The definition of Pseudo-Cushing state

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Cushing *versus* Pseudo-Cushing state

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Definition of Cushing “state”

Condition associated with increased cortisol

resulting either in adrenal production

(Cushing syndrome)

or in ACTH over-secretion

(Cushing disease)

by pituitary tumor or an other tumor

Definition of Pseudo-Cushing state

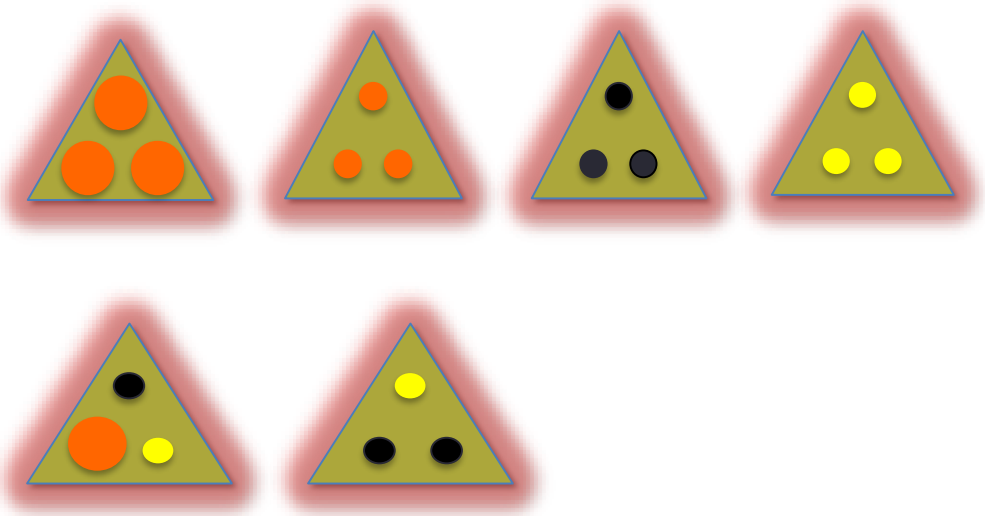
…. at the end !

How many types of Cushing?

How many types of Cushing?

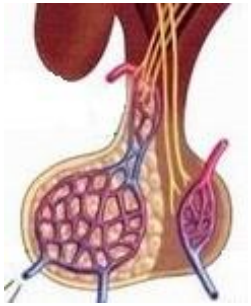
- Cortisol Producing Adenoma (ACTH-independent)

- Bilateral Adrenal Hyperplasia (ACTH-”independent”)

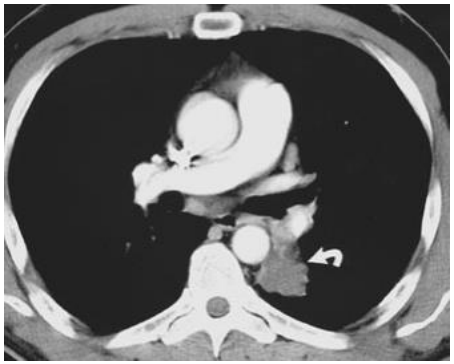


J Surg Pathol ‘11 Cancer Res ’03

✧ Cushing Disease (ACTH-dependent)



✧ Ectopic Cushing (ACTH-dependent)



Physiological conditions associated to Pseudo-Cushing state

Pseudo-Cushing's States
G Kaltsas, G Chrousos, and I I Androulakis

NCBI Bookshelf

- ✧ Surgery associated stress
- ✧ Severe illness
- ✧ Emotional stress
- ✧ Intense aerobic exercise
- ✧ Caloric restriction

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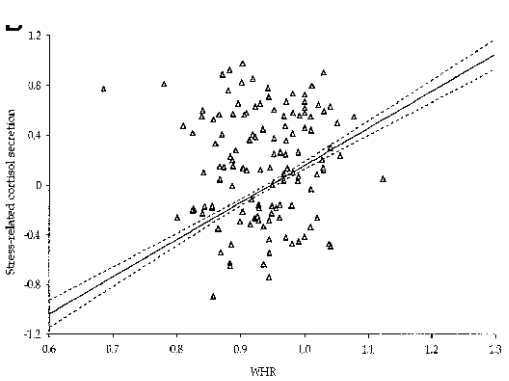
Physiological conditions associated to Pseudo-Cushing state

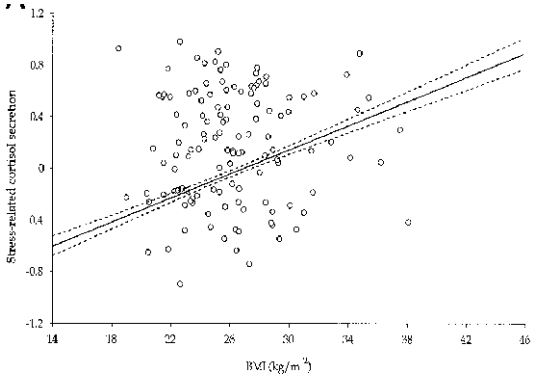
Stress-Related Cortisol Secretion in Men: Relationships with Abdominal Obesity and Endocrine, Metabolic and Hemodynamic Abnormalities*

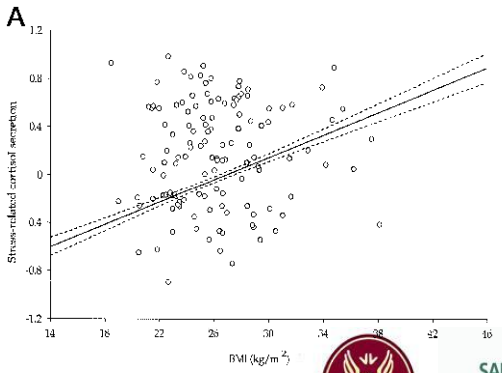
ROLAND ROSMOND, MARY F. DALLMAN, AND PER BJÖRNTORP

J Clin Endocrinol Metab '98

- Abdominal obesity
- Hypertension
- Hyperlipidemia
- Insulin resistance
- Poorly controlled T2DM
- PCOS







Non physiological conditions associated to Pseudo-Cushing state

RESPONSES TO CORTICOTROPIN-RELEASING HORMONE IN THE HYPERCORTISOLISM OF DEPRESSION AND CUSHING'S DISEASE

Pathophysiologic and Diagnostic Implications

PHILIP W. GOLD, M.D., D. LYNN LORIAUX, M.D., PH.D., ALEC ROY, M.D., MITCHEL A. KLING, M.D., JOSEPH R. CALABRESE, M.D., CHARLES H. KELLNER, M.D., LYNNETTE K. NIEMAN, M.D., ROBERT M. POST, M.D., DAVID PICKAR, M.D., WILLIAM GALLUCCI, B.S., PETER AVGERINOS, M.D., STEVEN PAUL, M.D., EDWARD H. OLDFIELD, M.D., GORDON B. CUTLER, JR., M.D., AND GEORGE P. CHROUSOS, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE '86

Corticotropin-Releasing Hormone: From Endocrinology to Psychobiology

Mark A. Smith[a], Mitchel A. Kling[a], Harvey J. Whitfield[a], Harry A. Brandt[a], Mark A. Demitrack[a], Thomas D. Geracioti[a], George P. Chrousos[b], Philip W. Gold[a]

Horm Res 1989;

Non physiological conditions associated to Pseudo-Cushing state

REVIEW

Alcohol-induced Cushing syndrome

Hypercortisolism caused by alcohol abuse

F. Besemer*, A.M. Pereira, J.W.A. Smit

Netherlands The Journal of Medicine JULY/AUGUST 2011, VOL. 69, NO 7/8

cohol this phenomenon was called alcohol-induced pseudo-Cushing's syndrome (1, 2). Alcohol-induced pseudo-Cushing's syndrome is indistinguishable from true Cushing's syndrome, although in the former less signs and symptoms seem to be present (3). Yanovski *et al.* (4) suggest the CRH test after administration of low-dose dexamethasone (2 mg/day for 2 days) to separate these two syndromes: a serum cortisol level above

results we paid attention to the population studied (normal/alcoholic) and the phase during which endocrinological testing was performed (actively drinking/abstinent). Furthermore, we subdivided the HPA axis into the various levels on which ethanol possibly exerts its effects.

Leiden, Rijnsbu

'96

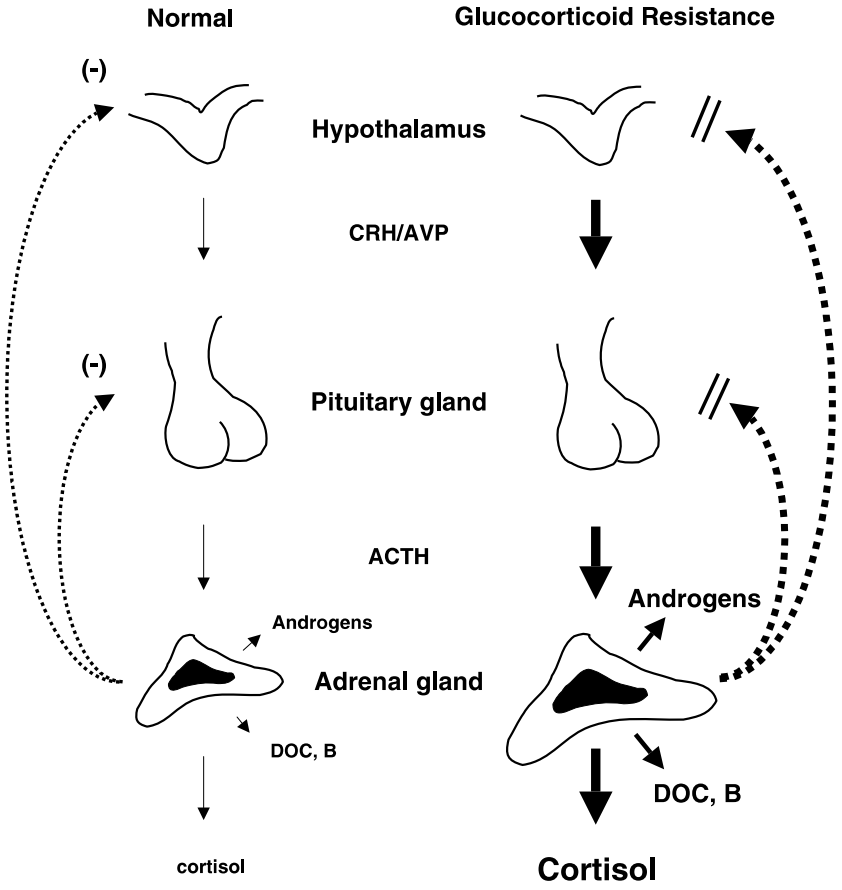
- ✧ Mechanism unclear
- ✧ Studies differently performed

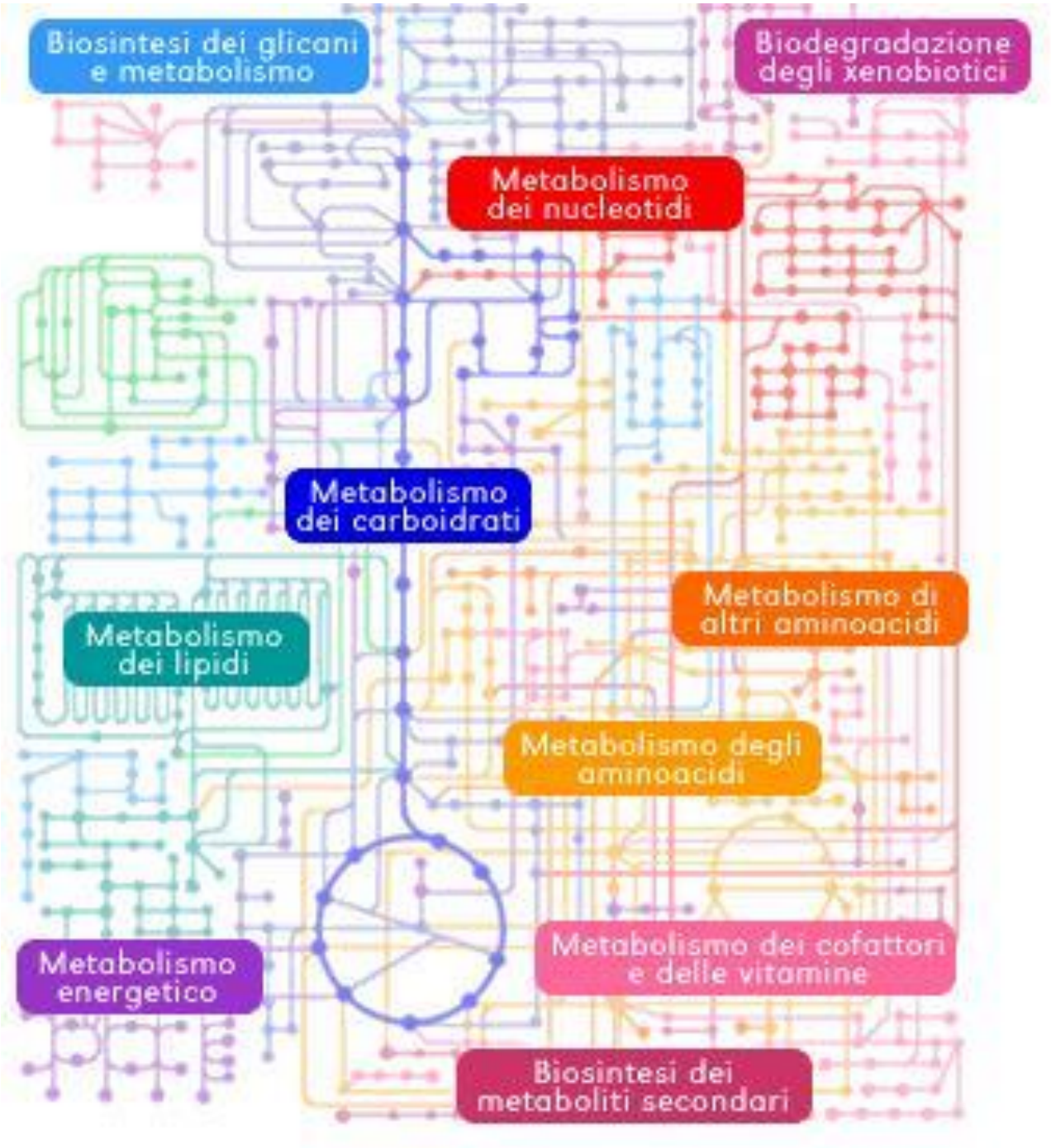
Non physiological conditions associated to Pseudo-Cushing state

Glucocorticoid and mineralocorticoid resistance/hypersensitivity syndromes

T Kino and **G P Chrousos**

Journal of Endocrinology (2001)





Clinical pictures and metabolic pathways

Clinical pictures and metabolic pathways

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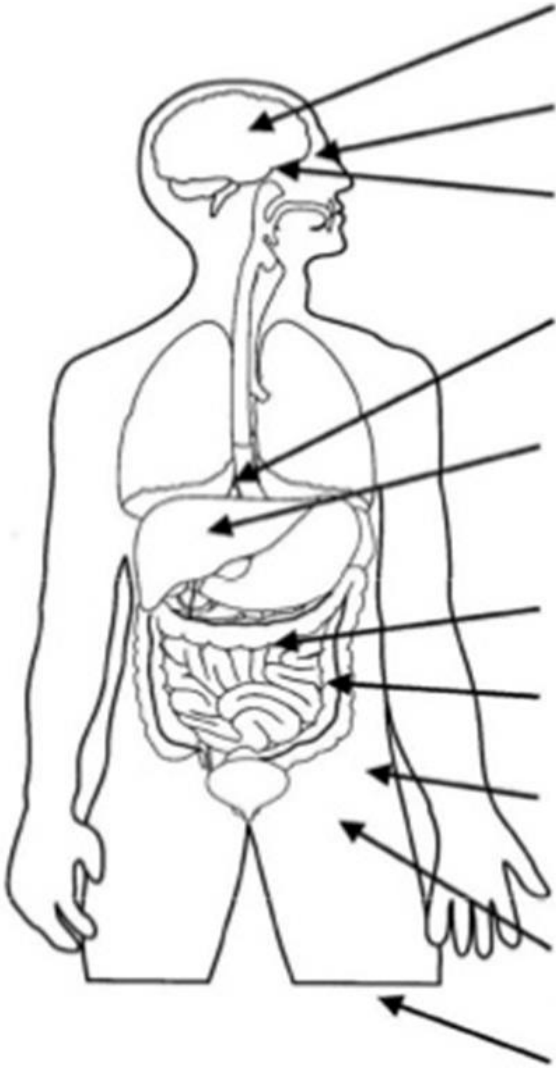
Cortisol effects



Cervello, SNC
Depressione, Psicosi

Occhi
Glaucoma

Sistema endocrino
↓ LH, FSH
↓ TSH
↓ GH

Metabolismo carboidrati
↑ deposito glicogeno
↑ resistenza insulina periferica
↑ gluconeogenesi
↑ produzione acidi grassi liberi
Effetto diabetogeno

Distribuzione tessuto adiposo
Obesità viscerale

Sistema cardiovascolare/renale
ritenzione Sali e acqua
ipertensione

Tessuto muscolare/connettivo
catabolismo proteine/collagene
assotigliamento cute e atrofia muscolare

Metabolismo osseo e calcio
osteoporosi

Sistema immunitario
azione anti-infiammatoria
immunosopressione

Clinical signs and symptoms of Cushing's syndrome	% frequency
Truncal obesity	79-97
Moon face	50-94
Glucose intolerance	39-90
Muscle weakness	29-90
Hypertension	74-87
Psychiatric alterations	31-86
Ecchymosis	23-84
Hirsutism	64-81
Menstrual change	55-80
Erectil dysfunction	55-80
Acne	26-80
Purple striae	51-71
Edema	28-60
Osteopenia and Osteoporosis	40-50
Polydipsia, polyuria	25-44
Nephrolithiasis	15-19
Pigmentation	4-16
Headache	0-47
Exophthalmus	0-33
T*inea versicolor* infection	0
Abdominal pain	0-21

Clinical signs and symptoms of Pseudo- Cushing's syndrome	% frequency
Moon face	90%
Muscle weakness	81%
Truncal obesity	75%
Purple striae	12.5%

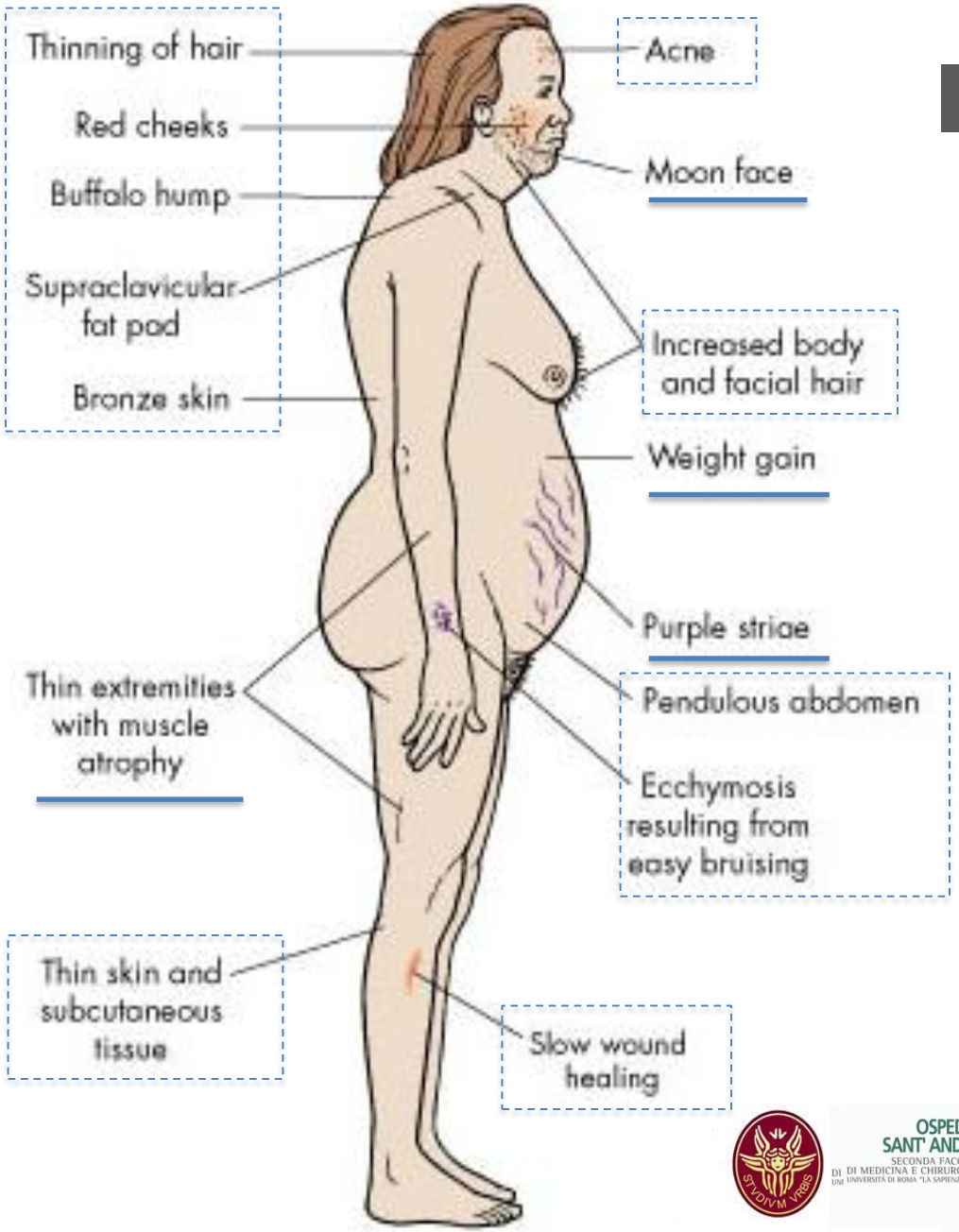
CUSHING'S SYNDROME—KILLING DISEASE: DISCRIMINATORY VALUE OF SIGNS AND SYMPTOMS AIDING EARLY DIAGNOSIS

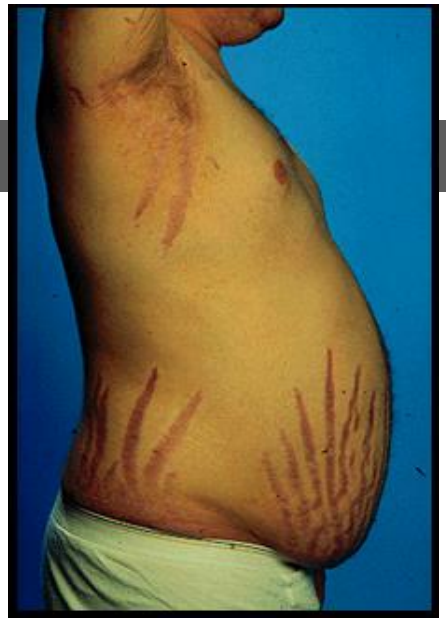
E. J. ROSS D. C. LINCH

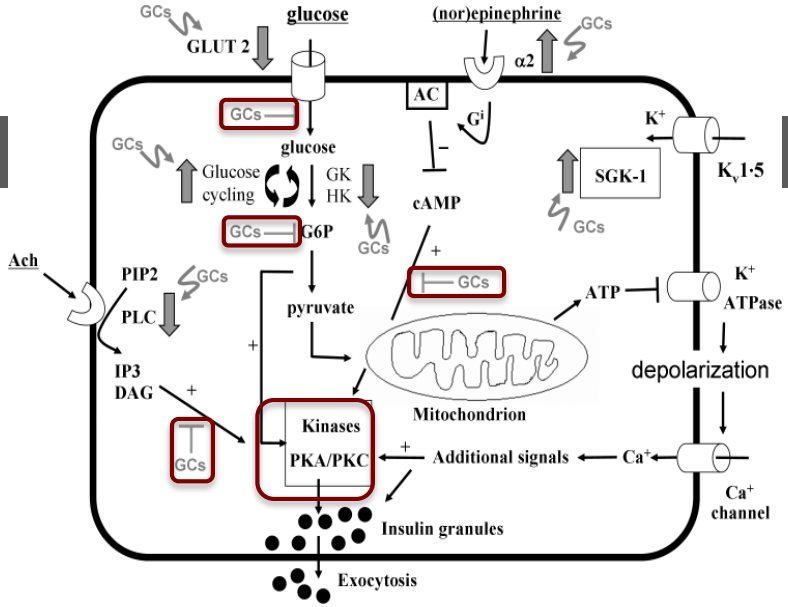
THE LANCET, SEPTEMBER 18, 1982

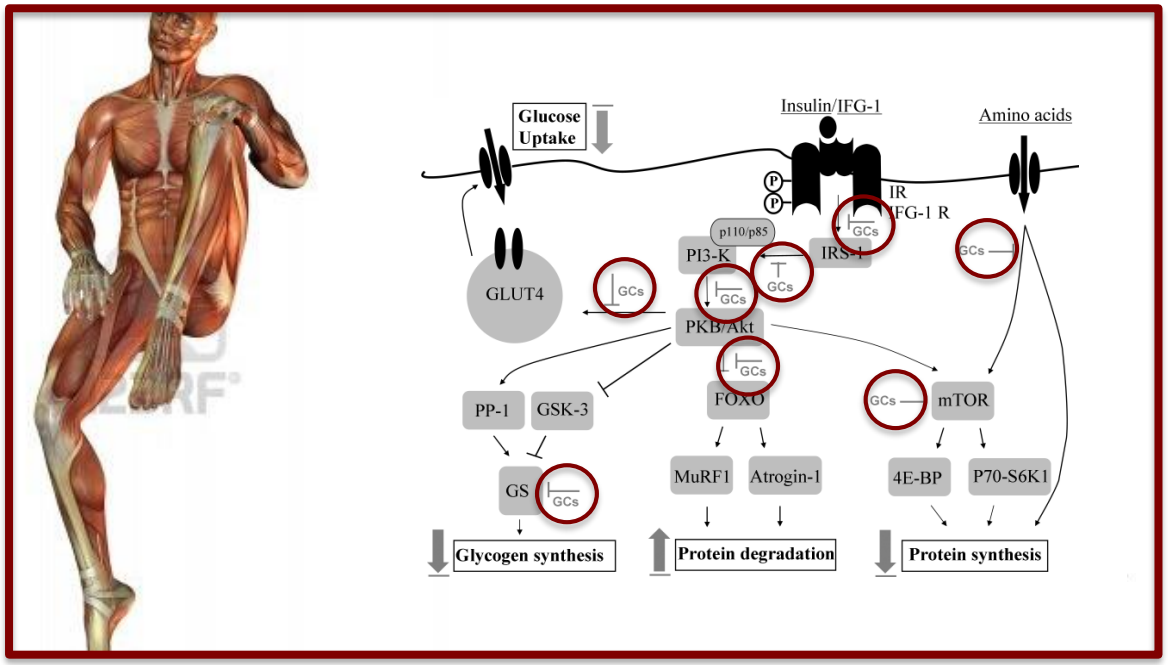
Clinical Cushing features

Clinical Pseudo-Cushing features









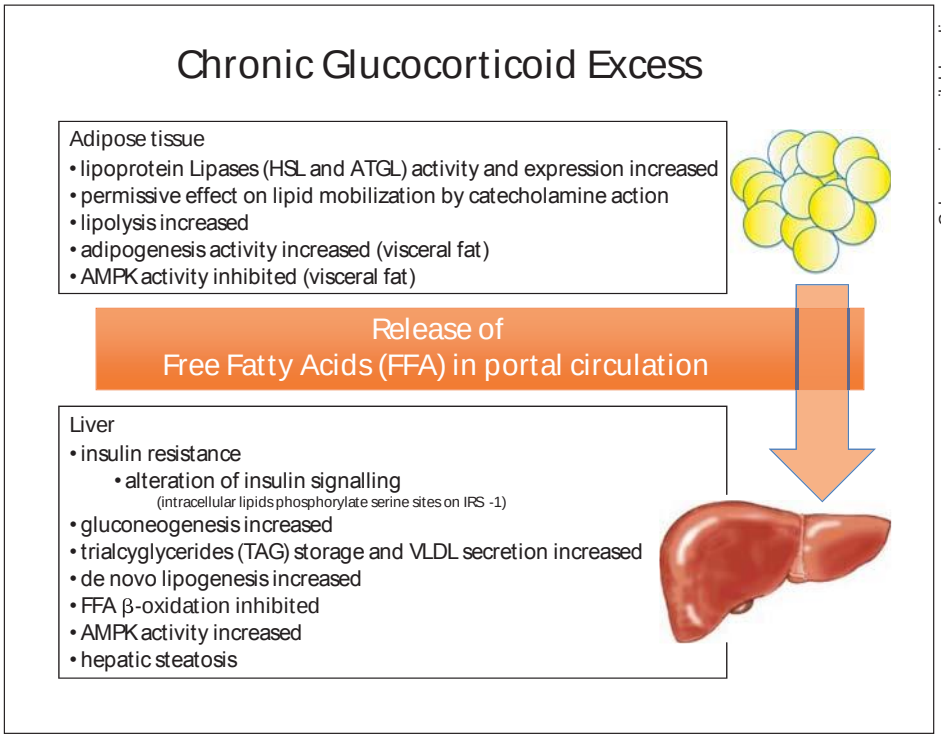
Van Raalte DH *et al*. modified

European Journal of Clinical Investigation '09

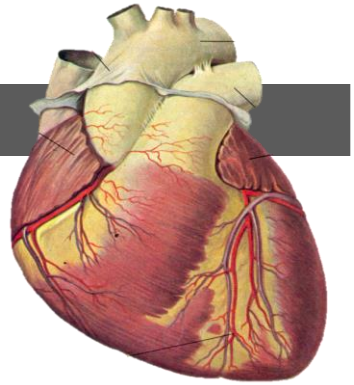
Pathophysiology of Dyslipidemia in Cushing's Syndrome

Giorgio Arnaldi Valerio Mattia Scandali Laura Trementino Marina Cardinaletti
Gloria Appolloni Marco Boscaro

Neuroendocrinology 201(



Heart damage in hypercortisolism



Heart failure

- ✧ Increased risk heart failure, myocardial infarction
- ✧ Left ventricular hypertrophy, concentric remodeling
- ✧ Myocardial fibrosis: glucocorticoid + mineralocorticoid combined effect
- ✧ ECG: QT interval prolongation (cardiotoxic effect cortisol)
- ✧ Vaso-vagal alterations: increased parasympathetic activity

Muiesan MI *et al*, J AmColl Card '03
Mihailidou AS *et al* Hypertension '09
Alexandraki KI *et al.* Clin Endocrinol '11
Fallo F *et al*, JEI '09

Cardiovascular Risk Factors and Common Carotid Artery Caliber and Stiffness in Patients with Cushing's Disease during Active Disease and 1 Year after Disease Remission

ANTONGIULIO FAGGIANO, ROSARIO PIVONELLO, STEFANO SPIEZIA, MARIA CRISTINA DE MARTINO, MARIAGIOVANNA FILIPPELLA, CAROLINA DI SOMMA, GAETANO LOMBARDI, AND ANNAMARIA COLAO

J Clin Endocrinol Metab 2003

Patients with Cushing's Syndrome Have Increase Intimal-Media Thickness at Different Vascular Levels: Comparison with a Population Matched for Similar Cardiovascular Risk Factor

N. Albiger, R.M. Testa, B. Almoto, M. Ferrari, F. Bilora, F. Petrobelli, A. Pagnan, F. Mantero, C. Scaroni

Horm Metab Res 2006; 38: 405-410

High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines

Tatiana Mancini*, Blerina Kola*, Franco Mantero†, Marco Boscaro* and Giorgio Arnaldi*

Clinical Endocrinology (2004) **61**, 768–777

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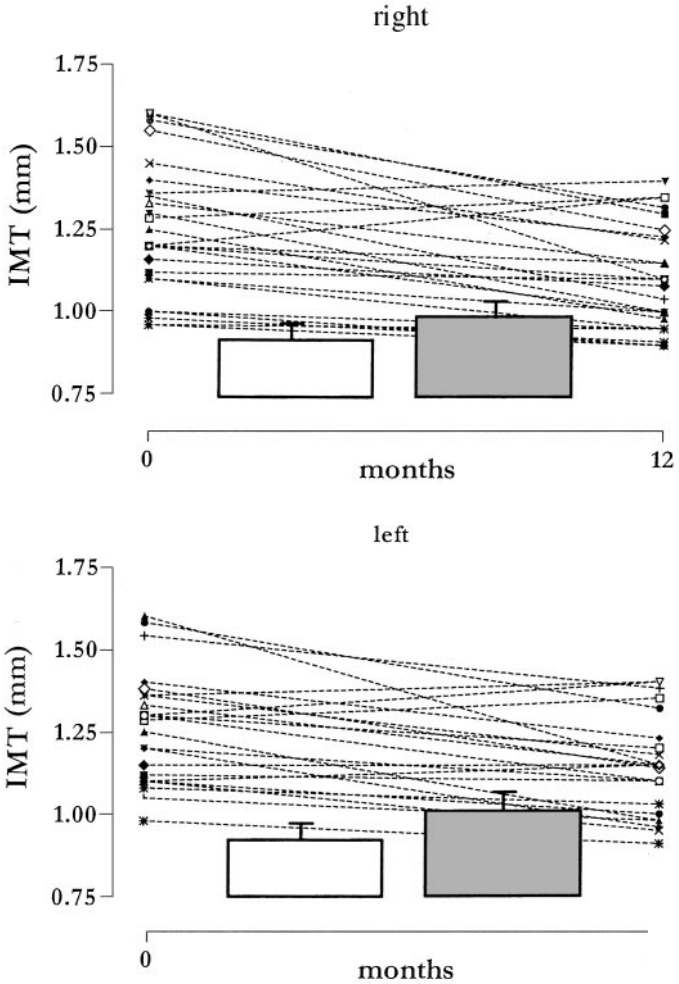
	Patients		Controls	
Serum triglyceride levels (mmol/liter)	1.95 ± 0.40	1.80 ± 0.30	1.51 ± 0.30	2.06 ± 0.40
Total blood cholesterol levels (mmol/liter)	6.20 ± 0.65[a]	5.50 ± 0.55	4.50 ± 0.40	5.66 ± 0.50
LDL-cholesterol levels (mmol/liter)	4.35 ± 0.60[c,e]	3.75 ± 0.50[a]	2.67 ± 0.30	3.85 ± 0.40
HDL-cholesterol levels (mmol/liter)	1.00 ± 0.08[b,c]	1.12 ± 0.09[c]	1.44 ± 0.06	1.31 ± 0.07
Total/HDL cholesterol ratio	6.10 ± 0.60[b,c]	5.10 ± 0.55[c]	3.10 ± 0.30	4.30 ± 0.40



before

after 1 year

J Clin Endocrinol Metab 2003

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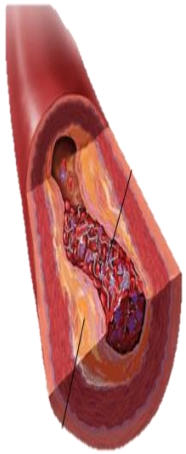
Review



The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications

Andrea M. Isidori[a], Chiara Graziadio[a], Rosa Maria Paragliola[b], Alessia Cozzolino[c], Alberto G. Ambrogio[d], Annamaria Colao[c], Salvatore M. Corsello[b], Rosario Pivonello[c], on behalf of the ABC Study Group

Journal of Hypertension 2015,

The renin – angiotensin system

The mineralocorticoid activity

The sympathetic nervous system

The vasoregulatory system

The vascular factor

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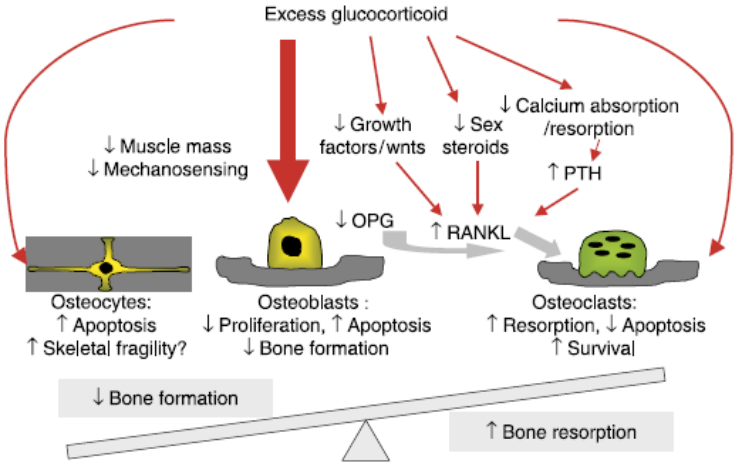
Treatment of skeletal impairment in patients with endogenous hypercortisolism: when and how?

A. Scillitani · G. Mazziotti · C. Di Somma · S. Moretti · A. Stigliano · R. Pivonello · A. Giustina · A. Colao · On behalf of ABC Group

Osteoporos Int (2014)



Neuro
endocrinology

Neuroendocrinology 2010;92(suppl 1):65–70
DOI: 10.1159/000314317

ORIGINAL ARTICLE

Endocrine Care

Subtle Cognitive Impairments in Patients with Long-Term Cure of Cushing's Disease

Jitske Tiemensma, Nienke E. Kokshoorn, Merlijn R. Biermasz, Bart-Jan A. Keijser, Moniek J. E. Wassenaar, Huub A. M. Middelkoop, Alberto M. Pereira and Johannes A. Romijn

(*J Clin Endocrinol Metab* 2010)

Conclusions: Cognitive function, reflecting memory and executive functions, is impaired in patients despite long-term cure of Cushing's disease.

Neuropsychiatric Disorders in Cushing's Syndrome

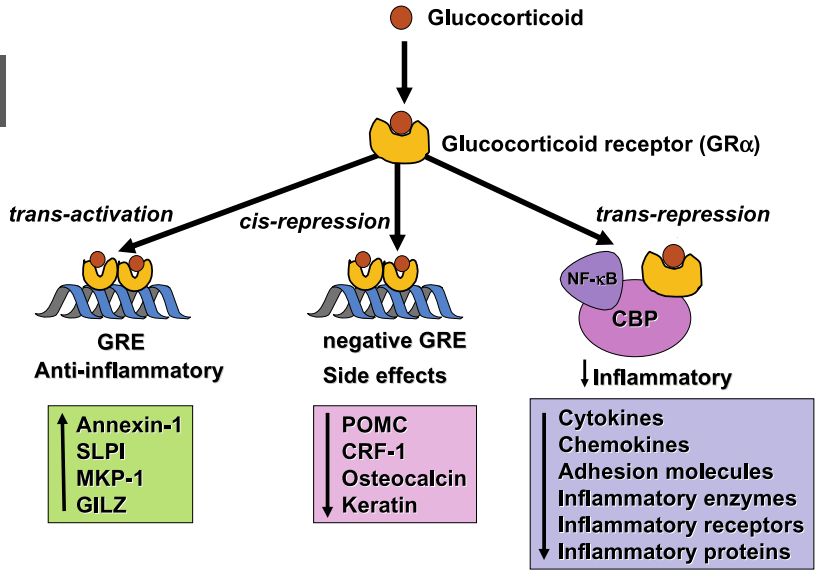
Alberto M. Pereira Jitske Tiemensma Johannes A. Romijn

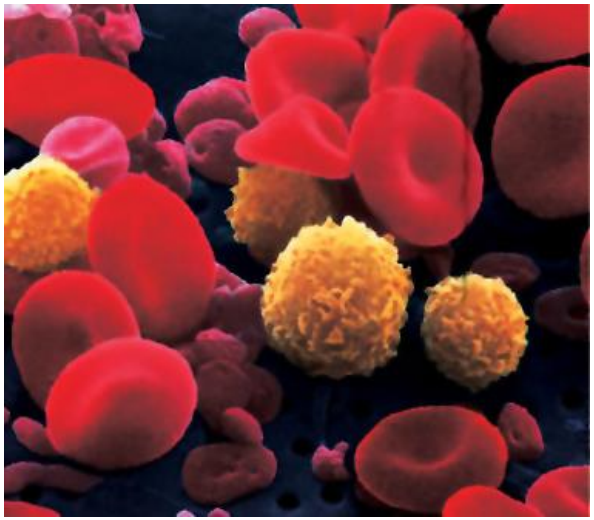
Glucocorticoids are crucial in the initiation and consolidation of the stress response. Patients with active Cushing's syndrome (CS) are exposed to excessive endogenous glucocorticoid levels. In these patients, psychopathology is often being observed. The most common co-morbid disorder is major depression, but to a lesser extent mania and anxiety disorders have also been reported. A severe clinical presentation of CS often also includes depression.

Psychiatric disorders

Peter J Barnes modified

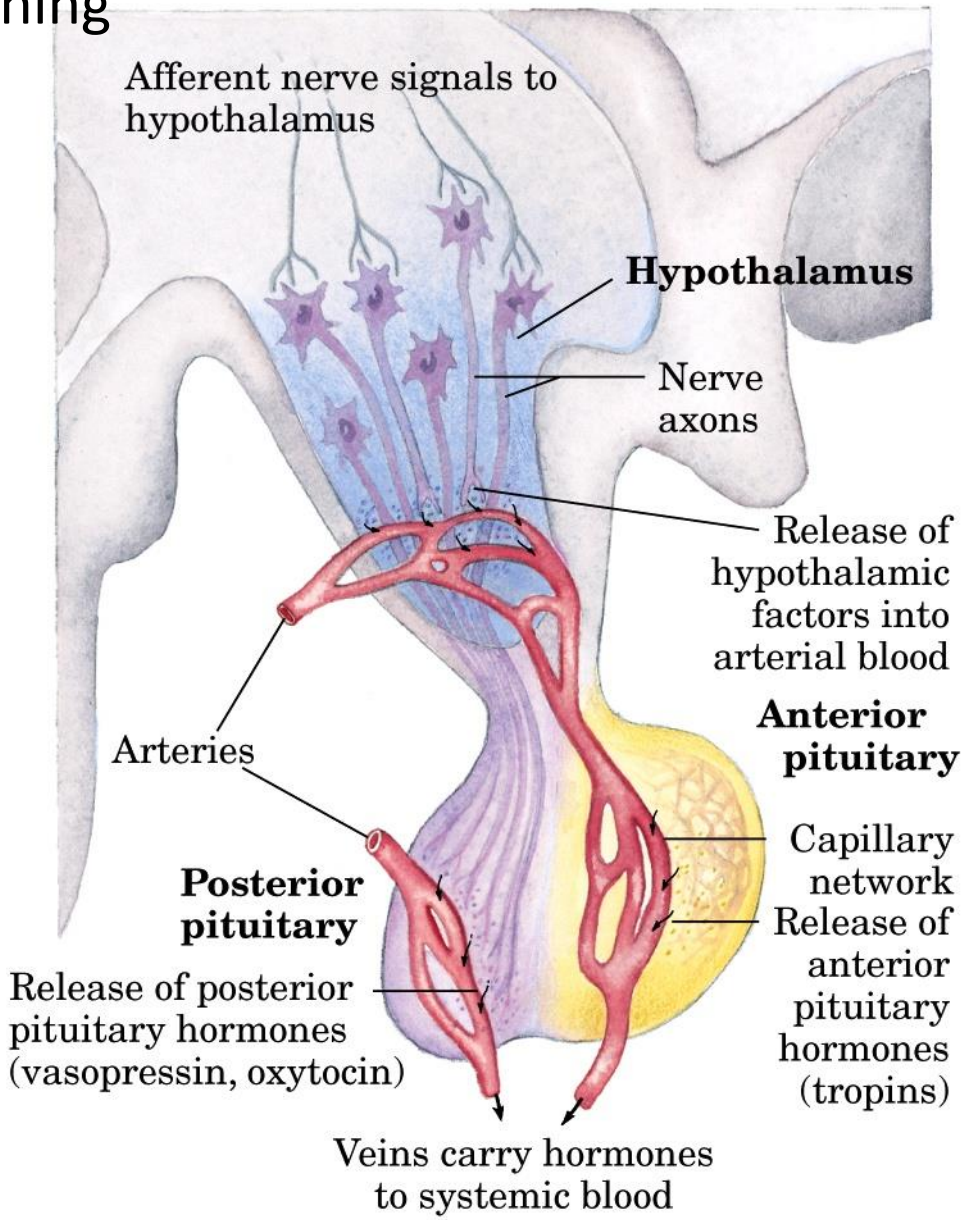
British Journal of Pharmacology 1476-5381.2010.



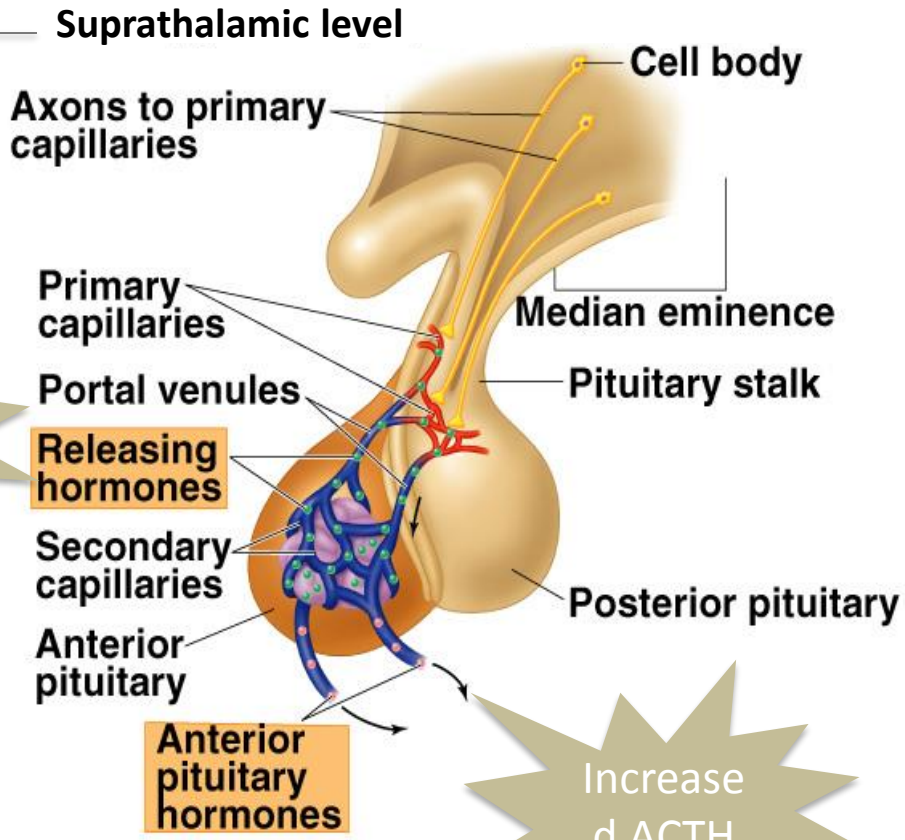


Depression & Pseudo-Cushing

- CRH administration is classically associated with depression
- An unsolved problem is the ineffectiveness of restoring a normal level of CRH in the presence of high cortisol levels
- Major depression is a heterogeneous syndrome:
  - increased level of CRH in depression and anorexia nervosa
  - significant decrease of CRH in "atypical depression" and Cushing



Hypotheses of alcohol mechanisms in Pseudo-Cushing



Increase d CRH

Different cortisol metabolism in CRH-secreting cells than other somatic cells after ethanol exposure

Increase d ACTH

Increase d Cortisol

Pituitary impaired responsiveness caused by down-regulation of CRH receptors or alchol interference at receptor or post-receptor level

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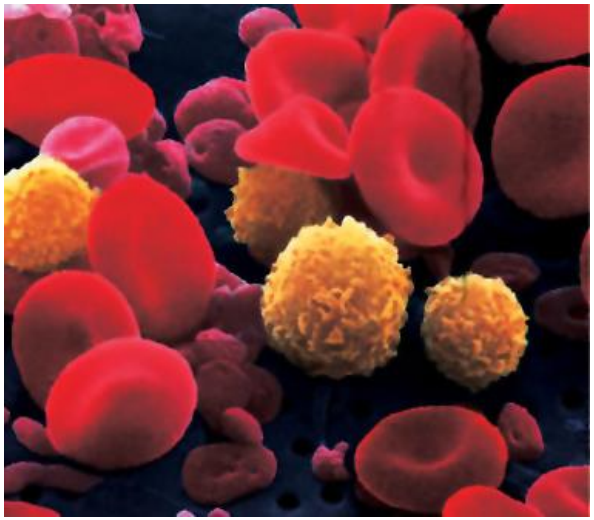
- Alcohol may influence the distribution of cortisol in the various blood compartments, leading to an increase in the amount of serum-free cortisol

- In alcoholic elevated serum-free cortisol levels are maintained, probably because of a defective resetting of the HPA axis

- The change in the cortisol distribution may influence the interaction between CBG and its membrane receptor activating the second messenger system



Manifestation of alcohol-induced pseudo-Cushing

- Both clinical and biochemical
- Only clinical
- Only biochemical
- Abuse and astinence from alcohol represent an evidence of the cyclical nature of Cushing (hormonal abnormalities disappear after a month abstinence from alcohol)
- Only some alcoholics develop Pseudo-Cushing: < 5%
  (different genetic background, different sensitivity to alcohol or cortisol)

Biochemical markers in Pseudo-Cushing

- Urinary free cortisol moderately elevated
- Dex test incompletely suppressed
- Circadian ritmicity blunted

Biochemical tests commonly used for the diagnosis of Cushing and Pseudo-Cushing

- ✧ Midnight serum or salivary cortisol
- ✧ Dexamethasone-CRH test
- ✧ Desmopressin test

Test used	Diagnostic Cut-off	Sensitivity (%)	Specificity (%)	reference
Midnight serum cortisol	7.5 µg/dl	96	100	19
	9.3 µg/dl	100	100	21
Midnight salivary cortisol	3.6 nmol/L	92	96	23
	15.2 nmol/L	93	100	24
CRH Test	basal serum cortisol >12 mg/dl and peak plasma ACTH>54 pg/ml	91.3	98.2	27
CRH Test	peak serum cortisol >21 mg/dl and peak plasma ACTH >45 pg/ml	94.8	91.2	27
Dexamethasone-CRH Test (serum cortisol 15 minutes after CRH administration)	1.4 µg/dl	100	100	20
	1.4 µg/dl	100	50	17
	1.4 µg/dl	100	62.5	21
	4 µ g/dl	100	86	21

(Attempt to) concluding remarks

Questions

1. Are depression symptoms, obesity, hirsutism, mestrual alteration the cause of HPA axis alterations or a consequence of cortisol excess?

2. We can consider these conditions such as a new source of cortisol excess?

3. We need to revise the definition of Cushing including causes indirectly related to the HPA axis?

4. We must provide a treatment to the Pseudo-Cushing beyond its resolution?

The Diagnosis and Differential Diagnosis of Cushing's Syndrome and Pseudo-Cushing's States

JOHN NEWELL-PRICE*, PETER TRAINER, MICHAEL BESSER, AND ASHLEY GROSSMAN

Endocrine Reviews 19(5): 647–672 '98

PseudoCushing: why a clinical challenge?

F. Pecori Giraldi[1,2]

J Endocrinol Invest '15

..... Michael Besser and Ashley Grossman headed the seminal review on pseudoCushing published nearly two decades ago [8], and I am sorry to state that only little progress has been made since then. .....

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Definition of Pseudo-Cushing state

Clinical and/or biochemical hypercortisolism characterized by a temporary activation of the HPA axis involving different pathways