) vs observation/pharmacological treatment 12.9 (4.0-21.7), $F=5.2$, $p=0.02$ and HADS-depression 6.0 (4.5-7.4) vs 2.5 (0.4-5.4), $F=4.4$, $p=0.04$.

We propose that chronic exposure to high levels of proopiomelanocortin-C derived peptides in Cushing's disease has long-term adverse effects on mood and social functioning, which may be the result of irreversible changes in neural function. Further studies will be required to define the precise pathways involved.

ABSTRACT P63

Antitumor and antiangiogenic activity of batimastat (BB-94) in experimental prolactinoma in rats

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The development of estrogen-induced pituitary prolactinoma in Fischer 344 (F344) rats is associated with an enhanced neovascularization. Based on the significance of matrix metalloproteinases (MMPs) for tumor growth and angiogenesis, we have studied the effect of batimastat (BB-94), a synthetic MMPs inhibitor (MMPI) on established prolactinoma induced by diethylstilbestrol in F344 rats. The effects of chronic treatment with BB-94 (at a dose of 30 mg/kg) on tumor weight, prolactin (PRL) secretion, cell proliferation, apoptosis and vascular density were compared with bromocriptine (BRC) administered at a dose of 3 mg/kg. We have found that chronic treatment with both substances caused a significant reduction in the pituitary weight. On the other hand, serum PRL concentration decreased only after administration of BRC. This dopamine agonist has also been found to exert strong proapoptotic effects. The density of microvessels identified by CD31 was markedly reduced only in the group treated with BB-94. Moreover, batimastat has been found to decrease cell proliferation evaluated by a number of PCNA-positive stained cell nuclei and this effect was less pronounced than that of BRC. The results of our study provide evidence for an inhibitory effect of a synthetic MMPI on the growth and angiogenesis in an experimental model of a human prolactinoma. The ability of batimastat to suppress established pituitary tumor growth suggests a novel application of MMPIs in the treatment of pituitary adenomas.

ABSTRACT P64

Selective Changes in Cell-Cycle Regulators in Thyrotropic Tumors Treated with Thyroid Hormone

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The molecular mechanism underlying thyroid hormone (TH) inhibition of thyrotrope cell growth is poorly understood. The object of our study was to identify TH-genes involved in thyrotrope cell regulation, by performing microarray analyses on Affymetrix Genechips. Using 3 pooled RNA samples from murine TtT-97 thyrotropic tumors plus/minus TH for 24 hours, we performed a duplicate screen of 13,000 genes. Interestingly, a number of genes were identified which may play important roles in thyrotrope growth inhibition and cell-cycle regulation. Specifically, selective changes in bone morphogenetic proteins (BMPs), and Wnt, which are important signaling molecules for pituitary organogenesis, were observed with TH treatment. A 6-fold decrease in Wnt-10a transcript levels was noted with TH treatment compared to hypothyroid controls. A divergent BMP response to TH treatment was noted, including: a 7-fold increase in BMP-7, a 2-fold increase in BMP-6, and a 3-fold decrease in BMP-4. Using RNase protection assays, which allowed the simultaneous quantitation of mRNAs encoding the BMPs 1- 8 and Wnts 1-14 (except 5a), we verified the selective changes as noted on the microarrays. Wnt and BMP pathways converge via the E2F/Retinoblastoma complex, and therefore may act in concert to inhibit growth via cell-cycle G1/S arrest. In addition, selective changes in cell-cycle regulators of the G2/M checkpoint were also identified on the microarray. Specifically, GADD45, an apoptotic gene responsive to thyroid hormone, was increased 7-fold after TH. Downstream effectors of GADD45, including cyclin-dependent kinase 1, and its activating subunit, cyclin B1, were decreased 5- and 3-fold, respectively. These results were confirmed with RNase protection assays. GADD45 has been shown to induce cell-cycle G2/M arrest in association with altered subcellular localization of cyclin B1. Based on these data, we speculate that inhibition of thyrotrope growth by thyroid hormone may be mediated via cell-cycle arrest at multiple checkpoints including G1/S and G2/M.

ABSTRACT P65

Secondary transnasal surgery after missed adenomas in Cushing's disease

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We evaluated the usefulness of secondary surgery in 13 patients with Cushing's disease who had been operated elsewhere by transnasal access without identification of an ACTH-adenoma and persistent disease. Operations were performed by DKL since 1986-1998. Inferior petrosal sampling (IPSS) was found to be necessary only in the two third operations and a case with unclear endocrine tests. In all cases intraoperative ACTH from peripituitary blood and direct microcytology was available. A minimum follow-up of 5 years was fulfilled.

In all cases an ACTH-adenoma of 2-3 mm diameter was confirmed by intraoperative cytology and full biochemical and clinical remission. In 9 of the 13 patients intraoperative ACTH was helpful in proving site and specificity of the adenoma. False hemi-hypophysectomy was performed in 5 cases before, in 4 according to a false positive IPSS. Three of these were the only patients with additional pituitary function loss. In the last patient ACTH was measured from the adenoma, border zone and anterior lobe. A clear gradient of ACTH concentration per mg was found. Two patients had a recurrence after a remission of one year. One was explored twice before and both had an adenoma with small invasion of the cavernous sinus. Effect of radiation was incomplete. One had additional ketokonazole and one bilateral adrenalectomy with remission. Intraoperative measurement of the ACTH-gradient bilateral from the cavernous sinus proved to be helpful in secondary explorations of missed adenomas. Probably this difficult method may be replaced by comparable preoperative cavernous sinus sampling. So far no surgical complications were observed. All secondary operations were of benefit to the patients and mostly of long duration. The two recurrences occurred in cases with slight cavernous sinus invasion.

ABSTRACT P66

Transsphenoidal Surgery for Pituitary Tumors in the US, 1996-2000; mortality, morbidity and the effect of hospital and surgeon volume

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Objective: Transsphenoidal surgery is performed in both community hospitals and academic settings of various sizes and locations. However, there is no data comparing size and volume on outcome measures. For many complex surgical procedures, larger provider caseload is associated with better patient outcome. We examined the volume-outcome relationship for transsphenoidal surgery for pituitary tumors

Methods: Retrospective cohort study using the Nationwide Inpatient Sample, 1996-2000. Multivariate regression analyses adjusted for age, sex, race, payer, geographic region, procedure timing, admission type and source, medical comorbidities and endocrine status.

Results: 5497 operations were performed at 538 hospitals by 825 identified primary surgeons, comprising about 20% of the national total over a 5 year period. Outcome was measured on a 4-level scale at hospital discharge: death (0.6%) discharge to long-term care (0.9%), to short-term rehabilitation (2.1%) and directly to home (96.2%). Outcomes were significantly better after surgery at higher-volume hospitals (OR 0.74 for five-fold larger caseload, $p=0.007$) or by higher-volume surgeon (OR 0.62, $p=0.02$). 5.4% of patients operated at lowest-volume-quartile hospitals were not discharged directly to home, compared to 2.6% at highest-volume-quartile hospitals. In-hospital mortality was lower with higher-volume hospitals ($p=0.03$) and surgeons ($p=0.09$). 0.9% of all patients operated at lowest-caseload-quartile hospitals died, compared to 0.4% at highest-volume-quartile hospitals. One or more postoperative complications were noted in 21.3% of admissions; complications were less frequent with higher-volume hospitals ($p=0.04$) or surgeons ($p=0.01$). Length of stay was significantly shorter with high-volume hospitals ($p=0.02$) and surgeons ($p=0.001$). Hospital charges were lower for high-volume hospitals, but not significantly so.

Conclusions. For transsphenoidal surgery for pituitary tumors, higher-volume hospitals and surgeons provided superior short-term outcomes with shorter length of stay and lower charges.

ABSTRACT P67

Outcome after Negative Inferior Petrosal Sinus Sampling for Cushing's Disease

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Between 1988 and 2002, 172 patients underwent 178 IPSS procedures as part of their evaluation for Cushing's disease. Threshold criteria for a pituitary source were an IPS:P basal ratio of 2:1 or IPS:P ratio of 3:1 after CRH.

Negative IPSS: 31 patients (33 cath) failed to meet threshold criteria.

Technically inadequate cath: In 7 cath (6 pts) there were technical difficulties with IPS cannulation and no IPS:P ratio could be measured. Curative transsphenoidal surgery was performed in three cases; three patients were lost to follow-up.

Technically satisfactory cath: There were 25 patients who did not meet criteria for a pituitary source (mean IPS:P 1.6). Five of 25 (20%) of these had a confirmed ectopic source from carcinoid tumors (mean IPS:P 1.4). Based upon the clinical picture and MRI findings, 11 (44%) patients underwent pituitary exploration despite a negative IPSS, 9 at MGH (mean IPS:P 1.5). Of these 9, 8 were cured after removal of a microadenoma. Tumor was found in two others who were not cured and one patient was lost to follow-up. Six patients (24%) were thought to have an ectopic source although no tumor has been found; five underwent adrenalectomy and one is on ketoconazole. Three undiagnosed patients have been lost to follow-up.

Positive IPSS: 141 patients (145 cath) met criteria for a pituitary source. 118 patients underwent transsphenoidal surgery at MGH. Cure rates were 91% (96/106) for newly diagnosed tumors, 75% (3/4) of those re-operated for residual tumor, and 50% (4/8) for recurrent disease.

Our data show that patients with an IPS:P ratio suggestive of an ectopic source of ACTH overproduction may still have Cushing's disease. Transsphenoidal exploration should be considered in all cases of technically inadequate sampling and in cases where no ectopic source can be identified after further imaging. Transsphenoidal surgery when IPSS is positive remains effective (cure rate 91%) even if the MRI is negative or equivocal.

ABSTRACT P68

Immunohistochemical evaluation of somatostatin sst2A and dopamine D2 receptors in pituitary adenomas of acromegalic patients: correlation with in vitro and in vivo response to somatostatin analogs and dopamine agonists and electron microscopy study

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In this study 24 pituitary adenomas from acromegalics (13 f, 11 m; age range 19-65 yrs) were characterized for somatostatin receptor subtype 2A (sst2A), dopamine D2 receptor (D2), GH and PRL by immunohistochemistry. The results were retrospectively correlated with the in vitro and in vivo hormone response to somatostatin analogs (SA) and dopamine agonists (DA). In 9 cases GH and PRL content was further studied by electron microscopy (EM) using immunogold technique. GH, PRL, sst2A and D2 immunoreactivity was semiquantitatively scored as 2 (highly positive), 1 (positive), 0 (negative). Sst2A immunoreactivity was scored 2 in 13 cases, 1 in 10, 0 in 1; D2 immunoreactivity was 2 in 13 cases, 1 in 9, 0 in 2; GH immunoreactivity was 2 in 15 cases and 1 in 9, PRL was 2 in 6 cases, 1 in 13, 0 in 5. In vitro GH secretion ranged from 52.5 to 3742.2 micrograms per litre, while PRL varied between 1.2 and 561.7 micrograms per litre in 14 cultures. In vivo, mean GH and PRL levels ranged from 2.2 ± 0.2 to 76.4 ± 1 , and 0.7 ± 0.02 to 333.4 ± 8.1 micrograms per litre, respectively. Sst2A immunoreactivity was positively correlated with in vitro ($p=0.003$) and in vivo ($p=0.02$) percent GH suppression by SA, as well as with the responsiveness to chronic treatment ($p=0.008$), considered as suppression of IGF-I levels by SA. D2 immunoreactivity was positively correlated with in vitro percent GH ($p=0.000$) and PRL ($p=0.005$) suppression by DA. EM study revealed 2 pure somatotroph adenomas, 5 somatomammotrophs with a variable expression of PRL (immunogold) in the same cells containing GH, although in different granules, 2 tumors formed by mixed cell types containing either GH and PRL or single hormones. Immunohistochemistry may be helpful in characterizing receptor expression in pituitary adenomas and to study the mechanisms regulating the response to medical therapy.

ABSTRACT P69

Interim analysis of studies on the relationship of growth hormone response to arginine-GHRH stimulation with IGF-I in a population of 81 older healthy men and women between the ages of 50 and 90

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Age associated decreases in GH and IGF-I have been attributed to impaired GH in sleep, GHRH resistance, and obesity. However, the relationship of GH to low IGF-I in aging is poorly understood. To elucidate this relationship we measured IGF-I and GH response (Nichols Institute) to GHRH - Arginine and related them to demographic parameters in 81 healthy men and women volunteers between the ages of 50 and 90. Mean peak hGH for the group was 35.8 ng/ml (2.3-185). The most significant parameter accounting for variance of the GH peak was BMI (22%; $p < 0.01$). Women had higher peak GHs than men (41.76 vs 20.09; $p < 0.02$). The two independent variables of gender and BMI together account for approximately 29% of total variance in peak value ($r^2 = 0.07$). Four individuals (5%) had peak hGHs of below 5 ng/ml and 7 (8.5%) had GH peaks between 5.3 - 8.2 ng/ml. Mean IGF-I in those with GH peaks of < 5 ng/ml, and between 5.3 and 8.2 were 107.3 ng/ml (range: 81-167) and 115.3 (range: 56-192), respectively. The mean IGF-I for the 81 volunteers was 117.9 ng/ml. Interestingly the correlation between IGF-I and GH peak was not significant. Another group of five volunteers (5%) were categorized as having growth hormone resistance, based on a mean peak hGH of 153 ng/ml, a mean IGF-I of 95.8 and a mean BMI of 21.3. Mean BMI was higher in all other groups. Our results indicate a number of potential causes for low IGF-I in aging, including low GH (high BMI, growth hormone deficiency, resistance to GHRH and/or arginine) or alternatively resistance to growth hormone. Further investigation into these and other causes for low IGF-I, and the relationship between IGF-I and GH will have important clinical implications for the health of our aging population.

ABSTRACT P70

Efficacy of octreotide LAR in newly diagnosed acromegalic patients

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The Italian Multicentre Study on Octreotide LAR.

Thirty-four patients (14 females), aged 31-64 years, with newly diagnosed acromegaly were treated with octreotide LAR for 48 weeks. Thirteen of 34 patients (38.2%) were shown to have a microadenoma while the remaining 21 (61.8%) had a macroadenoma. At baseline none of the patients had either visual field defects or cranial nerve palsies. Patients were started on octreotide LAR 20 mg q28d and the dose was up titrated to 30 mg q28d after 12-week treatment if GH (mean of 5 measurements) was ≥ 2.5 ng/mL: 12/34 patients (35.3%) were treated with octreotide LAR 20 mg and 22/34 patients (64.7%) with octreotide LAR 30 mg. During long-term treatment, serum GH and IGF-I levels were markedly decreased. After 24-week treatment, mean GH was decreased from 17.6 ± 15.2 ng/mL at baseline to 4.2 ± 5.7 ng/mL and a further decline was observed during the following 24 weeks, mean GH being 2.1 ± 1.6 ng/mL at week 48. By the end of the treatment period, 65.2% of the patients attained GH levels ≤ 2.5 ng/mL. Mean serum IGF-I was gradually decreased from 608 ± 298 ng/mL at baseline to 394 ± 217 ng/mL at the last control visit, 40% of the patients achieving normal sex- and age-matched values. During octreotide LAR treatment, tumour volume was reduced by 33.2% after 24 weeks and by 45.2% at the end of the treatment period. In particular, tumour size decreased by 54.6% after 48-week treatment in macroadenoma patients. All patients reported significant improvement or normalisation of the clinical symptoms/signs related to acromegaly. Local and systemic tolerability was very good. These data show that octreotide LAR is able to reduce GH/IGF-I secretion to safe values in the majority of patients with newly diagnosed acromegaly. Moreover, tumour volume was significantly reduced in both micro- and macroadenoma patients; in particular, in patients with macroadenoma where tumour size decreased by more than 50%.

ABSTRACT P71

Muscle strength, physical and sexual function in women with hypopituitarism

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Objectives: The physiologic role of testosterone in women remains poorly understood. Women with hypopituitarism have severely diminished androgen production from both the adrenal glands and the ovaries and thus represent an excellent model to study the consequences of androgen deficiency. We hypothesized that women with hypopituitarism would exhibit decreased muscle strength and function as well as objective measures of sexual function, possibly related to androgen deficiency.

Methods: We measured testosterone and free testosterone in 8 women with documented hypopituitarism and in 5 age- and BMI-matched, healthy volunteers. We also obtained objective measures of sexual function, maximal voluntary muscle strength and physical function in both groups of subjects in an IRB-approved study.

Results: Total and free testosterone levels were markedly diminished among women with hypopituitarism compared to normal volunteers ($P < 0.0001$). Women with hypopituitarism had significantly reduced chest press 1-RM strength (patients, 28.3 ± 4.1 kg vs. volunteers, 34.8 ± 1.9 kg, $P < 0.01$) without change in leg press 1-RM strength (166 ± 49 kg vs. 197 ± 46 kg, $P = NS$). Tests of physical function showed that 400 m walk time was significantly slower in patients (235 ± 28 sec vs. 195 ± 16 sec, $P < 0.05$), but leg power calculated from a timed 12-step stair climb was similar between groups (7.3 ± 2.4 watts vs. 8.6 ± 2.0 watts, $P = NS$). Although clitoral and labial blood flow were similar between the groups in this study, possibly due to small sample size, quantitative somatosensory testing showed high degrees of impairment in vibratory and thermal thresholds in patients with hypopituitarism compared to historic controls.

Conclusions: We postulate that testosterone deficiency in women with hypopituitarism leads to a decrease in muscle mass, that translates into reduced muscle strength and performance. Testosterone deficiency may also lead to impairment in objective sexual measurements. These data provide compelling rationale for placebo-controlled, randomized trials of testosterone replacement in women with hypopituitarism.

ABSTRACT P72

Value of MRI Performed the First Day After Transsphenoidal Pituitary Surgery

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The prevailing consensus holds that MRI studies obtained immediately after transsphenoidal surgery have little value. Most centers acquire the first MRI study 2 to 3 months after surgery believing that early postoperative studies are uninterpretable. However, if residual tumor could be reliably identified immediately after surgery, patients could benefit from an early return to surgery before postoperative fibrosis has a chance to develop. Surgery is thereby simplified, dramatically decreasing the risks associated with reoperation. We have routinely obtained MRIs of patients undergoing transsphenoidal surgery since the modality became available at our institution in 1986. We searched our database of more than 800 patients undergoing a transsphenoidal procedure for pituitary tumors and retrospectively reviewed patients' charts and MRI studies. MRIs obtained Day 1 after surgery were evaluated for the presence of normal gland, residual tumor, hematoma, foreign substances (e.g., Gelfoam), and fat grafts. Findings were compared to MRIs obtained 3 months after surgery and all subsequent follow-up studies. MRI findings were also compared to operative findings in patients requiring reoperations. Radiological interpretation of the Day 1 MRIs were usually accurate, and they were helpful in determining the need for reoperation. Obtaining a high-resolution MRI study on the first postoperative day, combined with the results of a permanent pathology section report and postoperative endocrinological studies, should improve the surgeon's ability to remove tumor and preserve the gland.

ABSTRACT P73

Isolated Familial Somatotropinoma: Narrowing the candidate interval for the IFS gene

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Isolated familial somatotropinoma (IFS) occurs in a family without MEN1 or Carney Complex (CNC). We established linkage between IFS and chromosome 11q13, mapping the IFS gene to 9.37 cM interval between markers D11S1335 and INT2. Deletion at this region has been reported in somatotropinomas from IFS kindreds. The first candidate was MEN1, but its sequencing appeared normal, indicating that the IFS is a tumor suppressor gene (TSG) distinct from MEN1. To reduce this interval, we performed allelotyping and haplotype analyses in a new IFS kindred in which the mother and one daughter developed acromegaly (25 and 14 yr, respectively). Interestingly, the mother presented at 38 yr a virilizing adrenal carcinoma. It is the first time that this association is reported. None of the affected and unaffected individuals exhibited MEN1 or CNC. In addition sequencing of MEN1 was normal. This study was approved by the Ethical Committee of HUCFF/UFRJ.

Leukocyte and tumor DNA were amplified using polymorphic markers from chromosome 11q13. Allelotyping of both tumors (somatotropinoma from the daughter and adrenal carcinoma) revealed loss of the chromosome that harbors the wild-type copy of the TSG. Haplotyping indicated that haplotype '2141213211211' between markers D11S956 and D11S527 was transmitted from the mother to the affected daughter but not to the unaffected children, indicating that this haplotype cosegregates with the mutant copy of the TSG. A meiotic recombination event between D11S4908 and D11S2072 was detected in one of the unaffected children, suggesting that the IFS gene is not located telomeric to D11S2072. This study suggests that the IFS gene is located within a region of chromosome 11 flanked by markers D11S1335 and D11S2072 (7.55 cM), and raise the possibility that the IFS gene is essential for modulation of both the somatotrope and the adrenal cortex cell proliferation. [This work was supported by CNPq]

ABSTRACT P74

Active disease after pituitary surgery and radiotherapy for acromegaly without any tumor tissue on MRI

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Conventional surgery of a pituitary tumor, followed in some cases by external radiotherapy, remains the treatment of choice in acromegaly. The results of the neurosurgical treatment, however, are frequently not satisfactorily, especially in patients with macroadenomas. In such cases, repeated surgery, additional radiotherapy or medical treatment with somatostatin analogs is necessary. On the other hand, there are patients who show no signs of a residual tumor on MRI after previous treatment, but are still symptomatic and do not fulfil the criteria of cure of acromegaly at the same time. From a group of 33 acromegalic patients hospitalized at the Dept. of Clin. Endocrinology in years 2001-2002, ten cases (6M and 4F), aged 30-71 years with active disease, but without any remnant tumor on MRI, were chosen. Eight patients were treated previously by neurosurgery (three of them received additional radiotherapy), one was treated only by radiotherapy, and the other one was not treated, but showed signs of an empty sella. Additionally, seven patients received slow release octreotide (Sanostatin LAR - 20 mg) for a period of 6-16 months. In all cases GH level failed to suppress below 2 mU/l (0.8 micrograms per litre) after oral glucose load, and no one has reached normal age- and sex-matched IGF-I levels. Moreover, repeated pituitary surgery or radiotherapy was not indicated in this group of patients. In conclusion, the lack of a residual pituitary tumor on MRI must not confirm the cure of acromegaly. Persistent disease should be treated medically in order to obtain clinical and biochemical cure. Chronic therapy with a new growth hormone receptor antagonist (pegvisomant) could be reasonable in these patients, because of the lack of the curative effects of a somatostatin analog.

ABSTRACT P75

Persistence of biochemical cure after octreotide withdrawal (4 years) in two patients with acromegaly treated with only pharmacotherapy

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The aim of this paper is to report on two acromegalic patients successfully cured by medical treatment alone. Two patients, aged 28 and 42 years, were referred because of the presence of acromegalic features. The diagnosis was biochemically confirmed by elevated serum IGF-I and GH (mean values: 75.14 µg/L and 8.27 µg/L) failing to suppress to $\leq 1.0\ \mu\text{g/L}$ after OGTT. One patient had a mesoadenoma and the other one a microadenoma. Because of the very good response to a short-term treatment with octreotide s.c. (mean GH: 2.00 and 1.40 µg/L in the two patients respectively; normal IGF-I in one patient and slightly above the normal range in the other one), both patients were continued on the long-term treatment with octreotide s.c. Clinical symptoms/signs of acromegaly completely disappeared in one patient while the other one reported recurrent episodes of headache prior to each injection of octreotide. After 7- and 4-year treatment with octreotide s.c., they were started on octreotide LAR 20 mg administered at 4-week intervals. During the long-term treatment with octreotide LAR (6 years), mean GH was decreased to around 1.0 µg/L and IGF-I was normalised in both patients. The patient complaining of headache on octreotide s.c. reported its complete disappearance after the first injection of octreotide LAR. Due to the persistence of GH levels $\leq 1.0\ \mu\text{g/L}$ and normal IGF-I values, it was decided to discontinue the medical treatment and to re-assess both patients. After 6-month off any therapy, mean GH was around 1.0 µg/L suppressing to $\leq 1.0\ \mu\text{g/L}$ after OGTT and IGF-I was within the age-matched normal range. OGTT is repeated at 6-month intervals and after 4-year withdrawal from octreotide LAR, GH continues to be suppressed to $\leq 1.0\ \mu\text{g/L}$ after OGTT and IGF-I is within the age-matched normal range. Their adenoma disappeared in both patients during octreotide LAR treatment.

ABSTRACT P76

Apoptotic effects of octreotide in rat and human pituitary cells: role of somatostatin type 2 and type 5 receptors

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The antiproliferative effect of octreotide has been only partially characterised. Aim of the present study was to evaluate the ability of octreotide (that preferentially binds sst2 and sst5), BIM23120 and BIM23206 (somatostatin analogues selective for sst2 and sst5 respectively) to induce apoptosis in rat and human pituitary cells. In GH3 cells, a rat somatotroph cell line expressing both sst2 and sst5, octreotide (10nM for 6h) induced a significant increase in caspase-3 activity (ranging from 220 to 430%), a protease that plays a key role in mammalian cell apoptosis. As far as the two selective somatostatin analogues were concerned, while BIM23120 (10nM) induced an increase in caspase-3 activity (ranging from 350 to 500%) similar to that observed after octreotide incubation, BIM23206 did not caused any significant modification in this protease activity. These observations seem to suggest that the apoptotic effect of octreotide is mediated by sst2. To confirm these data and to evaluate the effect of octreotide on apoptosis in human pituitary tumors, we studied a more sensitive apoptotic marker such as cleaved CK18. In GH3 cells, octreotide (10nM for 20h) caused a dramatic increase in cleaved CK18 levels (ranging from 500 to 800%), this effect being almost completely due to sst2 activation. In fact, a significant increase in cleaved CK18 levels was observed only after incubation with BIM23120. As far as human pituitary tumors were concerned, octreotide incubation induced a slight but significant increase in cleaved CK18 levels (ranging from 20 to 30%) in cellular extracts from a NFPA and a GH-oma. In conclusion, octreotide exerts an apoptotic effect in human pituitary tumor cells, this effect being almost completely due to sst2 activation at least in pituitary GH3 cell line. Further studies are needed to understand the role of somatostatin receptor subtypes in this cellular event in human pituitary adenomas

ABSTRACT P77

Evidence for thyroid hormone and not TRH as a major regulator of serum TSH bioactivity in humans

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We postulated that serum thyroid hormone concentration is a more important regulator of serum TSH bioactivity than hypothalamic TRH secretion in humans. We measured TSH bioactivity and glycosylation in 9 patients with primary hypothyroidism (41.3 y; 6F/3M) and 11 sex and age comparable controls (37.6y; 7F/4M) before and after 4-24 months of thyroxine replacement and in two thyroidectomized patients with TSH-secreting adenomas receiving high dose thyroxine before and after thyroxine withdrawal. Serum FT₄ and T₃ increased and TSH decreased in patients with primary hypothyroidism receiving thyroxine treatment (2.7 +/- 0.8 vs 14.4 +/- 1.0 pmol/L, P < 0.0001; 0.5 +/- 0.2 vs 1.7 +/- 0.1 nmol/L, P < 0.0001; 136.2 +/- 40.6 vs 4.5 +/- 0.7 mU/L, P < 0.01; respectively). TSH bioactivity in hypothyroid patients was low as compared to controls (0.48 +/- 0.1 vs 1.1 +/- 0.2, P = 0.004) and increased significantly during thyroxine replacement (0.48 +/- 0.1 vs 0.8 +/- 0.1, P = 0.01) to levels similar to controls (P = 0.14). A strong significant correlation (r = + 0.81, P = 0.004, Spearman) was observed between the absolute increments of TSH bioactivity and serum T₃ but not T₄ levels (r = -0.39, P = 0.30, Spearman) during thyroxine treatment. The degree of sialylation was elevated in hypothyroid patients before treatment (47% vs 29%, P = 0.002) and decreased significantly after thyroxine replacement (33%, P = 0.02) to levels similar to controls (P = 0.50). TSH bioactivity also decreased in the two thyroidectomized patients with TSH-secreting adenomas when serum thyroid hormone levels were decreased by thyroxine withdrawal (from 0.5 and 1.8 to 0.3 and 1.0, respectively). Altogether, these data indicate that serum T₃ concentration and not hypothalamic TRH secretion is a major regulator of the biological activity of serum TSH.

ABSTRACT P78

RhGH treatment is not associated with recurrence of the hypothalamic-pituitary tumor in postsurgical Growth Hormone Deficiency (GHD): preliminary data

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As showed in our previous reports, hypothalamic-pituitary neurosurgical procedures are most commonly associated with the appearance of GHD as the first hormonal damage, especially in Craniopharyngioma and non-functioning pituitary adenomas (NFPA), usually in a complex situation of panhypopituitarism.

The treatment of GHD Syndrome with rhGH is characterized by an improvement in quality of life, lipid profile, bone density and body composition. At the moment, few data are available on long-term safety profile of such a therapy.

In order to evaluate the hypothalamic-pituitary tumor recurrence, we retrospectively review the clinical records of all postsurgical GHD patients during rhGH replacement therapy from the Endocrinology Units of our Hospitals, observed at least after a 1-7 years follow-up (mean \pm SE 48 \pm 6 months). We have studied 48 patients (30 males and 18 females, aged 21-78 years), submitted to transsphenoidal (30 patients) or transcranial (18 patients) neurosurgical procedures. The histological findings showed: 17 NFPA (35.4%), 9 PRLomas (18.7%), 13 Craniopharyngiomas (27.1%), 1 GH-secreting adenomas (2.1%), 4 ACTH-secreting adenomas (8.3%), other neoplasms (1 hypophysitis, 1 Rathke's cyst, 1 glioma and 1 epidermoidal cyst; 8.3%). After surgery, the residual tumors present at baseline before starting the hormonal replacement therapy was 6.25% (3 NFPA patients); the recurrence of pituitary or CNS tumours was reported only in 1 NFPA patients. Our data suggest that GH does not increase the risk of the hypothalamic-pituitary disease recurrence, even in the case of residual tumoral mass at the moment of starting therapy. These results make us more confident in the long-term use of such a replacement treatment, but a continuous surveillance is mandatory.

ABSTRACT P79

Metastatic renal cell carcinoma to the sellar region masking a pituitary adenoma

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Pituitary adenomas are the most common tumor of the sellar region. Although rare, other nonadenohypophyseal lesions must be considered into the differential diagnosis of sellar mass including: meningiomas, vascular lesions, inflammatory and infectious processes, salivary gland pleomorphic adenomas arising within a Rathke's cleft cyst (Chimelli et al. Pituitary 2000), plasmocytomas and metastatic carcinomas.

We report a case of sellar lesion mimicking a pituitary macroadenoma with an aggressive behavior. A 66-year-old male presented with adrenocortical insufficiency and unilateral palpebral ptosis. He had a past medical history of right nephrectomy for renal cell carcinoma at the age of 65. And remained free of disease for 1 year. Endocrine evaluation revealed panhypopituitarism. Magnetic resonance imaging showed a sellar tumor with suprasellar extension and parasellar invasion. He underwent transsphenoidal partial resection followed by radiotherapy and systemic therapy with IL-2. Histopathological examination disclosed a clear cell tumor metastatic to the pituitary gland. He still alive.

This study was approved by the Ethical Committee of HUCFF/UFRJ.

The majority of the primary renal neoplasms are renal cell carcinomas (85%), and clear cell carcinoma is responsible for 80 percent of these tumors. The most frequent metastatic locations are regional lymphatics and lungs. Mortality associated to renal cell tumors is 90% at 5 years and pituitary metastases are rare. This case emphasizes the intrigued nature of renal cell carcinoma, particularly in a patient without another sites of disseminated disease. Although anterior pituitary involvement is rare, a review of previously reported cases of unusual lesions to the pituitary, pituitary metastasis from clear cell carcinoma often mimics clinically non functioning pituitary adenoma and should be considered in the differential diagnosis.

ABSTRACT P80

Thymic hiperplasia after hypercortisolism correction in ACTH-dependent Cushing syndrome: Importance of catheterism of the thymic vein

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Thymic tumors are very important in ACTH-dependent Cushing's syndrome, since they can represent an ectopic source of ACTH production. Thymic hyperplasia has been described after the resolution of hypercortisolism in several pathologies, causing great diagnostic dilemmas. We describe a case where the catheterization of the thymic vein was essential for the differential diagnosis of a thymic tumor. This was a female patient, 48 years of age, presenting secondary amenorrhea for five years, headaches, hirsutism, muscular weakness and hypertension. Hypercortisolism was determined by the absence of suppression with dexamethasone and loss of the circadian rhythm of cortisol secretion. Basal ACTH: 26.3 pg/mL (RV: 9 to 52). Desmopressin test with increment of 65% of cortisol and 165% of ACTH. MRI images were negative for pituitary tumor. She underwent a transphenoidal craniectomy with no tumor visualization. The suspected area showed normal pituitary tissue. Due to the persistence of the hypercortisolism, she was submitted to a bilateral adrenalectomy. Nine months after the latter, a chest CT and MRI showed an increase of the left thymic lobe, previously non-existent. She had a negative Octreoscan. Her ACTH was 128 pg/mL. The patient underwent simultaneous and bilateral catheterism of the petrosus sinuses and catheterization of the thymic and innominate veins. There was no gradient among the periphery, lower petrosus sinuses, thymic vein and innominate vein. A follow-up was decided. There was a spontaneous regression of the thymic lesion 38 months after the diagnosis. The catheterization of thymic vein was essential for the differential diagnosis of the thymic tumor after hypercortisolism resolution in ACTH-dependent Cushing's syndrome, especially in this case, where the ACTH source was occult, thus avoiding an invasive procedure for a benign entity with spontaneous resolution.

ABSTRACT P81

Malignant Prolactinoma: A Case Report

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INTRODUCTION: Pituitary carcinomas, or primary adenohypophyseal neoplasms with brain invasion or distant metastases are rare.

HISTORY: A 54 year old male presented in April 1997 with headaches, decreased libido and a 4x3 cm sellar/clival mass. His initial prolactin level was 5420 ng/mL. Bromocriptine was started (maximal dose 10 mg/day) but his prolactin decreased to only 1103 ng/ml with minimal decrease in tumor size over 12 months. He was switched to cabergoline (maximal dose 1.5 mg twice/week), however by June 1999, the tumor had grown slightly and his prolactin was 890 ng/mL. He consequently underwent transsphenoidal tumor debulking; his postoperative prolactin level was 57 ng/mL. He remained on cabergoline (1.5 mg twice/week) but his prolactin level continued to increase to 6650 ng/mL and the tumor grew with suprasellar extension. Consequently, a second transsphenoidal debulking was performed in September 2000 followed by fractionated external beam radiotherapy. Tumor pathology revealed increased cytological atypia and increased proliferation index (MIB-1) compared to the original tumor in 1999. In July 2001 the patient developed hip pain and was diagnosed with multiple bone lesions on bone scan that proved to be metastatic prolactinoma on biopsy. The dose of

Cabergoline was increased to 3 mg twice/week, Sandostatin was started and pelvic irradiation was given. Unfortunately, his prolactin increased to over 20,000 ng/ml and he soon developed lower cranial nerve palsies secondary to extensive tumor growth into the cerebello-pontine angle. He died in January 2002, almost 5 years after his initial diagnosis with a prolactin level of 39170 ng/ml.

CONCLUSIONS: Pituitary carcinomas constitute only 0.1 to 0.2% of all pituitary tumors. As in other case reports, these tumors' proliferative indices typically increase during disease progression. Despite aggressive current multi-modality treatment, pituitary carcinoma carries a grave prognosis. Whether new chemotherapeutic regimens or novel gene therapies will help control pituitary carcinomas remains to be clarified.

ABSTRACT P82

Ghrelin in macaque monkeys: tissue localization, dynamics and source of circulating ghrelin in both plasma and cerebrospinal fluid

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Ghrelin is an endogenous ligand for the growth hormone secretagogue-receptor, which stimulates both GH and food intake. Although recent evidence from ghrelin knockout mice and immunoneutralization studies with specific anti-ghrelin serum in conscious rats showed that endogenous ghrelin plays a minor role, if any, in the control of GH and food intake in the rodent, source of circulating ghrelin in the blood and cerebrospinal fluid in the primate remains to be elucidated. We first identified ghrelin-containing cells in the brain, pituitary, stomach, duodenum and colon. We then measured plasma levels of intact ghrelin (1-28) and GH by ultrasensitive EIAs (immune complex transfer-EIAs) in 10 adult male macaques before and after banana feeding. To elucidate the source of circulating ghrelin in plasma and CSF, we further measured ghrelin levels in plasma and CSF after total gastrectomy and iv injection of human ghrelin in anaesthetized macaques. Immunohistochemistry with an antibody (#106) against ghrelin 1-11 demonstrated abundant ghrelin-containing cells in the gastric mucosa, but not in the hypothalamus or pituitary. Ghrelin was detected in monkey plasma at the level of 130.2 plus/minus 67.1 picogram per millilitre (43picomol). Immediately after banana feeding, plasma levels of ghrelin decreased to 44.5% of basal levels, whereas plasma GH levels gradually increased after the feeding. By contrast, ghrelin was not detected in the CSF of macaques (0.3picomol). Total gastrectomy immediately decreased plasma ghrelin levels to 1/20 of initial levels. The iv injection of human ghrelin (1.0 microgram per kilogram) resulted in a prompt and marked increase in plasma levels of both ghrelin and GH, whereas a small and transient increase of ghrelin was observed in the CSF. The present results, demonstrating that the plasma ghrelin from the stomach does not penetrate the blood brain barrier, suggest that the clear postprandial fall in plasma ghrelin levels may be independent from meal initiation behavior in macaques.

ABSTRACT P83

Pituitary Adenoma - Neuronal Choristoma: Evidence of Neuronal Differentiation in Adenoma Cells

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Ganglion cell tumors of the hypothalamic-pituitary region, composed of well-differentiated neoplastic neurons are rare. The reported incidence is approximately 0.5% of all brain tumors. Sellar adenomas associated with neuronal choristoma (PANCH tumors) are located within the sella turcica. We report five cases of PANCH tumors in patients associated with acromegaly. All tumors were studied by histology and immunocytochemistry for pituitary hormones and for markers of neuronal differentiation. The tumors were biphasic, composed of pituitary adenoma cells, variably admixed with clusters of ganglionic neurons embedded in neuropil. In all cases, the pituitary adenoma compartment showed histological features consistent with the sparsely granulated variant of somatotroph adenoma. The cells exhibited typical inclusions (fibrous bodies) in the cytoplasm. The adenoma cells were positive for GH and two of them, for PRL as well. Ganglion cells were immunoreactive for NSE, synaptophysin and neurofilament (NF) protein. NF protein was also positive in the accumulated filaments of the stroma. In addition, the fibrous bodies of adenoma cells were immunoreactive for both cytokeratin 8 and NF protein. One of the histogenetic hypotheses for these tumors suggests the origin of neuronal component from neuronal differentiation of a preexisting sparsely granulated pituitary adenoma. Ultrastructural studies showed the presence of transitional cell forms between neurons and adeno-hypophysial cells in a single case of PANCH tumor. The presence of NF protein in adenoma cells, as it was clearly shown in all five cases of our study, further supports these findings. We conclude that the presence of NF protein in both pituitary adenoma and neuronal cells of PANCH tumors provides evidence of a common origin of these two elements.

ABSTRACT P84

Somatostatin Analogs in Acromegaly Treatment: Dissociation between Tumor Shrinkage and Hormonal Response

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Somatostatin (SST) acts through five specific receptor subtypes (SSTRs) comprising numerous functions. SSTRs are expressed in normal and neoplastic somatotroph cells, and SST and its analogs have been shown to normalize GH and IGF-I in up to 60% of acromegalic patients. However, tumor shrinkage is less frequent, and seldom exceeds 50% of size reduction. We investigated the effects of two SST analogs in a 23-yr old male acromegalic patient, without visual disturbances. The diagnosis of acromegaly was confirmed by elevated serum levels of GH and IGF-I and by the presence of a sellar mass with slightly suprasellar expansion on MRI. The patient was treated with lanreotide-SR, 30 mg every 10 days for six months and subsequently with octreotide-LAR, 30 mg every 28 days for additional six months. GH (nanogram per milliliter) dropped from the basal of 20.9 to 16.7 after lanreotide-SR and to 13.9 after octreotide-LAR. Pre-treatment IGF-I (nanogram per milliliter) was 698, 693 after lanreotide-SR, and 1252 after octreotide-LAR. Despite of poor hormonal response, tumor had 75% of volume shrinkage after therapy. Hormone control was achieved after transsphenoidal surgical removal of a GH-secreting macroadenoma. We evaluated mRNA expression of all SSTRs in the tumor by RT-PCR having BCR as an internal endogenous control. The five SSTRs mRNA contents were expressed in arbitrary units (AUOD) in relation to the expression observed in normal pituitary. The analysis showed that the tumor expressed $SSTR_3=0.40 \rightarrow SSTR_5=0.15 \rightarrow SSTR_4=0.13 \rightarrow SSTR_2=0.08 \rightarrow SSTR_1=0.01$ AUOD. In human somatotropinomas, SSTR2 and SSTR5 are responsible for GH secretion control, and SSTR3 uniquely triggers PTP-dependent apoptosis, followed by p53 activation and the pro-apoptotic protein Bax. We conclude that in our patient the dissociation between tumor shrinkage and GH/IGF-I response observed during SST analogs treatment could be due to higher expression of SSTR3 compared to the remaining SSTRs.

ABSTRACT P85

Some epidemiologic aspects of acromegaly.

Experience with 44 patients. Sixteen years follow-up

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Fifty four patients harboring GH secreting pituitary adenomas were evaluated from 1985 to 2001. The average delay in diagnosis determined from beginning of symptoms was about 7 years (range 1 to 20 years). Sex distribution was twenty three women and twenty one men with age at presentation range 19-58 years. Acral enlargement and soft-tissue changes were the most important clinical features presented in 100% of patients. Headaches in 24 patients (55%), arthralgias in 16 (36%), sweating in 12 patients (31%), amenorrhea in 14 (31%), paresthesias in 12 (28%), galactorrhea in 8 (19%), lumbalgias in 7 patients (17%) and visual impairment in 5 out of 44 patients (11%).

Complications related to the acromegalic syndrome were : hypertension in 61,5% of patients , diabetes mellitus in 30% , goiter in 20 % , cardiac disease in 8 % , sleep apnea in 16 % and malignancy in 9 % of cases represented for two breast and two thyroid cancer. Two patients died because metabolic complications and two because cardiovascular disease. At the time of presentation the MRI demonstrated macroadenomas in 40 patients (91,9 %) and microadenomas in 4 patients (9,09%). Mean random pretreatment GH serum concentration was 45 ng/mL. Forty patients were surgically treated by the transsphenoidal route and in four patients the transcranial approach was used. Surgery was performed by two experienced neurosurgeons. No patient achieve GH level below 10 ng/mL in the postoperative evaluation.

In this study we observed that acromegaly is a cronic and insidious disorder caused in the majority of cases by a GH secreting pituitary macroadenoma . The prevalence between sexes was equally distributed and mean age at presentation was 44 years. Growth hormone excess had severe health consequences increasing morbidity and mortality in acromegalic patients .

After surgical treatment all patients of this series had unacceptable high post operative GH levels and required adjunctive medical or radiation therapy.

ABSTRACT P86

Improvement of acromegaly after octreotide LAR treatment

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Octreotide is a somatostatin analog that inhibits growth hormone release showing higher potency than natural somatostatin so it has proved to be effective in acromegaly treatment. The objective of present study was to establish the effects of octreotide LAR (long acting release) preparation in patients with active acromegaly.

The following parameters were assessed: clinical response, safety of medication, GH and IGF-1 serum concentrations and pituitary tumor size. Eleven patients (6 men and 5 women) range 41,4 years old with diagnosis of active acromegaly were included. Octreotide was administered at 0,1 mg subcutaneously dose three times daily for four weeks to test the drug tolerability. Afterwards patients received octreotide LAR 20 mg intramuscularly separated by 28 days periods with an option to continue for 8 months. Basal average GH serum concentration was 27,6 ng/mL. After 6 months treatment reduction to 5.03 plus/minus 5.38 ng/mL in 9 patients ($p < 0.001$) was observed. Basal IGF-1 average serum concentration was

889.55 plus/minus 167.29 ng/mL with a reduction value to 483.00 plus/minus 239.71 ng/mL in 9 of 11 patients after 6 months treatment ($p < 0.005$). The drug was well tolerated with few adverse effects. Diarrhea, flatulence and steatorrhea were observed during the administration of subcutaneous octreotide in 18.2% of patients. Two patients had symptomatic biliary lithiasis that was successfully removed by surgery. Clinical symptoms improved and some of them disappeared such as headaches and sweatings. Tumor shrinkage was observed in 66,7% of cases. Monthly injections of 20 mg of octreotide LAR were effective to reduce GH and IGF-1 levels in patients with active acromegaly accompanied by improvement of clinical symptoms and significant tumor size reduction.

ABSTRACT P87

Dynamics of subcellular organelles, growth hormone, rab3B, SNAP-25, and syntaxin in rat pituitary cells caused by growth hormone releasing hormone and somatostatin

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Rab3B is involved in the exocytosis of synaptic vesicles and secretory granules in the central nervous system and the anterior pituitary cells. The aim of this study is to elucidate the role of rab3B in GH secretion and the mutual relationship with SNARE proteins. Adult male rats were injected intravenously with 10 mg of growth hormone releasing hormone (GHRH) or 10 mg of somatostatin (SRIF). Untreated rats were used in control studies. Their pituitary glands were served for histochemical examinations. Rab3B is localized on the limiting membrane of secretory granules and the cytosol. Confocal laser scanning microscopic observation of the immunohistochemical double stainings of rab3B and GH revealed the increased and decreased immunoreactivity of rab3B in GHRH- and SRIF-treated rats, respectively. Confocal laser scanning microscopic observation of the immunohistochemical double stainings of SNAP-25, syntaxin and rab3B revealed the co-localization of rab3B and these SNARE proteins in GHRH-treated rats, and their dissociation in SRIF-treated rats. These results suggest that rab3B is playing the principal roles in GH secretion of the anterior pituitary cells and that SNAP-25, syntaxin are acting as co-workers with rab3B in the functional regulation of GH secretion.

ABSTRACT P88

Lack of further growth in the size of a 2 pituitary growth hormone producing tumors following initial increase after initiation of pegvisomant therapy

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In a study designed to examine the conversion of patients from long-acting octreotide to pegvisomant, two of our study patients, neither of whom had received prior pituitary radiation, developed a slight increase in the size of their pituitary tumors while on pegvisomant therapy. Each patient was converted from long-acting octreotide to pegvisomant following a 30 day wash-out period. Both patients normalized their IGF-1 levels after 8 weeks of therapy on a pegvisomant dose of 10 mg/day. Each patient had an MRI prior to discontinuation of long-acting octreotide and again following 8 months of therapy with pegvisomant. In the first patient there was an increase in the size of residual (1-2 mm) 8 months following initiation of pegvisomant with no further increase in size over the course of the next 5 months. In the second patient there was a 2-3 mm increase in the size of the tumor 8 months following initiation of pegvisomant with no further increase in size on a subsequent MRI 5 months later. These patients, a minority of those included in the study, demonstrate small increases in the size of a GH producing pituitary tumor during treatment with pegvisomant. The increase in size could result either from cessation of octreotide LAR, from interruption of negative feedback of IGF-1 on the pituitary/hypothalamic unit, or from unrelated growth of the pituitary tumor. In neither of these patients was there further growth of the tumor despite continued therapy with pegvisomant over a subsequent 5 month period. Long-term followup will be required in these patients.

ABSTRACT P89

Growth Hormone (GH) Treatment Decreases Plasma Levels of Matrix Metalloproteinases 2 & 9 and Vascular Endothelial Growth Factor (VEGF) in GH-deficient Adults: Effects of Age of Onset of GH-deficiency

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Increased activity of matrix metalloproteinases (MMPs) has been implicated in numerous disease processes including cardiovascular (CV) disease. VEGF is involved in activation of the MMP system. As GH deficiency is associated with increased cardiovascular risk, our aim was to assess, whether plasma MMPs and VEGF levels can be altered by GH treatment.

Methods: 66 GH-deficient adults, aged 37.8+/-14.7 years, were recruited [childhood-onset (CO), n=34]. Plasma levels of MMP-2 and -9, VEGF and IGF-1 were measured at baseline (V1), at 12 months (V2) and at 24 months (V3) of GH treatment.

Results: IGF-1 levels rose significantly by V2 ($p < 0.001$), and remained unchanged at V3 ($p = 0.76$). Baseline IGF-1 levels were lower in those with CO ($p = 0.036$), with a tendency to a steeper decline in relation to age ($p = 0.075$). MMP9 presented the most pronounced and sustained decline: V1 1248±651 ng/ml; V2 949±457 ng/ml, V3 760±386 ng/ml ($p < 0.001$ for both). At baseline, there was a positive correlation between MMP-9 levels and age, with curve being significantly steeper for those with CO ($p = 0.024$). VEGF declined from 358±209 pg/ml at V1 through 310±225 pg/ml at V2 ($p < 0.001$), and 283±202 pg/ml at V3 ($p = 0.005$). Baseline VEGF levels were higher in those with adult-onset GH-deficiency ($p = 0.008$). MMP2 declined from V1 to V2 (1134±217 ng/ml vs 1074±203 ng/ml, respectively; $p < 0.001$), subsequently reaching a plateau at V3 ($p = 0.93$, for V2 vs V3). There was no difference in MMP-2 levels by age of onset of GH-deficiency ($p = 0.22$). There was a negative relationship between MMP9 vs IGF-1 and MMP2 vs IGF-1 ($p < 0.001$ and $p = 0.007$, respectively), as well as between VEGF and IGF-1 ($p < 0.001$).

Conclusions: Our novel findings reveal that GH treatment leads to a significant decrease in the non-traditional CV risk factors, MMPs and VEGF and may be implicated in the mechanisms underlying the cardiovascular benefits of GH in these individuals.

ABSTRACT P90

Risk for severe hypoglycemia without symptoms in patients with growth hormone deficiency investigated with insulin tolerance test

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Aims To assess the risk for severe asymptomatic hypoglycaemia during insulin tolerance test.

Background ITT is suggested as 'golden standard' for assessing of GH deficiency (GHD). Patients considered for investigation are those with a known hypothalamic-pituitary disease, cranially irradiated patients and those with GHD in childhood. These individuals often have a defect in counter-regulatory hormone responses to hypoglycemia, with e.g. GH-, and ACTH-deficiency as well as defects in norepinephrine and epinephrine responses. There are case-reports of unconsciousness and even deaths in children after an ITT.

Methods Sixteen patients (9 men) aged 22-59 years with median BMI of 25.5 kg/m² (range 20.0-33.7) were investigated with an ITT. Seven patients had panhypopituitarism, 4 had isolated GHD, and the rest had 2-3 pituitary hormone insufficiencies. All patients had GHD (GH ≤ 6.2 IU/L). After fasting since midnight and after intake of their morning medication, insulin 0.07 IE/kg (0.06-0.1) was given iv and B-glucose was monitored at -15, 0, 10, 15, 20, 25, 30, 35, 40-90 min. When the B-glucose level was ≤ 2.2 mmol/L it was monitored every other min and symptoms were registered. When the B-glucose level was ≤ 1.6 mmol/L glucose was given per orally and/or iv.

Results The lowest recorded B-glucose levels among the 16 patients varied between 1.0-1.9 (median 1.3 mmol/L). Five of them had no symptoms but despite of that their lowest B-glucose level were 1.1-1.9 mmol/L. In the other patients tiredness (N=6), dizziness (N=3), sweating (N=3) and paleness (N=3) were the most common symptoms.

Conclusion: Despite of a low dose of insulin (≤ 0.1 IE/kg) very low B-glucose levels were recorded during the ITT (lowest 1.0 mmol/L). Furthermore, the symptoms of hypoglycaemia were few and in 5 patients no symptoms were recorded. When using the ITT close B-glucose monitoring is recommended as the symptoms of hypoglycaemia were scarce and may be absent.

