Vert Phys PCB3743

Endocrinology 2
Fox Chapter 11 part 2
Pituitary and HPA axis

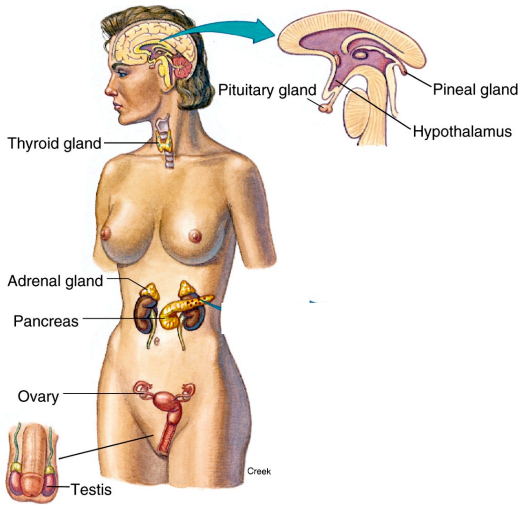
Hypothalamic-Pituitary Anatomy

Hypothalamus: brain region between brainstem and cerebrum that integrates sensory information and generates physiological responses to maintain homeostasis.

Pituitary Gland: attached to the underside of the hypothalamus by the **infundibulum** (pituitary stalk). Hypothalamus is connected to the pituitary by **hypothalamo-hypophyseal portal veins** that carry releasing hormones to the anterior pituitary, and by the **hypothalamo-hypophyseal tract** of axons projecting to the posterior pituitary.

Anterior Lobe: contains endocrine cells that secrete **tropic hormones** into the circulation that stimulate target organs in the body.

Posterior Lobe: contains axon terminals of **ADH and oxytocin** neurons that originate in the hypothalamus; releases ADH (water retention) and oxytocin (uterine contractions, milk release) into the blood stream.



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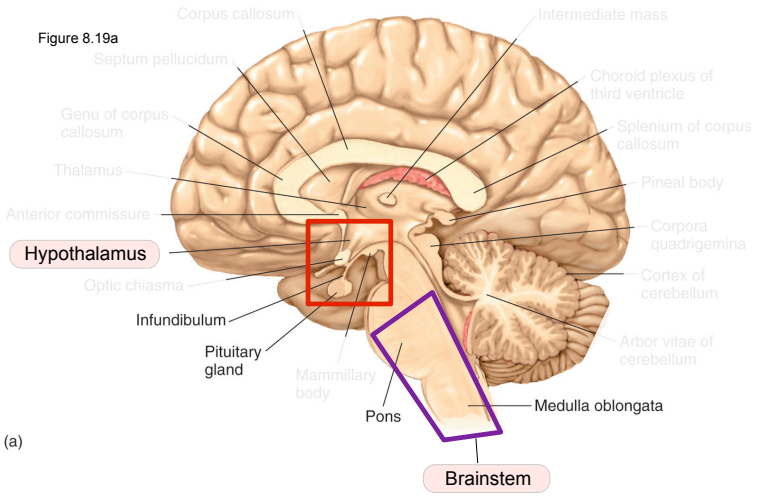

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Autonomic vs. Somatic Axes

(conscious sensation)

(voluntary movement)

Vision
Audition
Somatosensation
→ Thalamus → Sensory Cortex → Cognition → Motor Cortex → Spinal Cord → Behavior

Limbic System

Visceral
Chemoreception
Mechanoreception
Temperature
Rhythms
→ Hypothalamus → Physiological, Behavioral & Emotional Responses → Brainstem → Sympathetic, Parasympathetic Nerves
Pituitary → Endocrine Glands

(unconscious sensation)

(homeostatic & autonomic responses)

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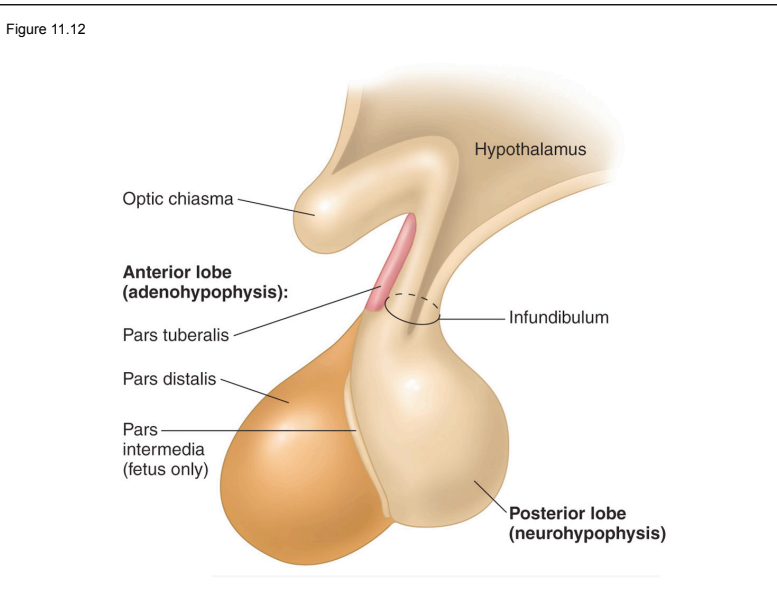

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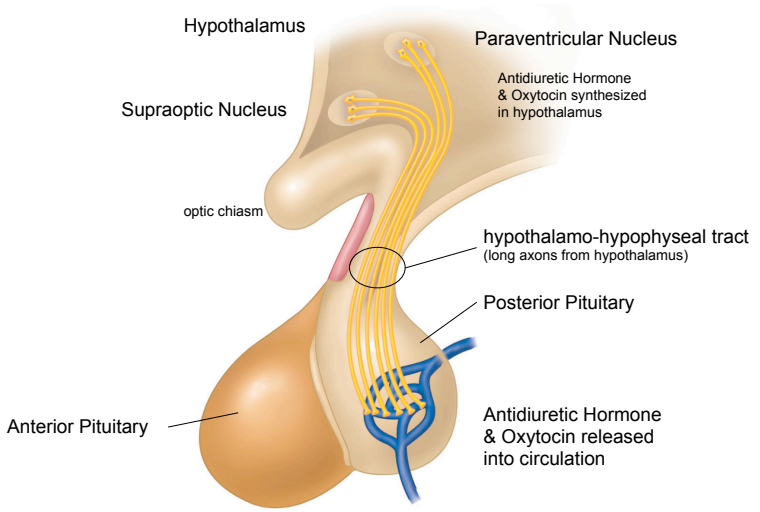
Figure 11.13



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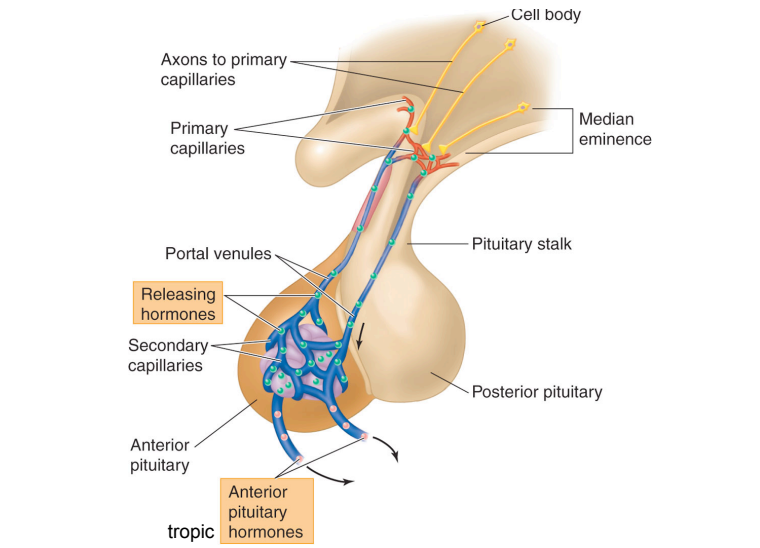

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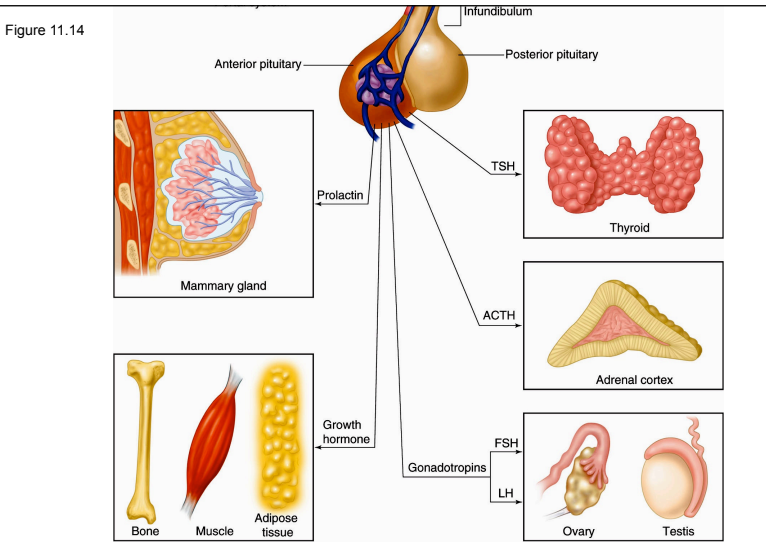

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Hypothalamic Pituitary axes

Hypothalamus regulates pituitary function with releasing and release-inhibitory hormones

Releasing hormones –> pituitary to cause release of **stimulatory hormones** –> increase target glands activity

Inhibitory hormones –> pituitary to suppress release of stimulatory hormones –> decrease target gland activity
(esp. dopamine -> less prolactin)

Transection of infundibulum –> decrease of all pituitary hormones **except prolactin** increases.

Examples of Hypothalamic Pituitary Axes: HPA, HPG, HPT axes

Target Hormones –> **negative feedback** to hypothalamus and pituitary –> **decreased levels** of releasing hormones and stimulatory hormones.

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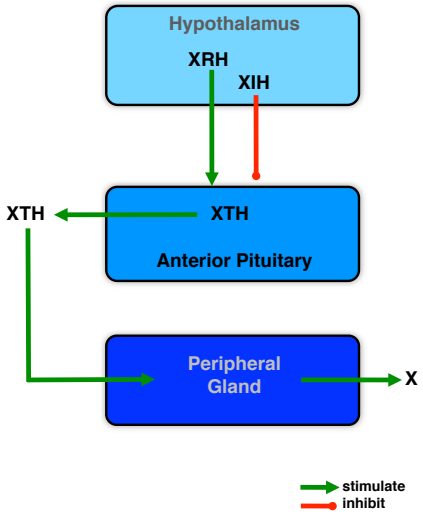
Feedforward Loop

Releasing hormone:
hypothalamus –> pituitary

Tropic hormone:
pituitary –> target gland

target gland –> secretes X



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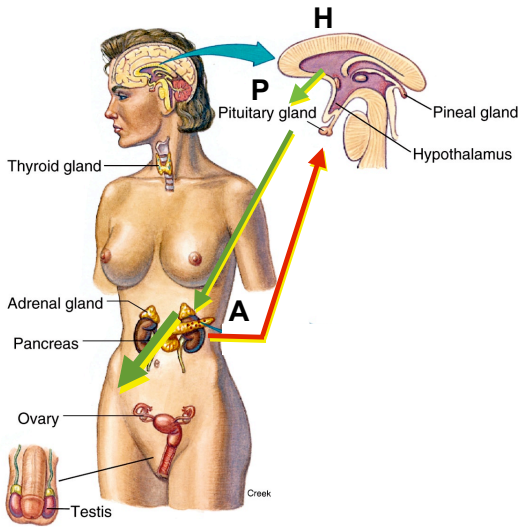
Hypothalamic Pituitary Adrenal (HPA) Axis



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Examples of Hypothalamic Pituitary Axes

	H-P-Adrenal Axis	H-P-Gonadal Axis	H-P-Thyroid Axis
Hypothal:	Corticotropin-releasing hormone (CRH)	Gonadotropin-releasing hormone (GnRH)	Thyrotropin-releasing hormone (TRH)
Anterior Pituitary:	Adrenocorticotropic hormone (ACTH)	Luteinizing hormone (LH)	Thyroid-Stimulating hormone (TSH)
Target Organ:	Adrenal Cortex	Ovaries & Testes	Thyroid Gland
Function:	Stimulate Corticosteroid Synthesis (Stress)	Stimulate Estrogen & Testosterone Synthesis (Reproduction)	Stimulate Thyroxine synthesis (Metabolism)

see Fox Table 11.6 & Table 11.7

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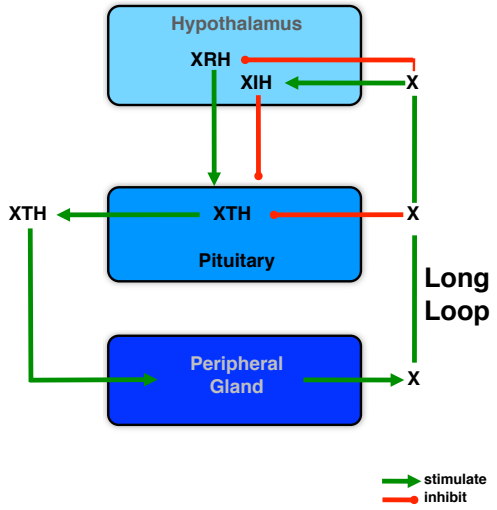
Feedback Loops



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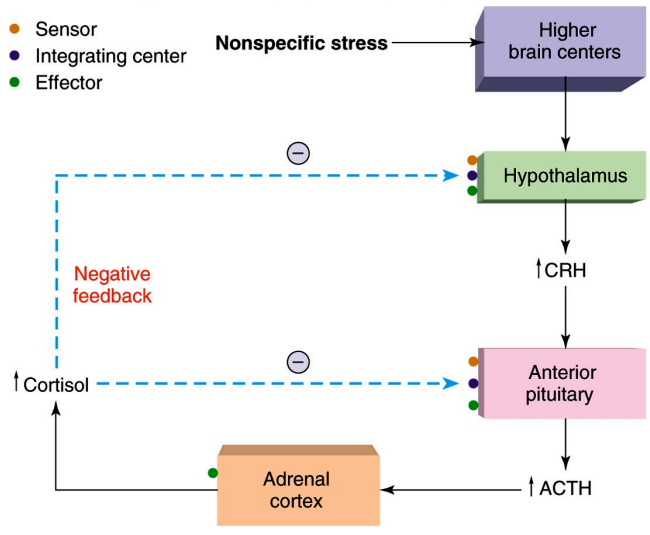

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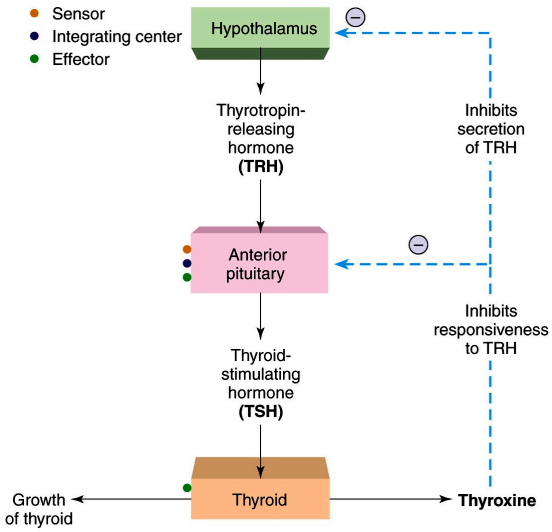

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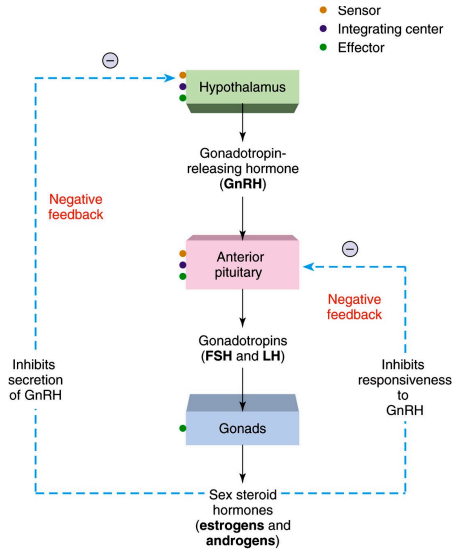

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Hypothalamic-Pituitary pathologies:

Hypersecretion due to

- **tumors**
- **lack of negative feedback**
- **inappropriate synthesis/degradation**

Real or Functional Hyposecretion due to

- **lack of releasing/tropic hormones**
- **lack of synthetic enzymes**
- **lack of receptors**

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Hypothalamic Pituitary Adrenal Axis (HPA) and Stress

Perturbation from homeostasis (maintenance of the constant internal environment)

"Fight or Flight" defined in 1900s by Cannon

Defined in 1930s as general response to "stress" by Selye in war veterans.

- increase in gastric secretion
- increase in adrenal secretion
- suppression of immune system

stress (neural input, disease, learned response)
-> hypothalamus **-> immediate** response & **long-term** response

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Immediate Endocrine Response via Autonomic Nervous System

hypothalamus –> brainstem
–> vagus –> increase heart-rate
–> sympathetic activation
–> spinal cord –> splanchnic nerve –> adrenal medulla

Adrenal Medulla
–> epinephrine, norepinephrine into blood stream
–> cardiovascular effects (heart rate, blood flow, blood pressure)
–> mobilize glucose, increase metabolism

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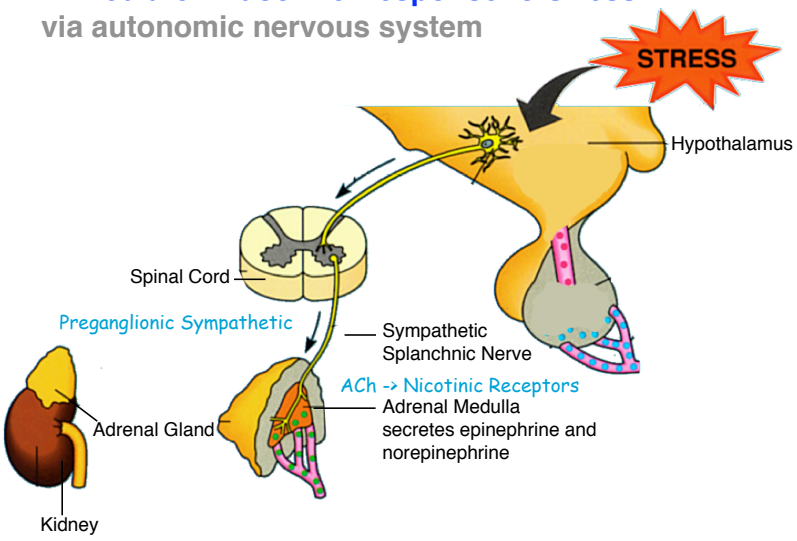
Immediate Endocrine Response to Stress
via autonomic nervous system



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Long-term, transcriptional stress response mediated by glucocorticoids (GC):

CRH from hypothalamus
–> long portal vessels –> anterior pituitary
–> pituitary cells called **corticotropes**
–> adrenocorticotropic hormone (**ACTH**)

ACTH in blood
–> cortex of adrenal gland
–> ACTH receptors increase cAMP
–> increased cholesterol conversion to cortisol by enzyme P450 in mitochondria & increased cortical growth

Glucocorticoids
–> transcriptional effects on cells expressing GC receptors

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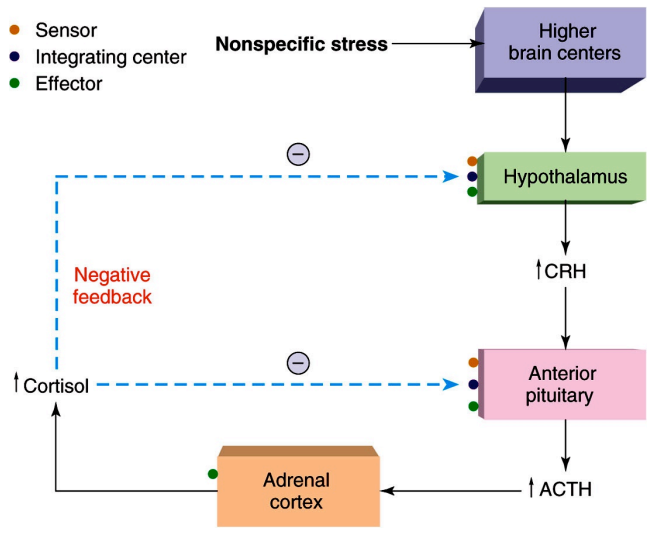
Figure 11.20



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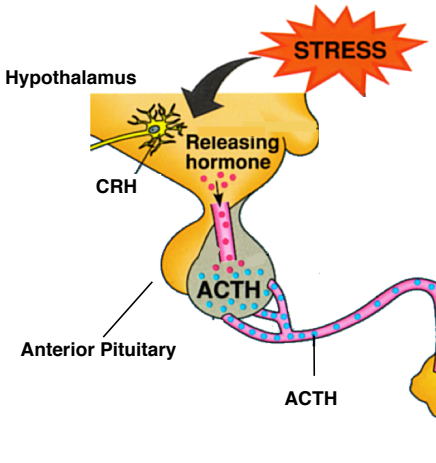
Long-Term Response to Stress:
secretion of mineralo- & glucocorticoids



Mineralocorticoids (aldosterone):
retention of Na+ and H20 by kidneys
increased blood volume and pressure

Glucocorticoids (cortisol):
convert protein and fat to glucose
suppress immune system

Adrenal Cortex
secretes
mineralocorticoids
and glucocorticoids

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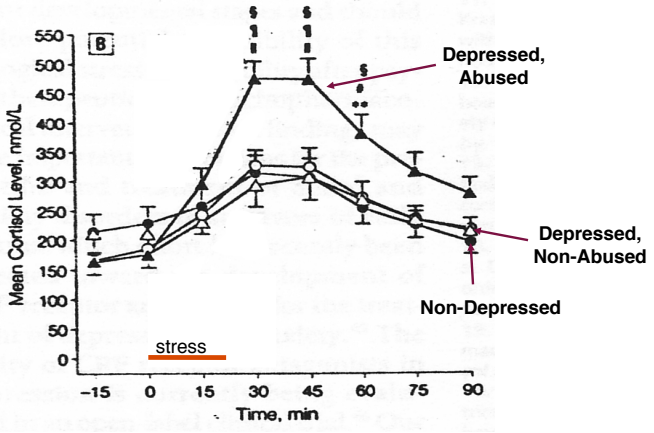
Enhanced Stress Response

Depressed women with Posttraumatic Stress Disorder (childhood abuse) show enhanced cortisol release in response to social stress.



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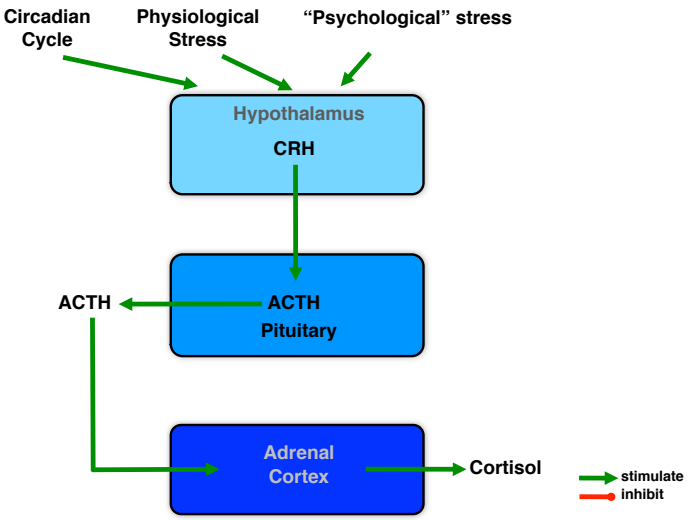
HPA axis: Positive Feed forward



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Corticotropes in Pituitary

Synthesize POMC -> ACTH

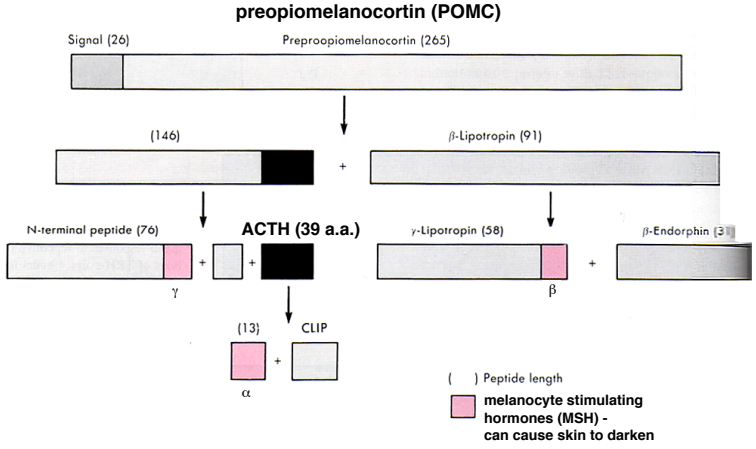

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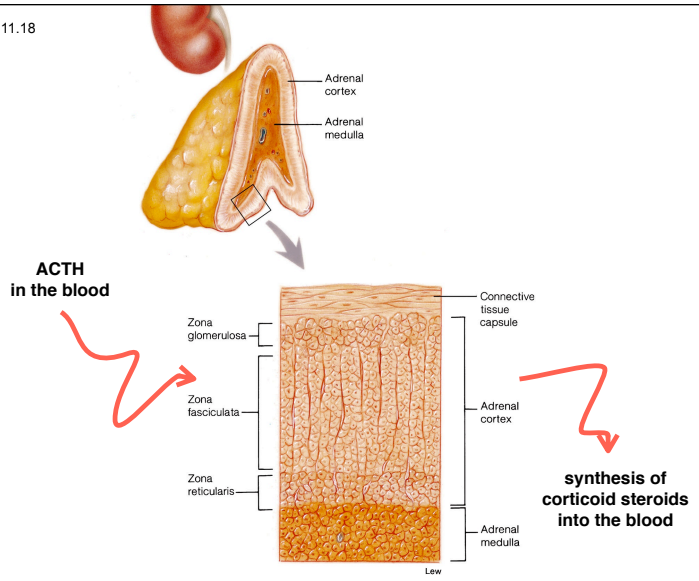
Figure 11.18



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Adrenal gland anatomy

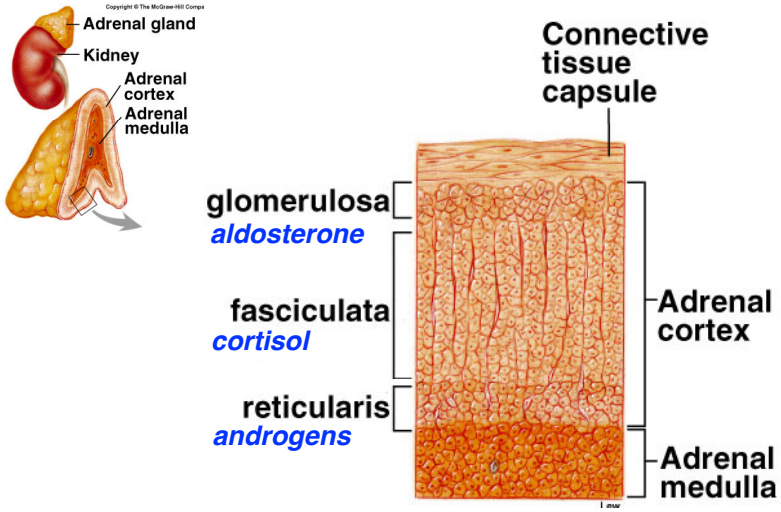

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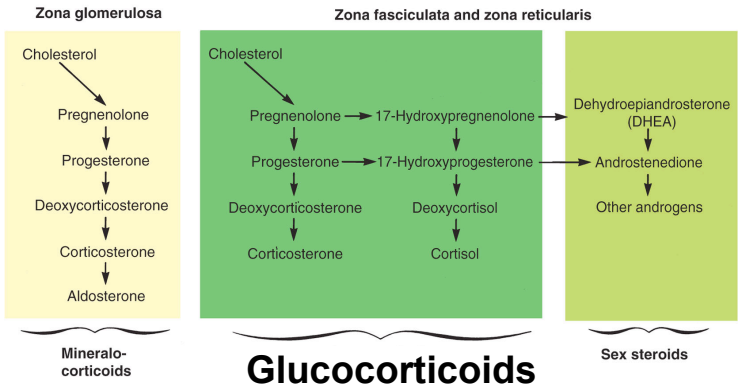
Figure 11.19



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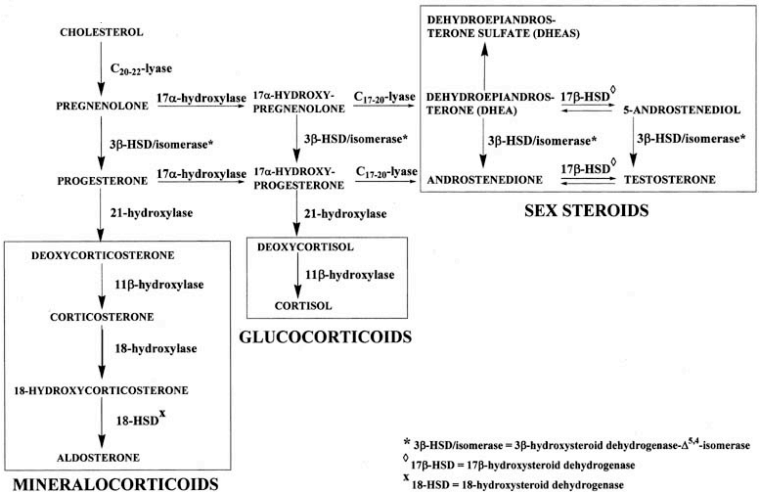
Steroid Synthesis in the Adrenal Gland



http://www.glowm.com/resources/glowm/cd/pages/v5/v5c001.html

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Actions of Glucocorticoids (GCs)

- Containment of stress response
- Suppression of swelling, suppression of immune system
  -> reduce tissue damage
- Mobilization of energy from muscle and fat
- Induce liver enzymes for detoxification
- Suppression of "optional" activities: reproduction, growth
- Adaptive in low doses, but problematic at high or chronic doses

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Negative Feedback of Cortisol onto Hypothalamus and Pituitary

- Cortisol levels are controlled by negative feedback loop of HPA.
- High Cortisol levels in the blood act on GC receptors in the hypothalamus and pituitary to decrease CRH & ACTH synthesis and release
- If cortisol synthesis is **blocked** (by drug that blocks synthetic enzyme, or by a disease that damages adrenal cortex), then ACTH levels stay **elevated** (trying to elevate cortisol levels)
- If excess glucocorticoids are administered, HPA detects **high negative feedback**, so then ACTH and cortisol levels should **fall**.
- **Dexamethasone suppression test** administers an artificial glucocorticoid to confirm that HPA responds to negative feedback.

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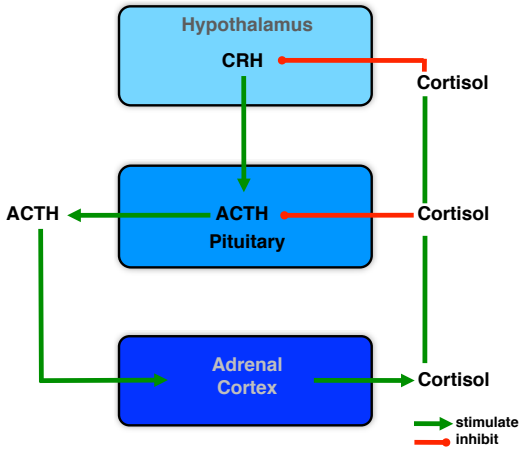
HPA axis: Negative Feedback

Cortisol feeds back to:
pituitary –> inhibit ACTH release
hypothalamus –> inhibit CRH release



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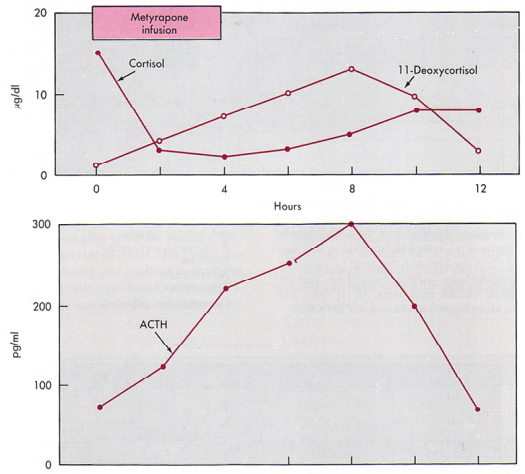
Feedback Loops: block negative feedback

metyrapone blocks conversion of 11-deoxycortisol -> cortisol;
so cortisol levels fall; pituitary responds by increasing ACTH levels



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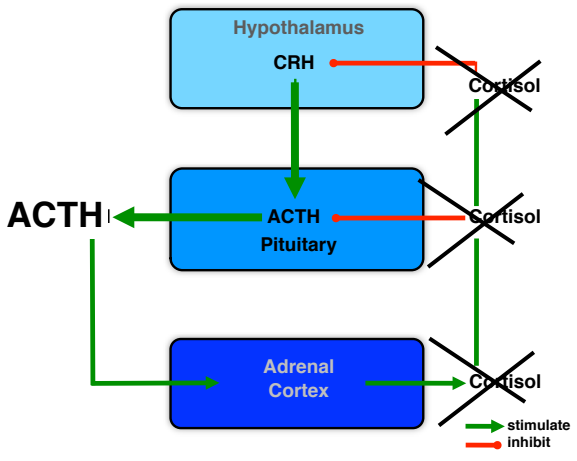
HPA axis: Remove Negative Feedback ACTH & CRH levels increase



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Dexamethasone suppression test

preRX with artificial GC (dexamethasone) suppresses cortisol response to CRH injection

note:
can use suppression test to assay functioning of internal feedback loops

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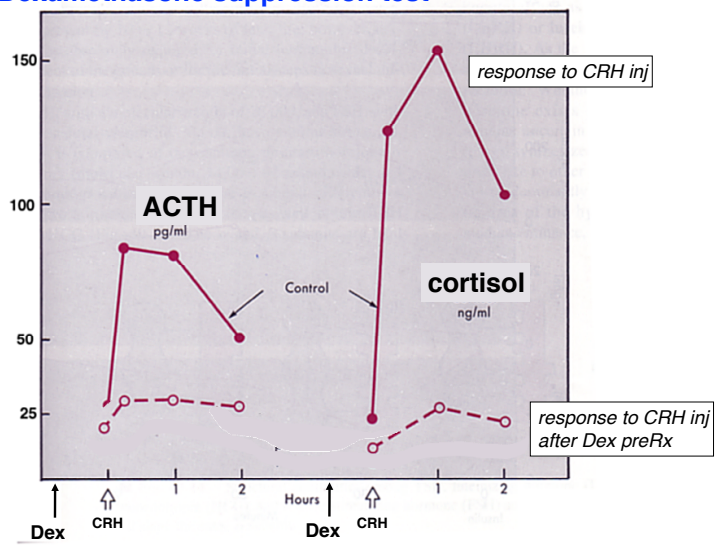
Dexamethasone suppression test



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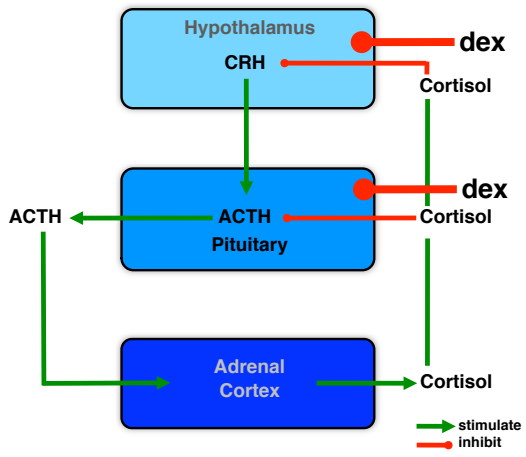
HPA axis: Enhanced Negative Feedback

Dex pretreatment -> blunted ACTH response to CRH



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Pathologies of HPA

Points of steroid disregulation

Defects in cortisol synthetic enzymes can result in too much mineralcorticoids (-> high blood pressure) or too much sex steroids (progesterone & androgens -> masculinization)

Addison's Disease: autoimmune destruction of adrenal cortex causes loss of corticosteroids, but excess ACTH

Tumors can oversecrete hormones.

Pheochromacytoma Tumors of adrenal medulla -> elevated epinephrine

Cushing's Syndrome: elevated cortisol
Tumors of Pituitary Gland (adenoma) or Lung (lung carcinoma) can produce too much ACTH

Tumors of Adrenal Gland can produce too much cortisol

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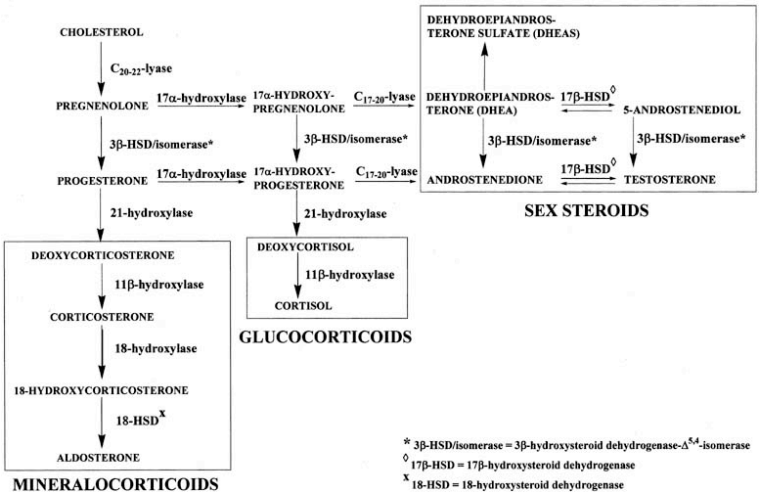
Steroid Synthesis in the Adrenal Gland



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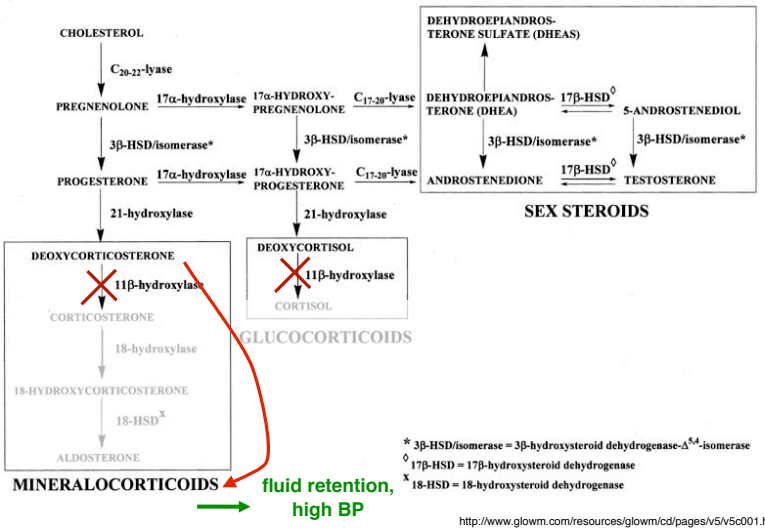
Steroid Synthesis in the Adrenal Gland

defect in 11-hydroxylase



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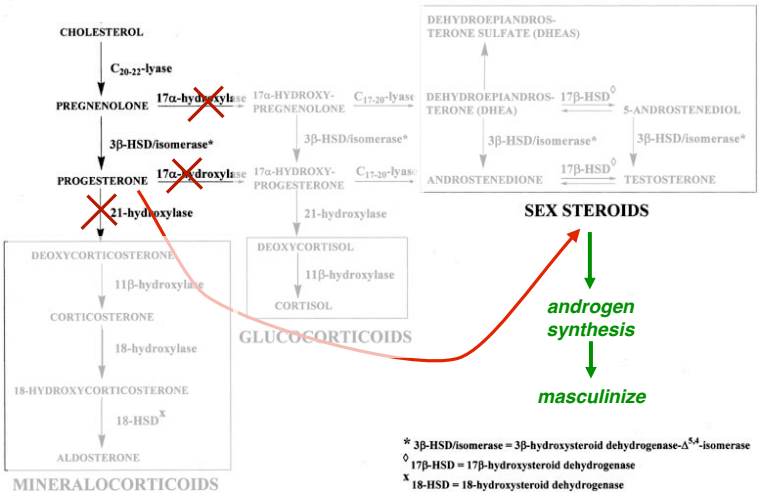
Steroid Synthesis in the Adrenal Gland

defect in 17- or 21-hydroxylase



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Pheochromacytoma tumors

Hypersecretion of epinephrine and norepinephrine from tumors of the adrenal medulla

Dramatic clinical episodes after stress (or even just change in posture):

headache, palpatiations, chest pain, cold sweats, anxiety and impeding sense of death.

hyper-epinephrine –> increase heart rate

hyper-norepinephrine –> decreased heart rate

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Addison's disease

Extreme adrenal steroid deficiency

Caused by autoimmune or infectious **destruction of adrenal cortex**.

Extreme intolerance of stress, loss of appetite, malaise, fasting hypoglycemia, low blood pressure, salt craving

No glucocorticoids, so:
–> no negative feedback
–> hypersecretion of ACTH
–> hyperpigmentation of skin (because ACTH acts as melanocyte-stimulating hormone)

Treatment: administer exogenous corticosteroids to replace function of adrenal cortex

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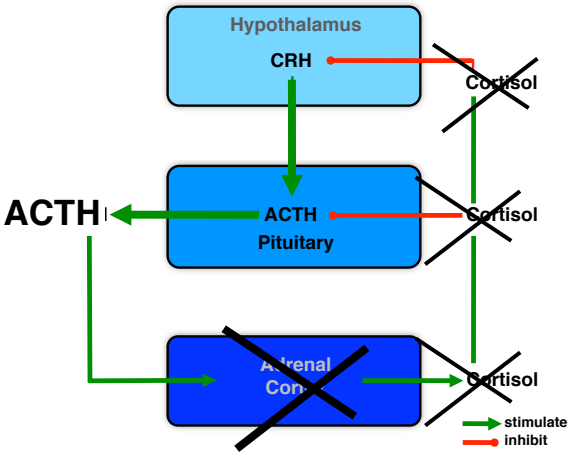
Addison's disease - low corticosteroids, elevated ACTH



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Addison's disease - low corticosteroids, elevated ACTH

- Note the generalised skin pigmentation (in a Caucasion patient) but especially the deposition in the palmer skin creases, nails and gums.

www-clinpharm.medschl.cam.ac.uk

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Cushing's Syndrome (1 in 100,000 people)

hypersecretion of cortisol

Loss of bone mass, loss of muscle mass, fragile skin and connective tissue(because cortisol mobilizes tissue for energy)

Obesity in abdomen and "hump" of hunchback

Enhanced infection without immune response (because cortisol suppresses immune system)

Insomnia, euphoria, or depression (because cortisol can cause mood swings)

Causes of Cushing's Syndrome:

Pituitary adenoma = **Cushing's Disease** (65%)

Ectopic ACTH production (e.g. lung tumor) (15%)

Adrenal adenoma (15%)

Adrenal carcinoma (5%)

(**iatrogenic** induced by chronic glucocorticoid drug use)

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Cushing's Syndrome

Harvey Cushing

1st use of x-rays for surgery, blood pressure to monitor anesthesia, imported BP cuff from Europe, role of pituitary

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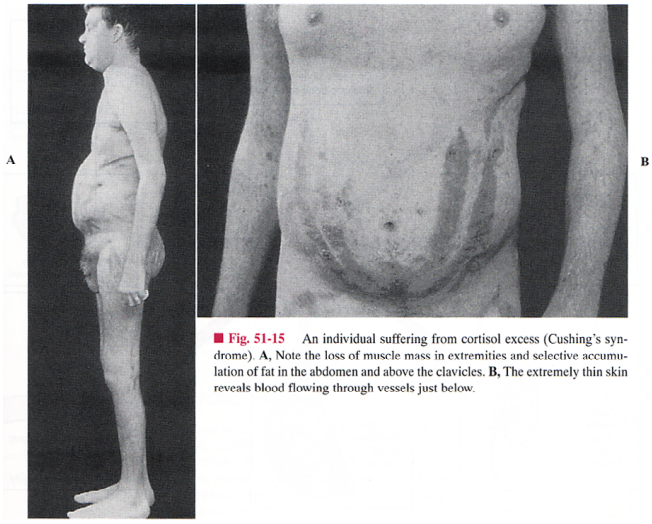
Cushing's Syndrome



■ Fig. 51-15 An individual suffering from cortisol excess (Cushing's syndrome). **A,** Note the loss of muscle mass in extremities and selective accumulation of fat in the abdomen and above the clavicles. **B,** The extremely thin skin reveals blood flowing through vessels just below.

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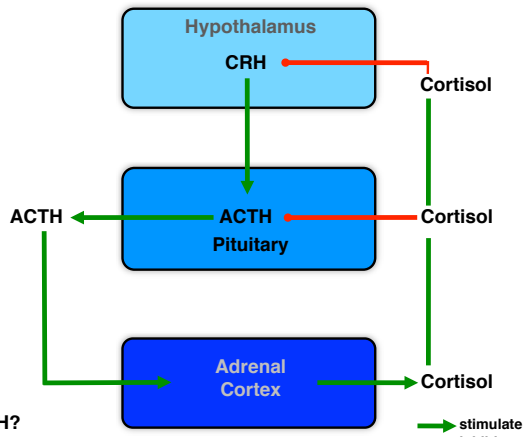
HPA axis: Analysis of Dysfunction



Response to CRH or ACTH?

Dexamethasone suppression test?

Expression of Glucocorticoid receptors?

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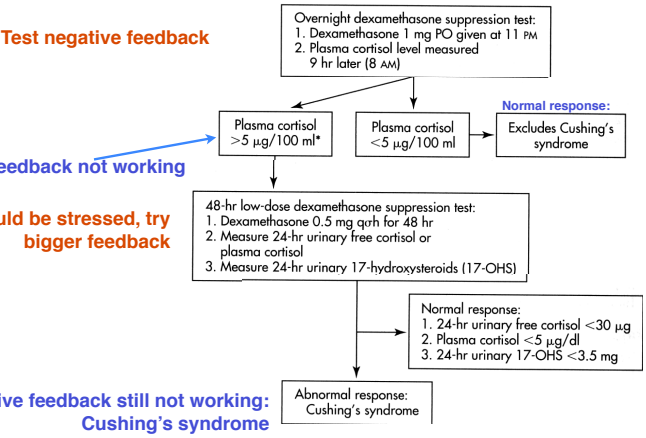
Diagnosis of Cushing's Disease

Test negative feedback



negative feedback not working

could be stressed, try bigger feedback

negative feedback still not working: Cushing's syndrome

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Diagnosis of Cushing's Disease

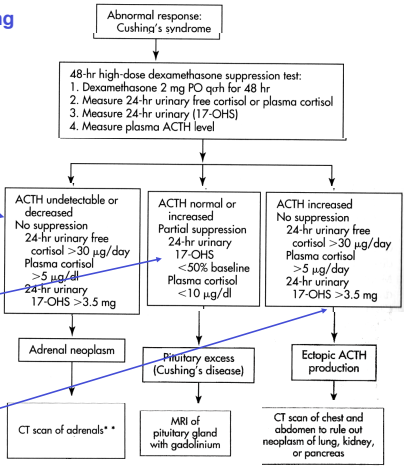
negative feedback still not working

determine if deficit is in pituitary: is ACTH decreased by GCs?

negative feedback on pituitary OK, so adrenal out of control

pituitary doesn't respond to neg feedback, so pituitary out of control = Cushing's Disease

ACTH actually above normal, so must be coming from extrapituitary source.



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