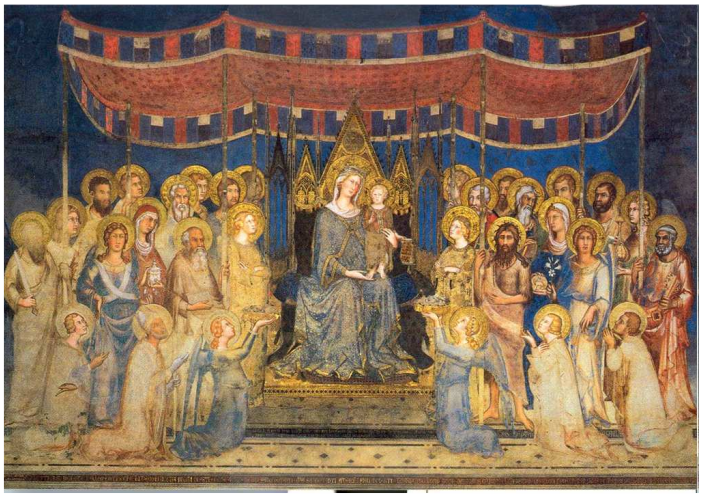
Simone Martini *(1330)* Guidoriccio da Fogliano all'assedio di Montemassi



Gli ormoni

1. Derivati di aminoacidi (dopamina*, catecolamine*, ormoni tiroidei**)
2. Piccoli neuropeptidi* (GnRH, TRH, somatostatina, ADH)
3. Proteine di grandi dimensioni* (insulina, LH, PTH)
4. Ormoni steroidei**
5. Derivati di vitamine** (retinoidi, vitamina D)

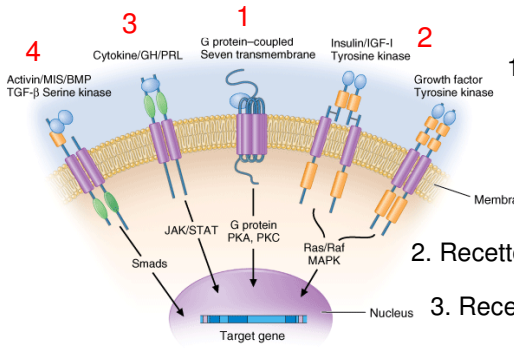
6. Fattori di crescita peptidici ad effetto locale*

Agiscono attraverso due classi di recettori

*recettori di membrana + cascata di signalling intracellulare

**recettori "nucleari" intracellulari

A. Recettori di membrana e loro vie di segnale



1. G-protein coupled 7 TM receptor (GPCR) family
2. Recettori tirosin chinasici
3. Recettori per citochine
4. Recettori serin chinasici

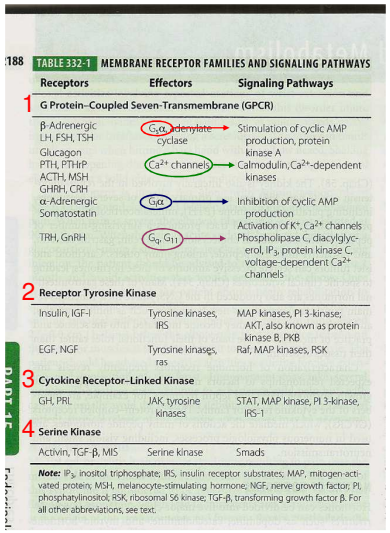
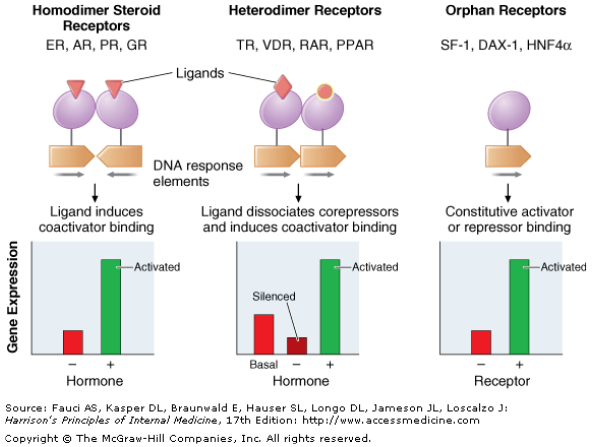


TABLE 332-1 MEMBRANE RECEPTOR FAMILIES AND SIGNALING PATHWAYS

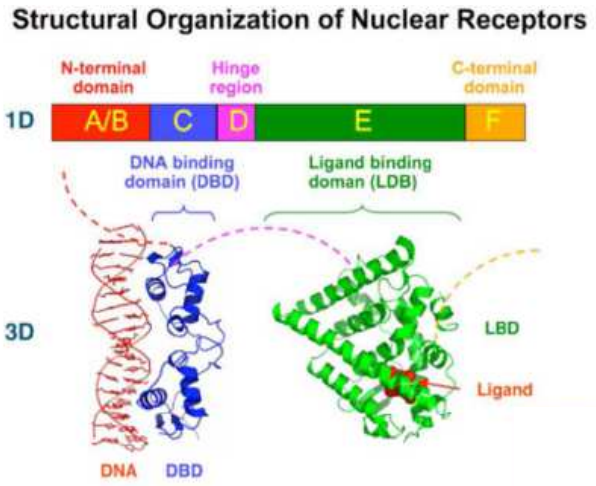
Receptors	Effectors	Signaling Pathways
1 G Protein–Coupled Seven-Transmembrane (GPCR)		
β-Adrenergic LH, FSH, TSH	$G_s\alpha$, adenylate cyclase	Stimulation of cyclic AMP production, protein kinase A
Glucagon PTH, PTHrP ACTH, MSH GHRH, CRH	Ca^{2+} channels	Calmodulin, Ca^{2+}-dependent kinases
α-Adrenergic Somatostatin	$G_i\alpha$	Inhibition of cyclic AMP production
TRH, GnRH	G_q, G_{11}	Activation of K^+, Ca^{2+} channels Phospholipase C, diacylglycerol, IP_3, protein kinase C, voltage-dependent Ca^{2+} channels
2 Receptor Tyrosine Kinase		
Insulin, IGF-I	Tyrosine kinases, IRS	MAP kinases, PI 3-kinase; AKT, also known as protein kinase B, PKB
EGF, NGF	Tyrosine kinases, ras	Raf, MAP kinases, RSK
3 Cytokine Receptor–Linked Kinase		
GH, PRL	JAK, tyrosine kinases	STAT, MAP kinase, PI 3-kinase, IRS-1
4 Serine Kinase		
Activin, TGF-β, MIS	Serine kinase	Smads

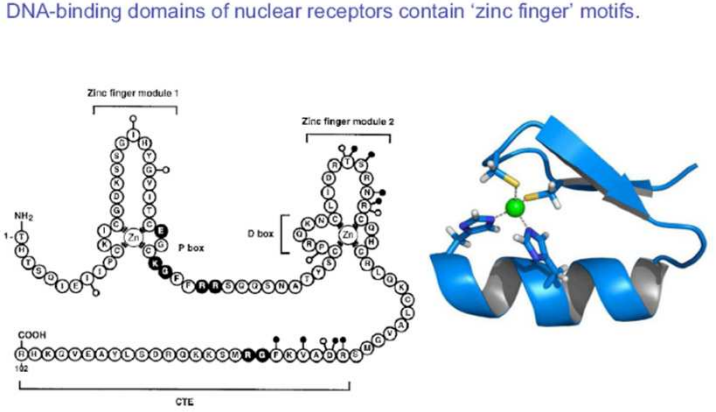
Note: IP_3, inositol triphosphate; IRS, insulin receptor substrates; MAP, mitogen-activated protein; MSH, melanocyte-stimulating hormone; NGF, nerve growth factor; PI, phosphatylinositol; RSK, ribosomal S6 kinase; TGF-β, transforming growth factor β. For all other abbreviations, see text.

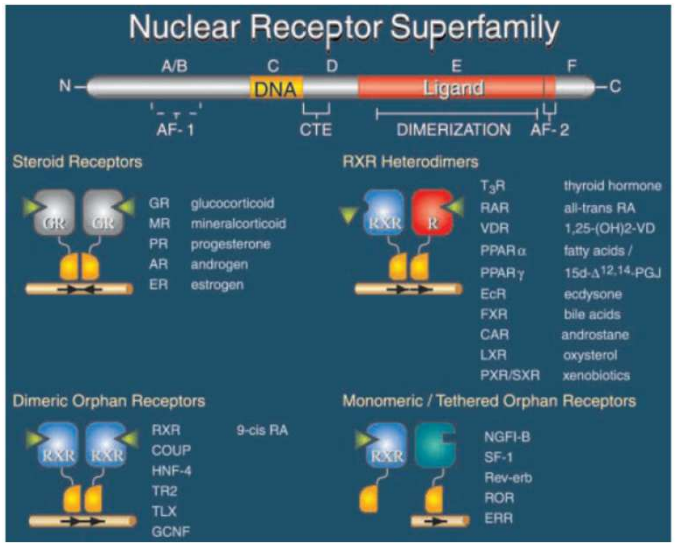
B. Recettori nucleari



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com







Nuclear Receptors, RXR, and the Big Bang

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Isolation of genes encoding the receptors for steroids, retinoids, vitamin D, and thyroid hormone and their structural and functional analysis revealed an evolutionarily conserved template for nuclear hormone receptors. This discovery sparked identification of numerous genes encoding related proteins, termed orphan receptors. Characterization of these orphan receptors and, in particular, of the retinoid X receptor (RXR) positioned nuclear receptors at the epicenter of the "Big Bang" of molecular endocrinology. This Review provides a personal perspective on nuclear receptors and explores their integrated and coordinated signaling networks that are essential for multicellular life, highlighting the RXR heterodimer and its associated ligands and transcriptional mechanism.

Table 1. Mammalian Nuclear Receptor Nomenclature and Ligands

Common Name	Common Abbreviation	Unified Nomenclature	Ligands
Androgen receptor	AR	NR3C4	androgens
Constitutive androstane receptor	CAR	NR1I3	xenobiotics
Chicken ovalbumin upstream promoter-transcription factor α	COUP-TFα	NR2F1	
Chicken ovalbumin upstream promoter-transcription factor β	COUP-TFβ	NR2F2	
Chicken ovalbumin upstream promoter-transcription factor γ	COUP-TFγ	NR2F6	
Dosage-sensitive sex reversal-adrenal hypoplasia congenital critical region on the X chromosome, gene 1	DAX-1	NR0B1	
Estrogen receptor α	ERα	NR3A1	estrogens
Estrogen receptor β	ERβ	NR3A2	estrogens
Estrogen related receptor α	ERRα	NR3B1	
Estrogen related receptor β	ERRβ	NR3B2	
Estrogen related receptor γ	ERRγ	NR3B3	
Farnesoid X receptor α	FXRα	NR1H4	bile acids
Farnesoid X receptor β[a]	FXRβ	NR1H5	
Germ cell nuclear factor	GCNF	NR6A1	
Glucocorticoid receptor	GR	NR3CI	glucocorticoids
Hepatocyte nuclear factor 4 α	HNF4α	NR2A1	[fatty acids]
Hepatocyte nuclear factor 4 γ	HNF4γ	NR2A2	[fatty acids]
Liver receptor homolog-1	LRH-1	NR5A2	[phospholipids]
Liver X receptor α	LXRα	NR1H3	oxysterols
Liver X receptor β	LXRβ	NR1H2	oxysterols
Mineralocorticoid receptor	MR	NR3C2	mineralocorticoids and glucocorticoids
Nerve-growth-factor-induced gene B	NGF1-B	NR4A1	
Neuron-derived orphan receptor 1	NOR-1	NR4A3	
Nur-related factor 1	NURR1	NR4A2	
Photoreceptor-cell-specific nuclear receptor	PNR	NR2E3	
Peroxisome proliferator-activated receptor α	PPARα	NR1C1	fatty acids
Peroxisome proliferator-activated receptor β/δ	PPARβ/δ	NR1C2	fatty acids
Peroxisome proliferator-activated receptor γ	PPARγ	NR1C3	fatty acids
Progesterone receptor	PR	NR3C3	progesterone
Pregnane X receptor	PXR	NR1I2	endobiotics and xenobiotics
Retinoic acid receptor α	RARα	NR1B1	retinoic acids
Retinoic acid receptor β	RARβ	NR1B2	retinoic acids
Retinoic acid receptor γ	RARγ	NR1B3	retinoic acids
Reverse-Erb α	REV-ERBα	NR1D1	[heme]
Reverse-Erb β	REV-ERBβ	NR1D2	[heme]
RAR-related orphan receptor α	RORα	NR1F1	[sterols]
RAR-related orphan receptor β	RORβ	NR1F2	[sterols]
RAR-related orphan receptor γ	RORγ	NR1F3	[sterols]
Retinoid X receptor α	RXRα	NR2B1	9-cis retinoic acid and docosahexanoic acid
Retinoid X receptor β	RXRβ	NR2B2	9-cis retinoic acid and docosahexanoic acid
Retinoid X receptor γ	RXRγ	NR2B3	9-cis retinoic acid and docosahexanoic acid
Steroidogenic factor 1	SF-1	NR5A1	[phospholipids]
Short heterodimeric partner	SHP	NR0B2	
Tailless homolog orphan receptor	TLX	NR2E1	
Testicular orphan receptor 2	TR2	NR2C1	
Testicular orphan receptor 4	TR4	NR2C2	
Thyroid hormone receptor α	TRα	NR1A1	thyroid hormones
Thyroid hormone receptor β	TRβ	NR1A2	thyroid hormones
Vitamin D receptor	VDR	NR1I1	1α,25-dihydroxyvitamin D_3 and lithocholic acid

Ligands in brackets indicate atypical ligands that, by structural studies, appear to be constitutively bound to their receptors.
[a]FXRβ exists only as a pseudogene in humans.

486 *Current Topics in Medicinal Chemistry*, 2012, *12*, 486-504

General Molecular Biology and Architecture of Nuclear Receptors

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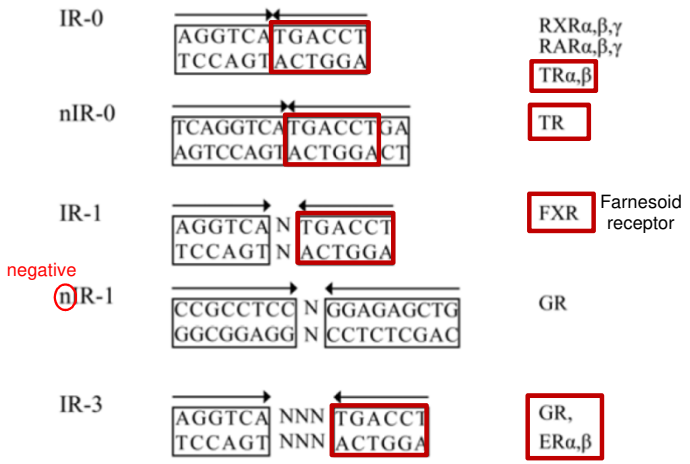
Abstract: Nuclear receptors (NRs) regulate and coordinate multiple processes by integrating internal and external signals, thereby maintaining homeostasis in front of nutritional, behavioral and environmental challenges. NRs exhibit strong similarities in their structure and mode of action: by selective transcriptional activation or repression of cognate target genes, which can either be controlled through a direct, DNA binding-dependent mechanism or through crosstalk with other transcriptional regulators, NRs modulate the expression of gene clusters thus achieving coordinated tissue responses. Additionally, non genomic effects of NR ligands appear mediated by ill-defined mechanisms at the plasma membrane. These effects mediate potential therapeutic effects as small lipophilic molecule targets, and many efforts have been put in elucidating their precise mechanism of action and pathophysiological roles. Currently, numerous nuclear receptor ligand analogs are used in therapy or are tested in clinical trials against various diseases such as hypertriglyceridemia, atherosclerosis, diabetes, allergies and cancer and others.

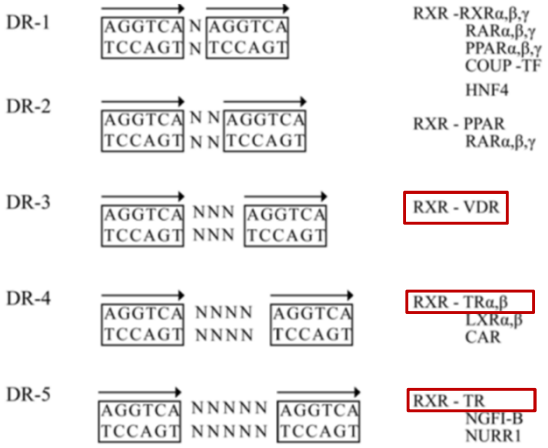
Fig. (3). ***Different architecture of selected response elements of nuclear receptors***. IR - inverted repeat, ER - everted repeat, DR - direct repeat, 'N' indicates any nucleotide, "n" indicates negative response elements.

IR= inverted repeat



ER= everted repeat

DR= direct repeat



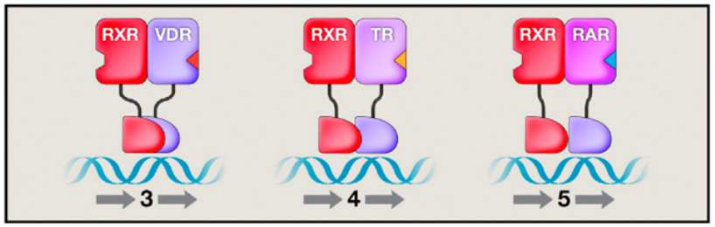
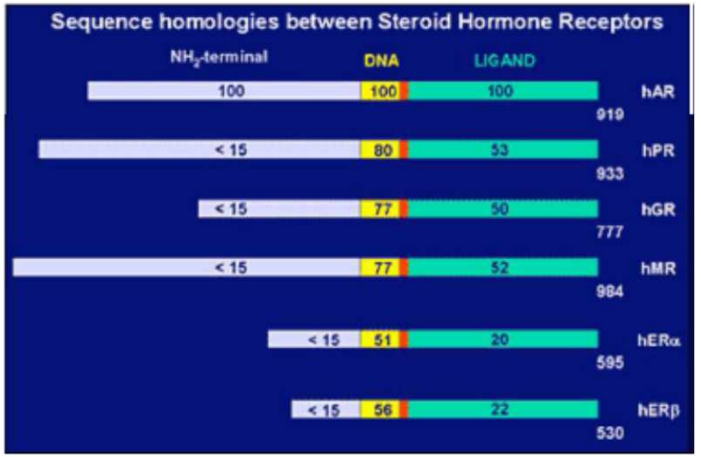
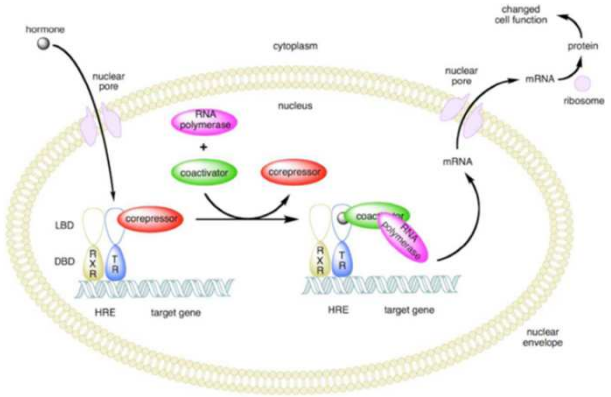


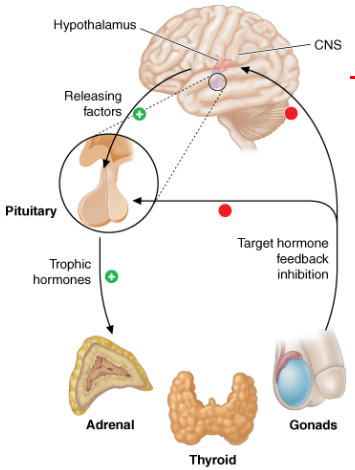
Figure 3. The 3-4-5 Rule
Receptors bind DNA as monomers to a single hexad motif, as homodimers to a palindrome of two hexad motifs, or as RXR heterodimers to a tandem repeat of the hexad motif. Heterodimers bind AGGTCA direct repeats (DRs) spaced by three (DR3; vitamin D response element), four (DR4; thyroid response element) or five (DR5; retinoic acid response element) nucleotides as described in the 3-4-5 rule.



Steroid hormones - are ligands for 'nuclear' receptors

Steroid hormones are often required to dimerize with a partner to activate gene transcription.



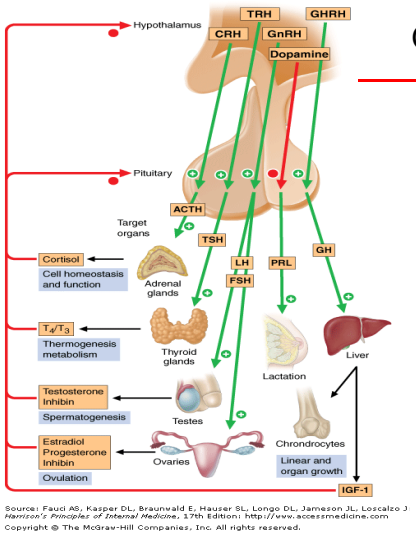


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

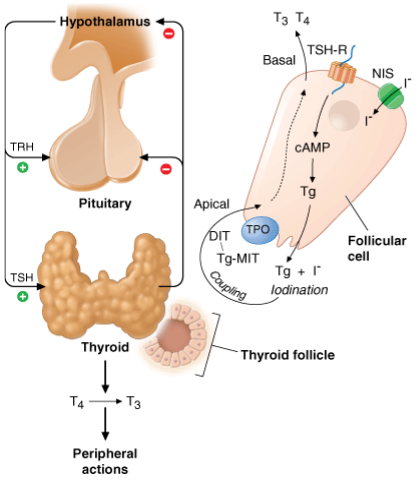
Gli assi endocrini

Meccanismi di regolazione a feedback

Gli assi ipofisari

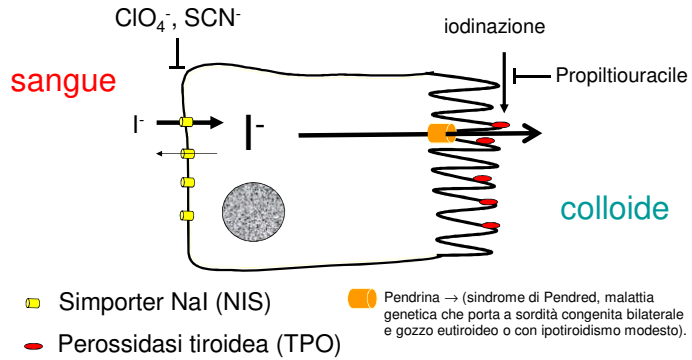


L'asse tiroideo

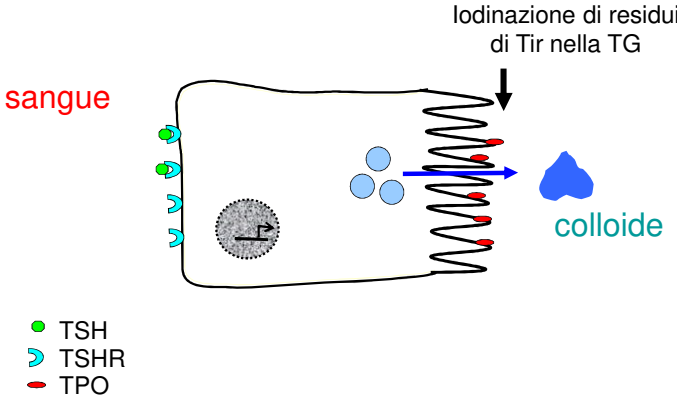


Regolazione della sintesi degli ormoni tiroidei

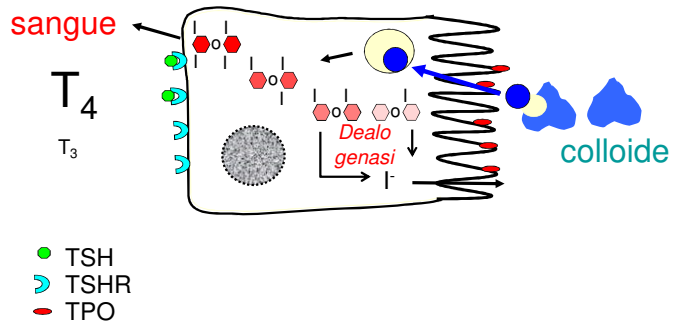
Trasporto di ioduro da parte della cellula follicolare della tiroide



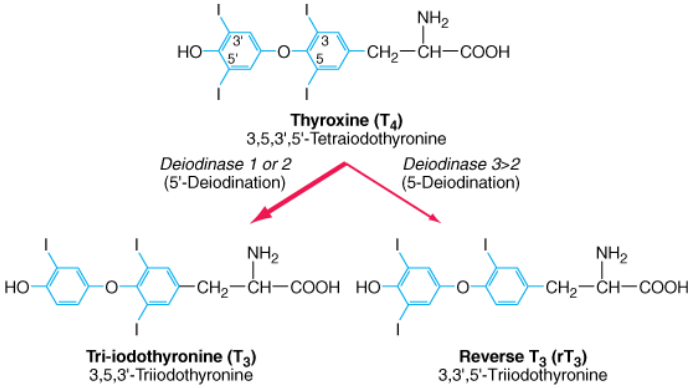
Sintesi della tireoglobulina



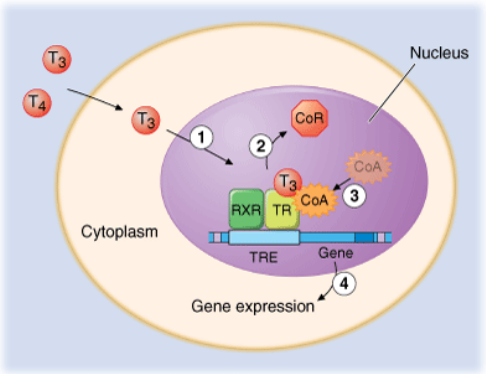
Increzione degli ormoni tiroidei



Gli ormoni tiroidei



Gli ormoni tiroidei – meccanismo d'azione



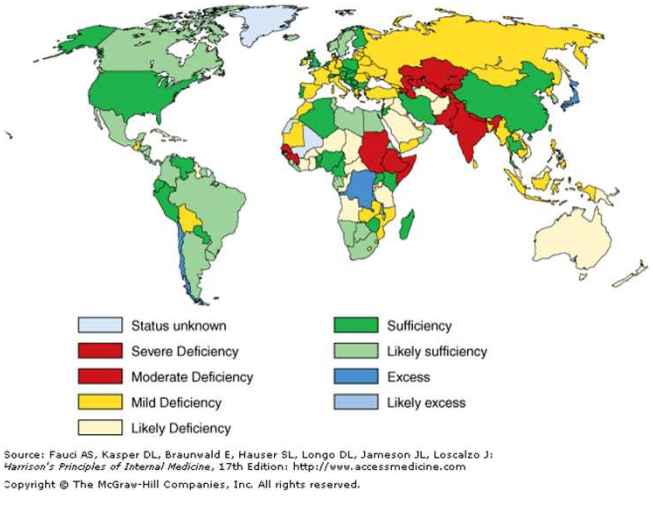
Cause di ipotiroidismo

Primary
- Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
- Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
- Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon-α and other cytokines, aminoglutethimide
- Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
- Iodine deficiency
- Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis
- Overexpression of type 3 deiodinase in infantile hemangioma

Transient
- Silent thyroiditis, including postpartum thyroiditis
- Subacute thyroiditis
- Withdrawal of thyroxine treatment in individuals with an intact thyroid
- After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

Secondary
- Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
- Isolated TSH deficiency or inactivity
- Bexarotene treatment
- Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Note: TSH, thyroid-stimulating hormone; TSH-R, TSH receptor.

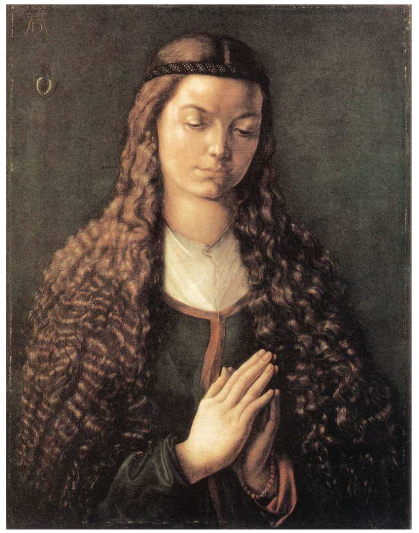


1614-20
Oil on canvas, 114 x 93.5 cm

Galleria Palatina (Palazzo Pitti), Firenze

Rogier van der Weyden

Madonna di Duràn
anni 1435-40
cm. 99,5 x 50,4
Prado, Madrid.



Albrecht Dürer, Portrait of a Young Fürleger with Loose Hair
1497
Oil on canvas, 56 x 43 cm
Städelsches Kunstinstitut, Frankfurt

THYROID
Volume 18, Number 4, 2008
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Commentary

The Many Reasons Why Goiter Is Seen in Old Paintings

J. Barry Ferriss

Introduction

GOITER IS OFTEN SEEN IN PAINTINGS from over the centuries, for a variety of reasons. Most goiters were painted incidentally; the artist's model had an iodine deficiency (endemic) goiter, and the artist painted what he, or rarely she, saw. Occasionally, an incidental goiter may have been due to another cause, such as postpartum thyroiditis or perhaps rarely defective thyroid hormone biosynthesis ("dyshormonogenesis").

Although the great majority were portrayed by chance, sometimes a goiter was deliberately included. The purpose may have been to elicit an emotion such as pity or revulsion, to mock or to indicate a person's place of origin (1). In addition, goiter has been included as a sign of poverty: it also has been used autobiographically and even as an erotic device.

The great artistic innovations of the Renaissance, perspective and the study of human anatomy (2), led to clear and realistic works of art. While goiter may be seen or suspected in paintings from before this time, it is particularly well illustrated in works from the Renaissance (3) and Baroque eras, and to an extent in the output of the periods that followed.

With the arrival of Impressionism, however, techniques changed and detail often became less important. From about the same time, the increasing use of photography lessened the need for clear and lifelike pictures. For these reasons and because of the decline of endemic goiter in at least some Western countries (4), goiter is seen less often in more recent paintings.

A few of the great array of pictures that include endemic goiter will be reviewed. Other reasons for goiter appearing in old paintings and drawings will also be illustrated.

Iodine-Deficiency (Endemic) Goiter

Iodine deficiency goiter is often seen in old paintings, as endemic goiter was common in much of Europe in the past (5). When an artist's model had a goiter, this was faithfully reproduced. A small goiter was sometimes considered an adornment (5,6) and indeed may have been thought of as normal (5). Goiter was particularly common in mountainous areas such as central Italy and Switzerland (7). For example, at least 41% of women and 24% of men were judged to have goiter in portraits dating from the Renaissance to the 20th century, in the canton of Berne in Switzerland (8). Goiter is often seen in Renaissance and Baroque paintings in Florence, at the foothills of the Apennine Mountains; it is rare, however, in works of the same era in Venice, on the iodine-rich sea.

Up to the age of puberty the prevalence of iodine deficiency goiter is similar in males and females, but thereafter it is much higher among women. The prevalence peaks in early adult life and subsequently falls with age in both sexes (9). This explains why most paintings with endemic goiter are of young women.

Endemic goiter is seen in the beautiful *Judith and Her Maidservant* by the early 17th-century Italian artist Artemisia Gentileschi (Fig. 1). We see a smooth round swelling in the young woman's neck (6).

There are innumerable other instances of endemic goiter in paintings. Goiter is seen in many other Italian works, such as those by Raphael, Botticelli, and del Sarto (not shown). Goiter is also occasionally visible in paintings from Northern Europe, such as the lovely *Virgin and Child* by Rogier van der Weyden (Fig. 2) and in several works by Rubens and by Durer (not shown). Other examples are reported elsewhere (5).

A good illustration of how goiter was copied is seen in the two versions of *The Finding of Moses*, by Orazio Gentileschi (Fig. 3). In the original painting Pharaoh's daughter has a goiter, with both thyroid lobes being clearly visible. In the second, more refined version, almost certainly copied from the first (10), Pharaoh's daughter again has a goiter, very similar in outline to that in the original. The full picture was copied with variations, but the goiter has been accurately reproduced, a feature that art historians may have overlooked.

Pregnancy and Postpartum Thyroiditis

It has long been known that the thyroid gland increases in size during normal pregnancy for a number reasons, including increased iodine loss (9). The thyroid may enlarge by up to 50% in areas of even mild iodine deficiency and may not fully regress after delivery (11). It seems plausible to suppose that the goiter of an artist's model was from time to time increased by a current or previous pregnancy.

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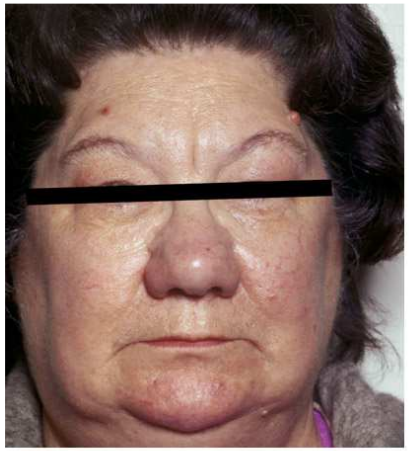
Cork, Ireland.

Thyroid (2008)
18, 387

Sintomi e segni dell'ipotiroidismo

(in ordine decrescente di frequenza)

Symptoms	Signs
Tiredness, weakness	Dry coarse skin; cool peripheral extremities
Dry skin	Puffy face, hands, and feet (myxedema)
Feeling cold	Diffuse alopecia
Hair loss	Bradycardia
Difficulty concentrating and poor memory	Peripheral edema
Constipation	Delayed tendon reflex relaxation
Weight gain with poor appetite	Carpal tunnel syndrome
Dyspnea	Serous cavity effusions
Hoarse voice	
Menorrhagia (later oligomenorrhea or amenorrhea)	
Paresthesia	
Impaired hearing	



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

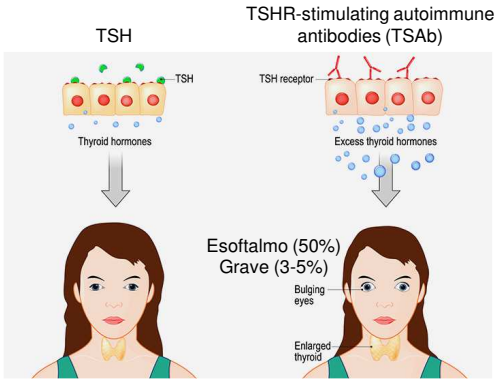
Cause di tireotossicosi

Primary hyperthyroidism
- Graves' disease
- Toxic multinodular goiter
- Toxic adenoma
- Functioning thyroid carcinoma metastases
- Activating mutation of the TSH receptor
- Activating mutation of $G_{s\alpha}$ (McCune-Albright syndrome)
- Struma ovarii
- Drugs: iodine excess (Jod-Basedow phenomenon)

Thyrotoxicosis without hyperthyroidism
- Subacute thyroiditis
- Silent thyroiditis
- Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
- Ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue

Secondary hyperthyroidism
- TSH-secreting pituitary adenoma
- Thyroid hormone resistance syndrome: occasional patients may have features of thyrotoxicosis
- Chorionic gonadotropin-secreting tumors[a] → TSH basso
- Gestational thyrotoxicosis[a]

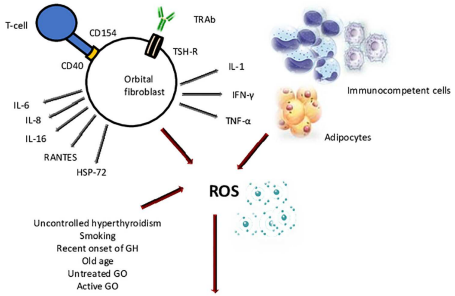
Morbo di Flaiani-Basedow-Graves
Flaiani 1805, Graves 1835, von Basedow, 1840



Normale Gozzo tossico diffuso

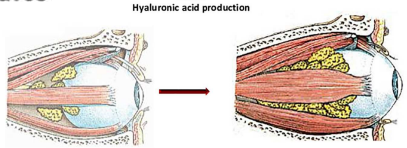
Morbo di Flaiani-Basedow-Graves
Flaiani 1805, Graves 1835, von Basedow, 1840

Marty Feldman
1934 – 1982



Antioxidant Therapy in Graves' Orbitopathy

Lanzolla G, Marcocci C and Marinò M (2020) Antioxidant Therapy in Graves' Orbitopathy. Front. Endocrinol. 11:608733. doi: 10.3389/fendo.2020.608733



Normal eye Graves' Orbitopathy

European Thyroid Journal

Research Article

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Modulating TSH Receptor Signaling for Therapeutic Benefit

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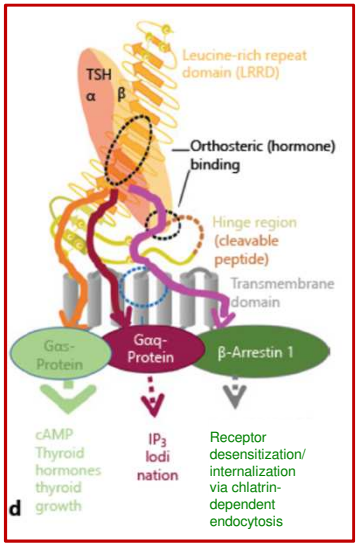
Autoimmune thyroid-stimulating antibodies are activating the thyrotropin receptor (TSHR) in both the thyroid and the eye, but different molecular mechanisms are induced in both organs, leading to Graves' disease (GD) and Graves' orbitopathy (GO), respectively. Therapy with anti-thyroid drugs to reduce hyperthyroidism (GD) by suppressing the biosynthesis of thyroid hormones has only an indirect effect on GO, since it does not causally address pathogenic TSHR activation itself. GO is thus very difficult to treat. The activated TSHR but also the cross-interacting insulin-like growth factor 1 receptor (IGF-1R) contribute to this issue. The TSHR is a heptahelical G-protein-coupled receptor, whereas the IGF-1R is a receptor tyrosine kinase. Despite these fundamental structural differences, both receptors are phosphorylated by G-protein receptor kinases, which enables β-arrestin binding. Arrestins mediate receptor internalization and also activate the mitogen-activated protein kinase pathway.



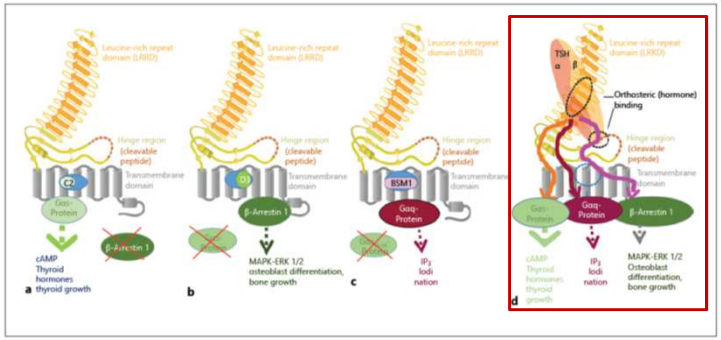


Fig. 5. Biased positive allosteric modulators (agonists) of the TSHR. Schemes of biased interaction in the allosteric binding pocket (blue). **a** C2 [4] activates only cAMP and not the β-arrestin pathway. **b** D3 [77] recruits only β-arrestin 1 and thereby activates the MAPK-ERK1/2 pathway. Gαs is not activated. **c** BSM1 [78] activates only Gαq and neither Gαs nor $Gα_{12-13}$. **d** Extracellular bound TSH activates all 3 pathways. In conclusion, different intramolecular signaling pathways are present in the TSHR, which could be blocked individually by small molecules.

Krause et al (2020) Eur. Thyroid J. 9, 66-77

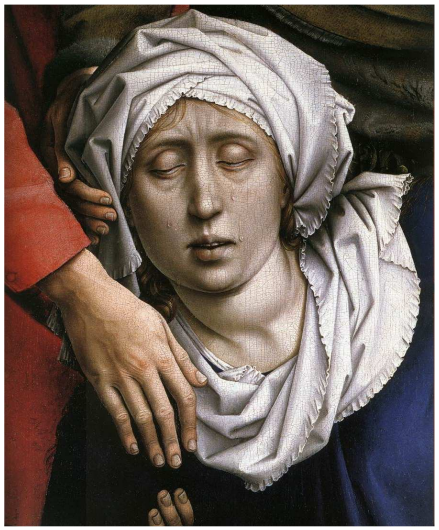
β-Arrestin has 2 main tasks, initializing receptor desensitization/internalization (clathrin-mediated endocytosis) and/or activation of mitogen-activated protein kinase (MAPK). The latter activation is followed by phosphorylation of extracellular signal-regulated kinases (ERK), p38, and AKT (protein kinase B) [4, 36]. The TSHR is predominantly internalized by β-arrestin 2 [37]. TSH-induced β-arrestin 1 signaling via MAPK/ERK is involved in osteoblast differentiation [4]. Arrestin 1 scaffolds TSHR and IGF-1R to enable crosstalk [37].

Sintomi e segni della tireotossicosi

(in ordine decrescente di frequenza)

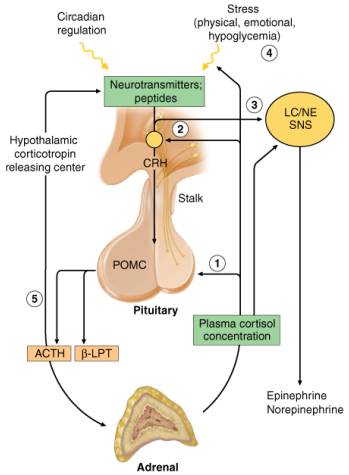
Symptoms	Signs[a]
Hyperactivity, irritability, dysphoria	Tachycardia; atrial fibrillation in the elderly
Heat intolerance and sweating	Tremor
Palpitations	Goiter
Fatigue and weakness	Warm, moist skin
Weight loss with increased appetite	Muscle weakness, proximal myopathy
Diarrhea	Lid retraction or lag
Polyuria	Gynecomastia
Oligomenorrhea, loss of libido	

[a]Excludes the signs of ophthalmopathy and dermopathy specific for Graves' disease.



Rogier van der WEYDEN
Deposition (detail)
c. 1435
Oil on oak panel
Museo del Prado
Madrid

L'asse ipotalamo-ipofisi-corticosurrene



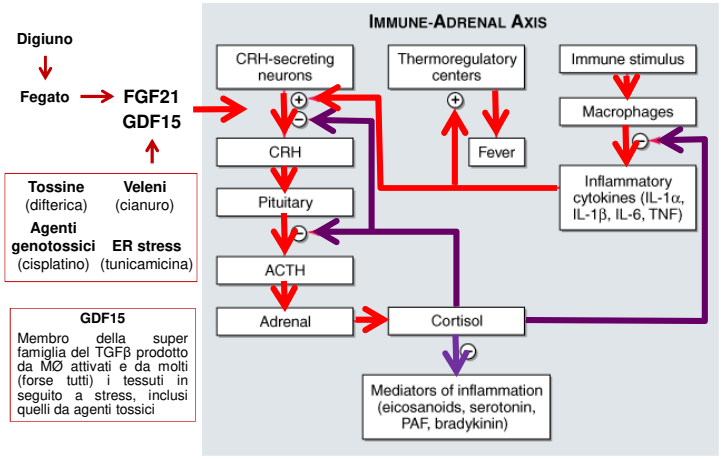
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Activation of the hypothalamic–pituitary–adrenal axis by exogenous and endogenous GDF15

PNAS 2021 Vol. 118 No. 27 e2106868118

Irene Cimino[a,1], Hanna Kim[b,1], Y. C. Loraine Tung[a], Kent Pedersen[c], Debra Rimmington[a], John A. Tadross[a,d], Sara N. Kohnke[a], Ana Neves-Costa[a], André Barros[a], Stephanie Joaquim[b], Don Bennett[a], Audrey Melvin[a], Samuel M. Lockhart[a], Anthony J. Rostron[a,e], Jonathan Scott[a], Hui Liu[a], Keith Burling[a], Peter Barker[f], Menna R. Clatworthy[f,g,h], E-Chiang Lee[a], A. John Simpson[a], Giles S. H. Yeo[a], Luis F. Moita[a,e], Kendra K. Bence[b], Sebastian Beck Jorgensen[a], Anthony P. Coll[a], Danna M. Breen[b], and Stephen O'Rahilly[a,2]

An acute increase in the circulating concentration of glucocorticoid hormones is essential for the survival of severe somatic stresses. Circulating concentrations of GDF15, a hormone that acts in the brain to reduce food intake, are frequently elevated in stressful states. We now report that GDF15 potently activates the hypothalamic–pituitary–adrenal (HPA) axis in mice and rats. A blocking antibody to the GDNF-family receptor α-like receptor completely prevented the corticosterone response to GDF15 administration. In wild-type mice exposed to a range of stressful stimuli, circulating levels of both corticosterone and GDF15 rose acutely. In the case of *Escherichia coli* or lipopolysaccharide injections, the vigorous proinflammatory cytokine response elicited was sufficient to produce a near-maximal HPA response, regardless of the presence or absence of GDF15. In contrast, the activation of the HPA axis seen in wild-type mice in response to the administration of genotoxic or endoplasmic reticulum toxins, which do not provoke a marked rise in cytokines, was absent in *Gdf15*$^{-/-}$ mice. In conclusion, consistent with its proposed role as a sentinel hormone, endogenous GDF15 is required for the activation of the protective HPA response to toxins that do not induce a substantial cytokine response. In the context of efforts to develop GDF15 as an antiobesity therapeutic, these findings identify a biomarker of target engagement and a previously unrecognized pharmacodynamic effect, which will require monitoring in human studies.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Losca
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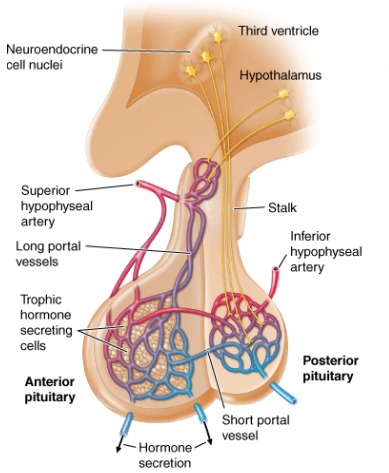

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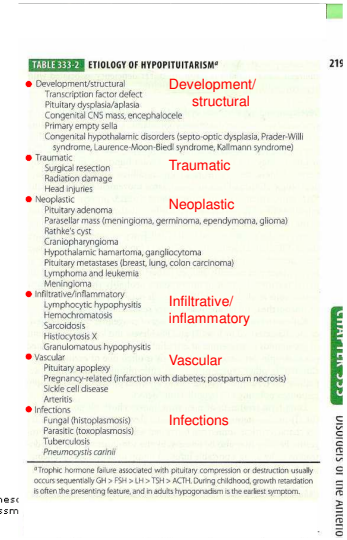


TABLE 333-2 ETIOLOGY OF HYPOPITUITARISM[a]

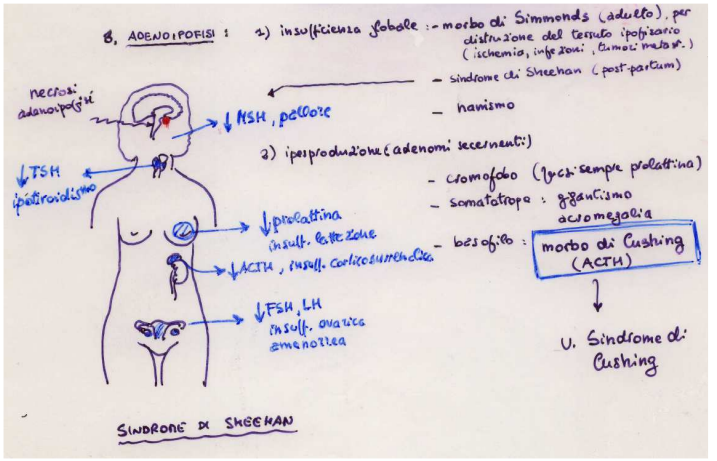
- Development/structural
  - Transcription factor defect
  - Pituitary dysplasia/aplasia
  - Congenital CNS mass, encephalocele
  - Primary empty sella
  - Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Kallmann syndrome)
- Traumatic
  - Surgical resection
  - Radiation damage
  - Head injuries
- Neoplastic
  - Pituitary adenoma
  - Parasellar mass (meningioma, germinoma, ependymoma, glioma)
  - Rathke's cyst
  - Craniopharyngioma
  - Hypothalamic hamartoma, gangliocytoma
  - Pituitary metastases (breast, lung, colon carcinoma)
  - Lymphoma and leukemia
  - Meningioma
- Infiltrative/inflammatory
  - Lymphocytic hypophysitis
  - Hemochromatosis
  - Sarcoidosis
  - Histiocytosis X
  - Granulomatous hypophysitis
- Vascular
  - Pituitary apoplexy
  - Pregnancy-related (infarction with diabetes; postpartum necrosis)
  - Sickle cell disease
  - Arteritis
- Infections
  - Fungal (histoplasmosis)
  - Parasitic (toxoplasmosis)
  - Tuberculosis
  - *Pneumocystis carinii*

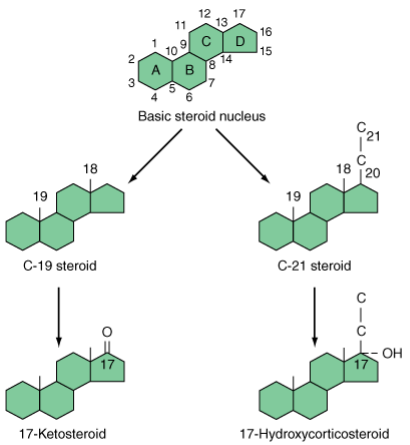
Development/ structural
Traumatic
Neoplastic
Infiltrative/ inflammatory
Vascular
Infections

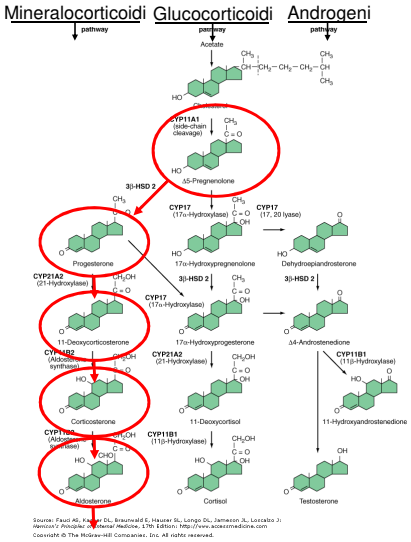
[a]Trophic hormone failure associated with pituitary compression or destruction usually occurs sequentially GH > FSH > LH > TSH > ACTH. During childhood, growth retardation is often the presenting feature, and in adults hypogonadism is the earliest symptom.

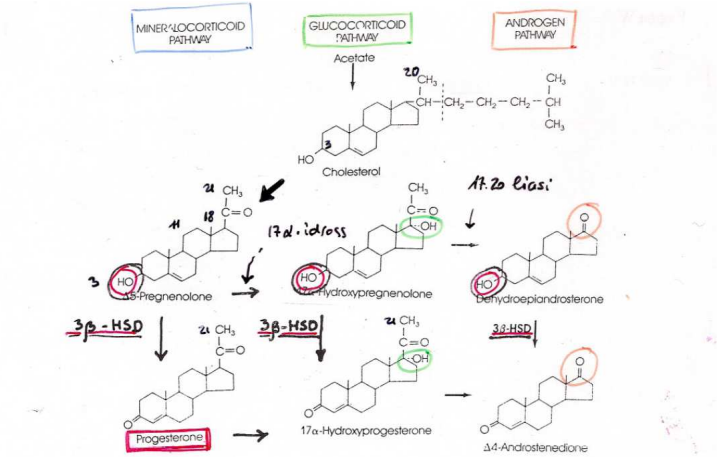
A. Neuroipofisi

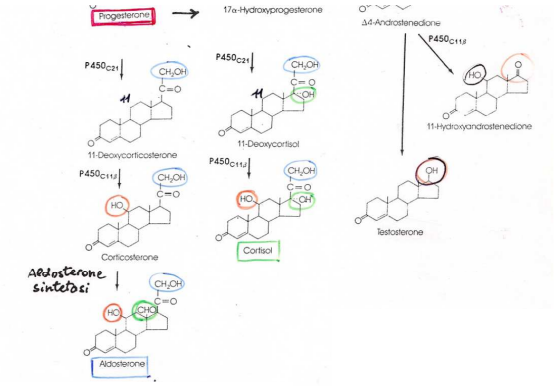
Vedi equilibrio idrosalino



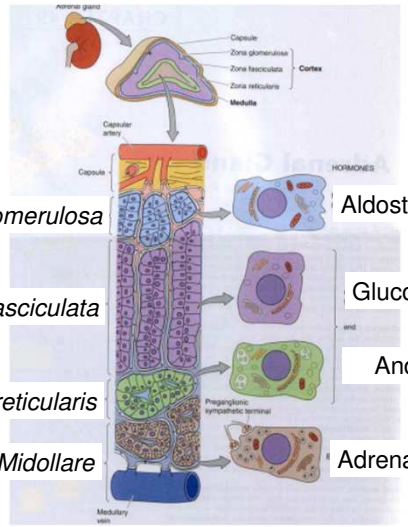








Via dei mineralocorticoidi | Via dei glucocorticoidi | Via degli androgeni



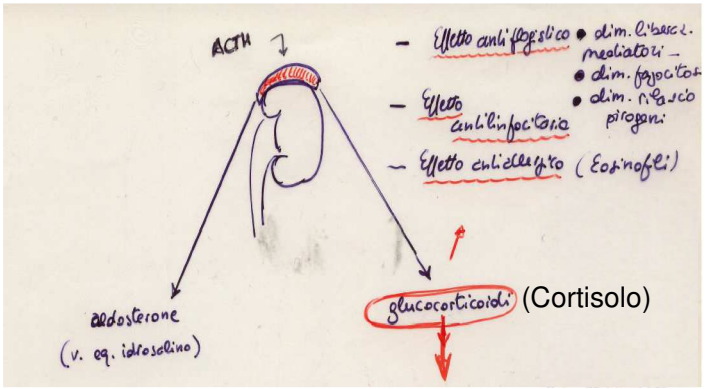
Zona glomerulosa Aldosterone

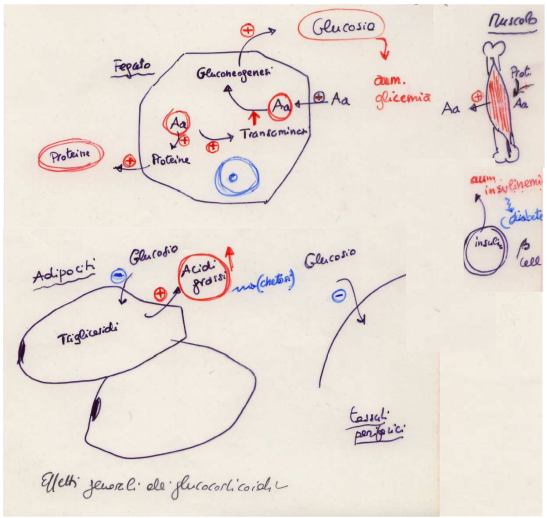
Zona fasciculata Glucocorticoidi

Androgeni

Zona reticularis

Midollare Adrenalina

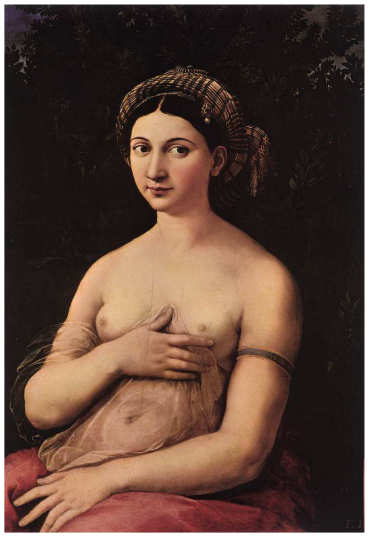




Potenza relativa di corticosteroidi naturali e di sintesi

Name	Glucocorticoid potency	Mineralocorticoid potency	Duration of action ($t_{1/2}$ in hours)
Hydrocortisone (Cortisol)	1	1	8
Cortisone acetate	0.8	0.8	oral 8, intramuscular 18+
Prednisone	3.5-5	0.8	16-36
Prednisolone	4	0.8	16-36
Methylprednisolone	5-7.5	0.5	18-40
Dexamethasone	25-80	0	36-54
Betamethasone	25-30	0	36-54
Triamcinolone	5	0	12-36
Fludrocortisone acetate	15	200	-
Deoxycorticosterone acetate	0	20	-
Aldosterone	0.3	200-1000	-

Ma …. l'affinità del MR per cortisone e aldosterone è la stessa (mentre il GR lega solo i glucocorticoidi); e la concentrazione circolante del cortisolo è molto più alta di quella dell'aldosterone. Come è possibile allora che si realizzi l'effetto dell'aldosterone se il recettore è "occupato" dal cortisolo?



RAFFAELLO Sanzio
Ritratto di giovane
(La Fornarina,1518-19)
Galleria Nazionale
d'Arte Antica, Roma

Medicine and art

Lancet 2002; **360:** 2061–63

The portrait of breast cancer and Raphael's *La Fornarina*

Carlos Hugo Espinel

Diagnosis

La Fornarina's deformation might be a depiction of five clinical signs: a mass, a retraction, skin discoloration, a possible lymph node and arm swelling. The discoloration suggests skin invasion, perhaps into the dermatic lymphatics, and the arm swelling, lymphoedema. La Fornarina's signs are compatible with the diagnosis of cancer of the left breast, at an advanced stage.

La Fornarina presents signs that not only are diagnostic but also allow staging of the malignancy. Dated at about 1520,[3,4] Raphael's painting precedes Severinus's scientific report by 100 years.[3,4] It also precedes all reported depictions of breast cancer in art.[17,18] The portrait is, therefore, a very early, perhaps the first, graphic evidence of breast cancer.

CORRESPONDENCE

THE LANCET • Vol 361 • March 29, 2003 • www.thelancet.com

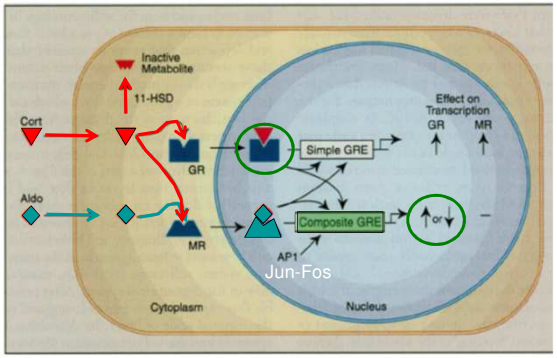
e-mail submissions to correspondence@lancet.com

***La Fornarina*: breast cancer or not?**

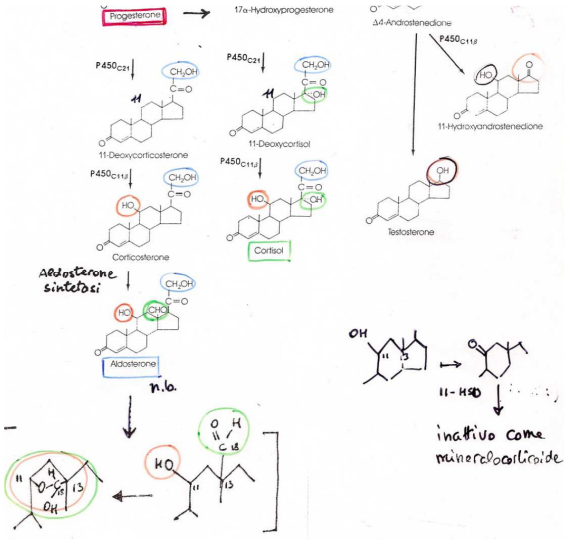
Mineralocorticoids, Glucocorticoids, Receptors and Response Elements

John W. Funder

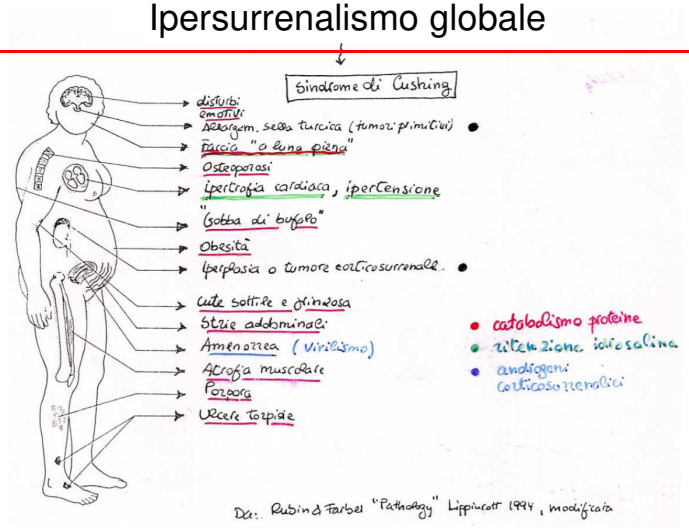
SCIENCE • VOL. 259 • 19 FEBRUARY 1993 1132–1133



[commento su Pierce & Yamamoto (1993) Science 259, 1161-1165]



Ipersurrenalismo globale



Journal of Clinical Investigation
Vol. 42, No. 4, 1963

IN VIVO AND *IN VITRO* STUDIES OF ADRENAL SECRETIONS IN CUSHING'S SYNDROME AND PRIMARY ALDOSTERONISM *

By EDWARD G. BIGLIERI, SATOSHI HANE, PAUL E. SLATON, JR., AND PETER H. FORSHAM WITH THE TECHNICAL ASSISTANCE OF MARY ANNE HERRON AND SHIRO HORITA

(*From the Metabolic Research Unit and the Department of Medicine, University of California School of Medicine, San Francisco, Calif.*)

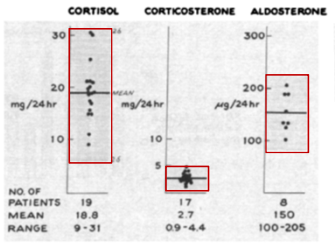


FIG. 1. SECRETORY RATES IN NORMAL SUBJECTS. Stippled areas indicate 2 SD.

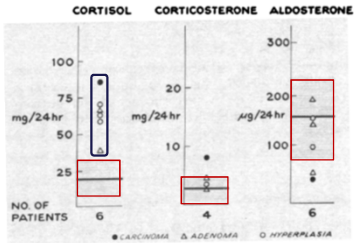


FIG. 2. SECRETORY RATES IN CUSHING'S SYNDROME. Stippled areas indicate 2 SD in normal subjects.

SUMMARY

In Cushing's syndrome, cortisol secretion was consistently elevated. Corticosterone secretion was normal, except in a single case of malignancy. Aldosterone secretion ranged from normal to low. Analysis of hyperplastic glands showed normal concentrations of cortisol, 11-desoxycortisol, aldosterone, corticosterone, and desoxycorticosterone. Analysis of adenomas revealed normal cortisol content, lowered corticosterone content, and low to absent aldosterone content. The suppressed ipsilateral adrenal gland revealed low cortisol and corticosterone content, but normal amounts of aldosterone, desoxycorticosterone, and 11-desoxycortisol. Patients with Cushing's syndrome had normal urinary aldosterone. The suppressed adrenal tissue remaining in patients who had adenomas surgically removed, as well as that in two patients who had prolonged steroid therapy, was capable of secreting normal amounts of aldosterone.

In primary aldosteronism, cortisol secretion was normal. In three of seven patients, there was an increase in corticosterone secretion. Aldosterone secretion was greatly increased. The tumor's content of cortisol was normal, but there was increased content of corticosterone, desoxycorticosterone, and aldosterone. Normal aldosterone secretion and responses are preserved in the presence of exogenous or endogenous cortisol excess.

Endocrine (2020) 70:607–615
https://doi.org/10.1007/s12020-020-02460-9

ORIGINAL ARTICLE

Apparent mineralocorticoid excess caused by novel compound heterozygous mutations in *HSD11B2* and characterized by early-onset hypertension and hypokalemia

Peng Fan[1] · Yi-Ting Lu[1] · Kun-Qi Yang[1] · Di Zhang[2] · Xue-Ying Liu[1] · Tao Tian[1] · Fang Luo[1] · Lin-Ping Wang[1] · Wen-Jun Ma[1] · Ya-Xin Liu[2] · Hui-Min Zhang[1] · Lei Song[1] · Jun Cai[1] · Ying Lou[1] · Xian-Liang Zhou[1]

Apparent mineralocorticoid excess (AME, OMIM #218030) is an ultrarare autosomal recessive form of monogenic hypertension. Although the biochemical and hormonal features of AME were first described in 1977 by New et al. [1], the first causative mutation in *HSD11B2* was not discovered until 1995 in a consanguineous Iranian family with AME [2]. Since then, only ~100 AME cases have been described clinically and genetically worldwide, and the prevalence of AME remains uncertain. However, AME is most commonly found in consanguineous families or certain ethnic groups [3–5].

AME is characterized by juvenile hypertension, hypokalemia, hypernatremia, low plasma renin activity and aldosterone concentration, metabolic alkalosis, and responsiveness to spironolactone [6]. It has a spectrum of phenotypes ranging from life-threatening hypertension in infancy to a milder form of the disease in adults [7]. Because of the broad diversity and overlapping clinical features, precise diagnosis of AME is highly reliant on genetic evidence [8].

AME is caused by a mutation in *HSD11B2*, which has been mapped to chromosome 16q22 and consists of five exons. It encodes 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), which is a microsomal enzyme mainly expressed in mineralocorticoid target tissues, such as distal nephron [9]. 11βHSD2 plays an important role in the peripheral inactivation of cortisol to cortisone, thus protecting the mineralocorticoid receptor (MR) from inappropriate activation by cortisol [10]. *HSD11B2* mutations lead to a deficiency in the 11βHSD2 enzyme [11], resulting in excessive cortisol stimulating the MR and causing intense water and sodium retention, hypokalemia, and hypertension [12].

Widespread Negative Response Elements Mediate Direct Repression by Agonist-Liganded Glucocorticoid Receptor

Milan Surjit,[1] Krishna Priya Ganti,[1,2] Atish Mukherji,[1,2] Tao Ye,[1] Guoqiang Hua,[1] and Pierre Chambon[1,*]
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Cell 145, 224–241, April 15, 2011

The glucocorticoid (GC) receptor (GR), when liganded to GC, activates transcription through direct binding to simple (+)GRE DNA binding sequences (DBS). GC-induced direct repression via GR binding to complex "negative" GREs (nGREs) has been reported. However, GR-mediated transrepression was generally ascribed to indirect "tethered" interaction with other DNA-bound factors. We report that GC-induces direct transrepression via the binding of GR to simple DBS (IR nGREs) unrelated to (+)GRE. These DBS act on agonist-liganded GR, promoting the assembly of *cis*-acting GR-SMRT/NCoR repressing complexes. IR nGREs are present in over 1000 mouse/human ortholog genes, which are repressed by GC in vivo. Thus variations in the levels of a single ligand can coordinately turn genes on or off depending in their response element DBS, allowing an additional level of regulation in GR signaling. This mechanism suits GR signaling remarkably well, given that adrenal secretion of GC fluctuates in a circadian and stress-related fashion.

Table 2. Side Effects Generated by GC Therapy Are Related to Those Produced by GC-Induced Transrepression of IR nGRE-Containing Genes

(A) IR nGRE-Containing Genes Whose GC-Induced Transrepression Could Generate Side Effects Related to Those Produced by GC Therapy (see also Table S3)

Debilitating Side Effects upon GC Therapy	Gene Symbol	Gene Name	a	b	References
Skin atrophy, bruising, thinning, brittle skin, and disturbed wound healing (Schacke et al., 2002)	*Krt 14, Krt 5*	Keratin 14 (IR1), Keratin 5 (IR1)	+	–	Ramot et al., 2009, This study (see Figures 3A and 3H)
	TGFβ1	Transforming growth factor beta 1 precursor (IR1)	+	–	Frank et al., 1996
	Smad4	SMAD family member 4 (IR2)	–	+	Chen et al., 2000
	Tnc	Tenascin C (IR2)	+	–	Fassler et al., 1996
	Trpv3	Transient receptor potential cation channel subfamily V member 3 (IR2)	–	+	Cheng et al., 2010
	Ccnd1	Cyclin D1 (IR0)	+	+	This study (see Fig. S3A)
	Cdk4	Cyclin-dependent kinase 4 (IR2)	+	+	Rogatsky et al., 1999
Impaired skeletal growth and osteoporosis (Schacke et al., 2002, Kleiman and Tuckermann, 2007)	*Tnfrsf11b*	Osteoprotegerin (IR2)	+	+	Sasaki et al., 2001
	Bcl2	Bcl- 2 (IR1)	+	–	Mocetti et al., 2001
	Bcl2l1	Bcl- XL (IR1)	+	–	Lu et al., 2007
	TGFβ1	Transforming growth factor beta 1 precursor (IR1)	–	+	Geiser et al., 1998
	Smad 4	SMAD family member 4 (IR2)	–	+	Tan et al., 2007
	Ghr	Growth hormone receptor (IR1)	+	+	Gevers et al., 2002
	Gnas	Adenylate cyclase stimulating G-alpha protein (IR1)	–	+	Weinstein et al., 2004
	Wnt5a	Wingless-related MMTV integration site 5A (IR1)	–	+	Yang et al., 2003
	Ahsg	Alpha -2- HS- glycoprotein precursor (IR0)	–	+	Szweras et al., 2002
	Col11a2	Collagen, type XI, alpha 2 chain precursor (IR2)	–	+	Li et al., 2001
Hyperglycemia and diabetes (Schacke et al., 2002, Kleiman and Tuckermann, 2007)	*Ins*	Insulin precursor (IR1, IR2)	+	+	Delaunay et al., 1997, This study (see Figure 3H)
	Insr	Insulin receptor (IR1)	+	+	Caro and Amatruda., 1982, This study (see Fig. 3H)
Muscle atrophy/myopathy (Schakman et al., 2008a)	*ctnnb1*	Beta –catenin (IR1)	+	+	Schakman et al., 2008b
	Akt1	Protein kinase B (IR2)	–	+	Schakman et al., 2008a
	Tpm2	Tropomysin beta chain (IR1)	–	+	Ochala et al., 2007
Impaired HPA axis and adrenal insufficiency (Schacke et al., 2002)	*Mc2r*	ACTH receptor (IR1)	+	+	Chida et al., 2007, This stu (see Figure 3H)
	Mrap	ACTH receptor accessory protein (IR1)	+	+	Metherell et al., 2005, This study (see Figure 3H)
Circadian rhythm disorder, metabolic syndrome, bipolar disorder, and mania (Bechtold et al., 2010, Duez and Staels, 2008)	*Clock*	Circadian locomoter output cycle kaput protein (IR1)	–	+	Roybal et al., 2007
	Nr1d1	Reverbα (IR1)	+	–	Torra et al., 2000; Preitner et al., 2002; This study (see Figure 3H)
	Rora	RORα (IR2)	+	–	This study (see Figures S4E and S4C)
Anxiety and depression (Schacke et al., 2002)	*Ucn2*	Urocortin 2 (IR1)	+	+	Chen et al., 2004, 2006; Neufeld-Cohen et al., 2010
	Crhr2	Corticotropin releasing hormone receptor 2 (IR1)	–	+	Bale et al., 2000
Hypertension (Schacke et al., 2002)	*Hsd11b2*	Corticosteroid 11-beta-dehydrogenase isozyme 2 (11β-HSD2) (IR1)	+	+	Stewart et al., 1996, This study (see Figure 3A)

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Obesity-induced excess of 17-hydroxyprogesterone promotes hyperglycemia through activation of glucocorticoid receptor

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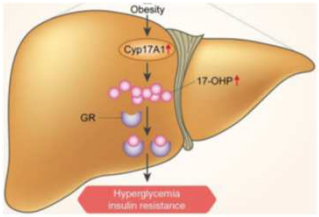
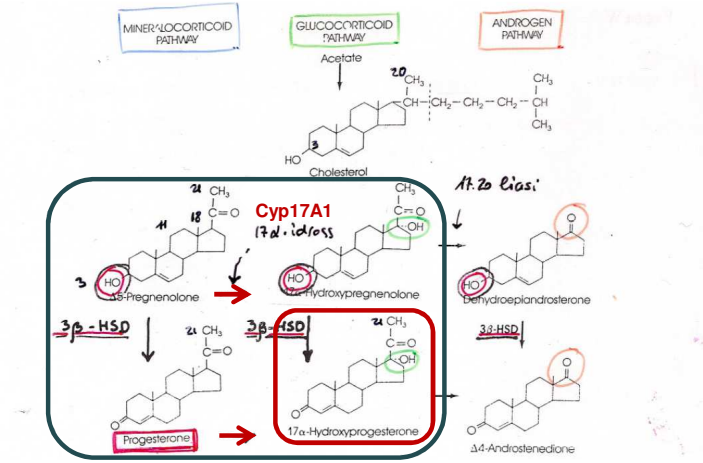
Type 2 diabetes mellitus (T2DM) has become an expanding global public health problem. Although the glucocorticoid receptor (GR) is an important regulator of glucose metabolism, the relationship between circulating glucocorticoids (GCs) and the features of T2DM remains controversial. Here, we show that 17-hydroxyprogesterone (17-OHP), an intermediate steroid in the biosynthetic pathway that converts cholesterol to cortisol, binds to and stimulates the transcriptional activity of GR. Hepatic 17-OHP concentrations are increased in diabetic mice and patients due to aberrantly increased expression of Cyp17A1. Systemic administration of 17-OHP or overexpression of Cyp17A1 in the livers of lean mice promoted the pathogenesis of hyperglycemia and insulin resistance, whereas knockdown of Cyp17A1 abrogated metabolic disorders in obese mice. Therefore, our results identify a Cyp17A1/17-OHP/GR–dependent pathway in the liver that mediates obesity-induced hyperglycemia, suggesting that selectively targeting hepatic Cyp17A1 may provide a therapeutic avenue for treating T2DM.





Disruption of a key ligand-H-bond network drives dissociative properties in vamorolone for Duchenne muscular dystrophy treatment

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Duchenne muscular dystrophy is a genetic disorder that shows chronic and progressive damage to skeletal and cardiac muscle leading to premature death. Antiinflammatory corticosteroids targeting the glucocorticoid receptor (GR) are the current standard of care but drive adverse side effects such as deleterious bone loss. Through subtle modification to a steroidal backbone, a recently developed drug, vamorolone, appears to preserve beneficial efficacy but with significantly reduced side effects. We use combined structural, biophysical, and biochemical approaches to show that loss of a receptor-ligand hydrogen bond drives these remarkable therapeutic effects. Moreover, vamorolone uniformly weakens coactivator associations but not corepressor associations, implicating partial agonism as the main driver of its dissociative properties. Additionally, we identify a critical and evolutionarily conserved intramolecular network connecting the ligand to the coregulator binding surface. Interruption of this allosteric network by vamorolone selectively reduces GR-driven transactivation while leaving transrepression intact. Our results establish a mechanistic understanding of how vamorolone reduces side effects, guiding the future design of partial agonists as selective GR modulators with an improved therapeutic index.

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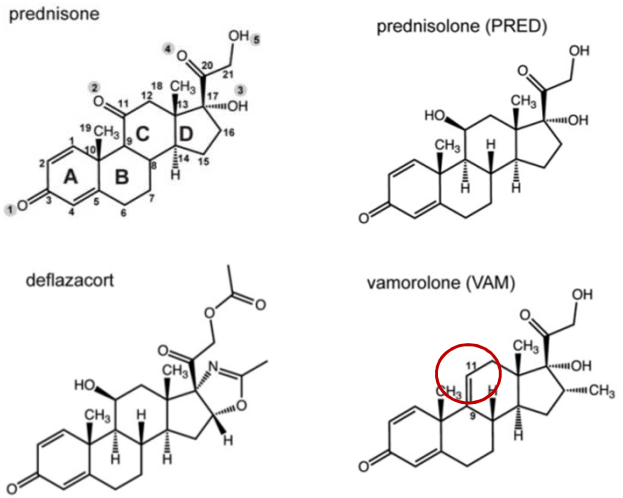
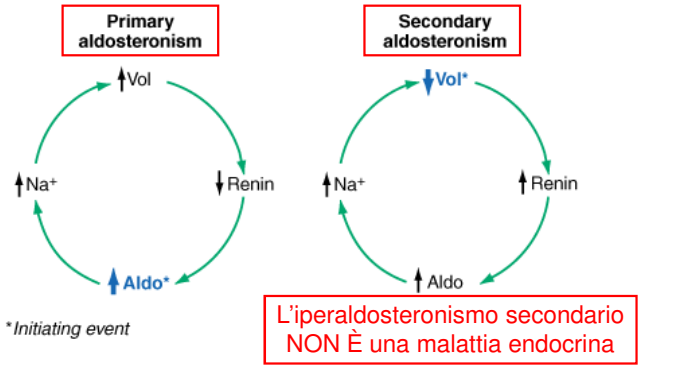
Duchenne muscular dystrophy (DMD) is the most common and severe form of muscular dystrophy with an incidence rate of 1 in 5,000 boys (1). Symptoms begin early in childhood and manifest as weakness and degeneration of muscle tissues. The loss of muscle strength becomes most obvious in the pelvic area and gradually progresses to the upper limbs. Chronic muscle degeneration ultimately leads to cardiac and respiratory muscle weakness and wasting, with an average life expectancy below 30 y. DMD is an X-linked disorder that is characterized by mutations to the *DMD* gene, the largest gene in the human genome, and loss of the encoded dystrophin protein (2). The dystrophin protein provides structural support to muscle fiber plasma membranes and alleviates mechanical stress during muscle contraction by forming a complex to connect the intercellular cytoskeleton to extracellular matrix (3).

Activation of the proinflammatory nuclear factor-κB (NF-κB) pathway is observed in muscles of DMD patients from birth and is believed to cause chronic inflammation in muscle that contributes to disease onset and progression (4, 5). The current standard care for DMD is pharmacologic treatment with corticosteroids such as prednisone and deflazacort, which potently suppress NF-κB signaling. As a result of treatment, DMD patients' muscle tissues exhibit reduced fibrosis and stabilized muscle strength while mouse DMD models showed improved muscle regeneration (6). However, like other corticosteroid treatments, DMD patients experience adverse side effects with long-term treatment. In particular, corticosteroid treatment frequently results in a decreased bone mineral density, resulting in an increased rate of osteoporosis and risk of vertebral and long bone fractures (7). Another noteworthy side effect of corticosteroid treatment is muscle weakness and atrophy caused by increased protein catabolism through atrogene pathways (8, 9). While different dosing regimens for prednisone and deflazacort have been tested to tip the balance toward greater efficacy with fewer side effects (10, 11), drugs able to separate (dissociate) efficacy from safety concerns are highly needed. Vamorolone (previously named as VBP15) was recently discovered to show properties of a dissociative steroidal drug, that decreased muscle inflammation and improved muscle strength in mouse models of DMD (12, 13). Moreover, open label initial clinical trials with vamorolone showed dose-responsive efficacy, while improving side effects associated with traditional corticosteroid treatments (14, 15).



Iperaldosteronismo



L'iperaldosteronismo secondario NON È una malattia endocrina

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Iposurrenalismo globale

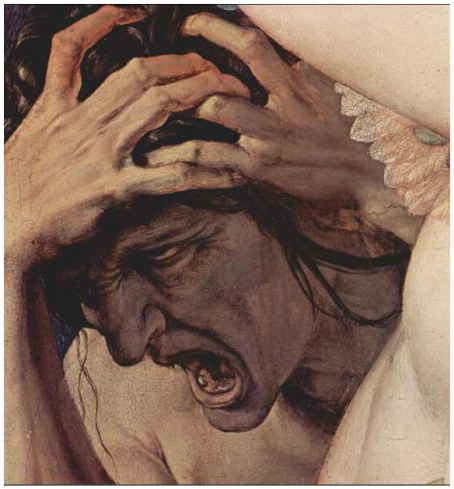
a. Insufficienza cronica (morbo di Addison) p.e. da distruzione bilaterale da tbc o malattie autoimmuni

- Debolezza muscolare, astenia
- Ipotensione
- Ipoglicemia
- Tendenza allo shock per infezioni e/o lesioni lievi
- Iperpigmentazione cutanea (MSH)

b. Insufficienza acuta (morbo di Waterhouse-Friederichsen) spesso da setticemia meningococcica)

- Shock a rapida evoluzione

Agnolo BRONZINO
Venere, Cupido e il Tempo (Allegoria della Lussuria, 1540-45)
National Gallery, London



Agnolo BRONZINO
Venere, Cupido e il Tempo, dettaglio (Allegoria della Lussuria, 1540-45)
National Gallery, London

Tiziano (1528)
Ritratto di Girolamo Fracastoro
National Gallery, Londra

His work *De Contagione* (1546) contains the first scientific suggestion that epidemic diseases could be transmitted by contagion caused by a different type of rapidly multiplying minute body. He speculated they were transmitted either by direct contact or through the air or by material such as soiled clothes or linen, which he called fomites. He also gave the first description for typhus.