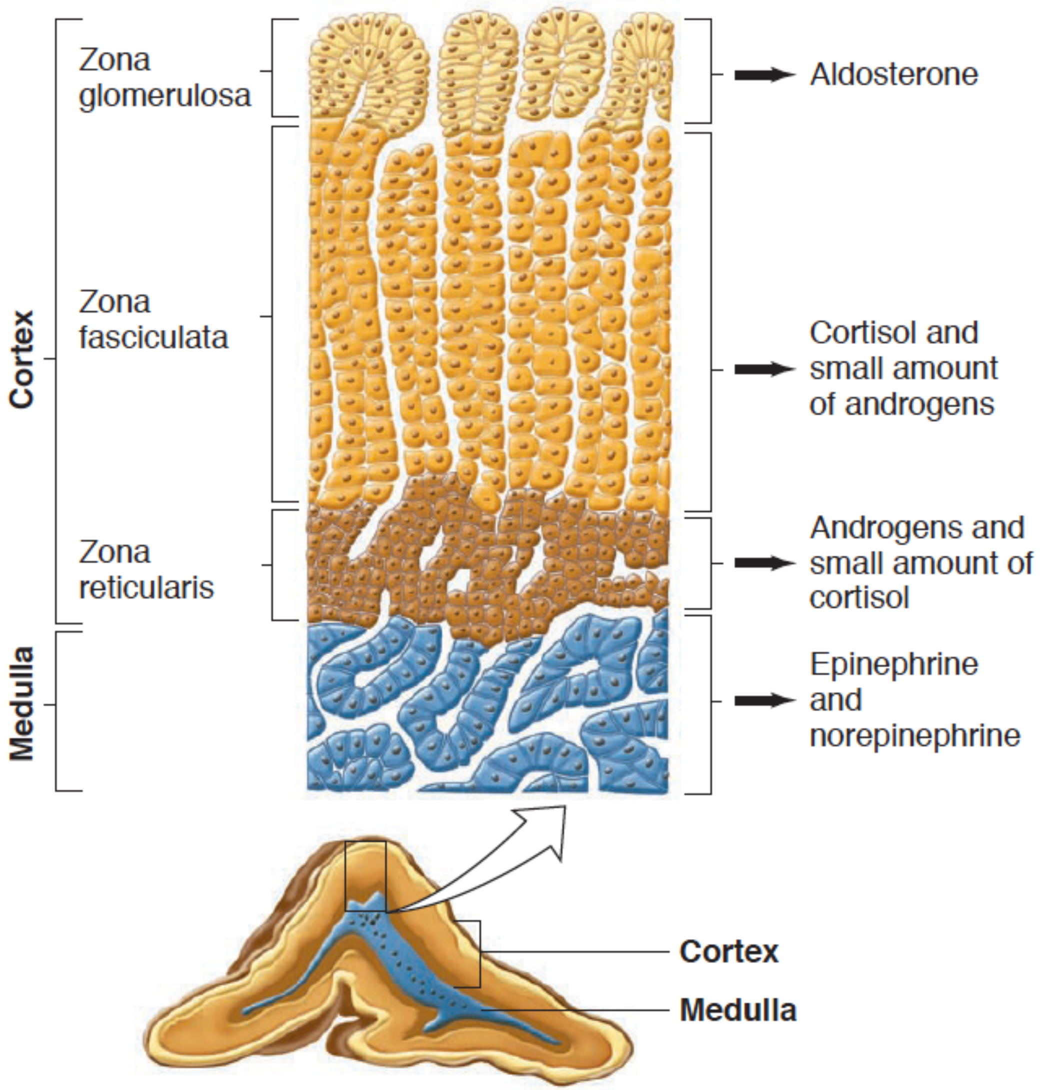
Adrenal Gland and Stress Hormones

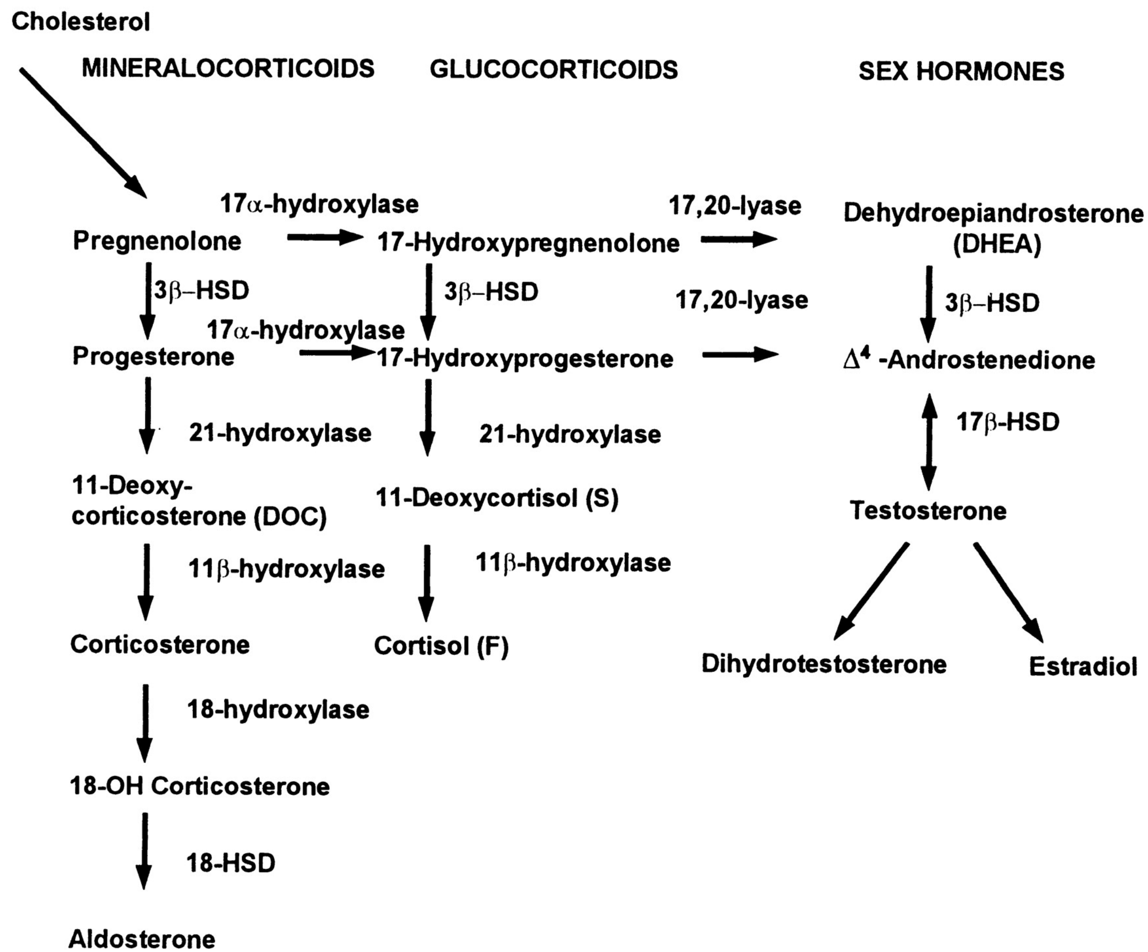
Learning Objectives

- Name three zones in the adrenal cortex and major regulator(s) of each zone.
- Name three steroidogenesis pathways and their major products.
- Explain briefly the physiological mechanism of adrenogenital syndrome.
- Describe the physiological actions and roles of aldosterone.
- Explain briefly the renin-angiotensin system.
- Describe the negative feedback regulation of aldosterone and its relationship to blood volume/blood pressure homeostasis.
- Describe hepatic and extrahepatic metabolic actions of glucocorticoids. Discuss their relationship.
- State the major findings caused by adrenal hypersecretion of mineralocorticoids.
- State the major findings caused by adrenal hypersecretion of glucocorticoids.
- Name the major hormones secreted from the adrenal medulla. Discuss the differences of epinephrine (epi) and norepinephrine (NE) in cardiovascular actions (physiological levels).
- List the major metabolic actions of catecholamines.
- Contrast the thresholds for actions vs. plasma levels of epi and NE under common conditions, like exercise, and in the disease pheochromocytoma

Adrenal Gland Anatomy

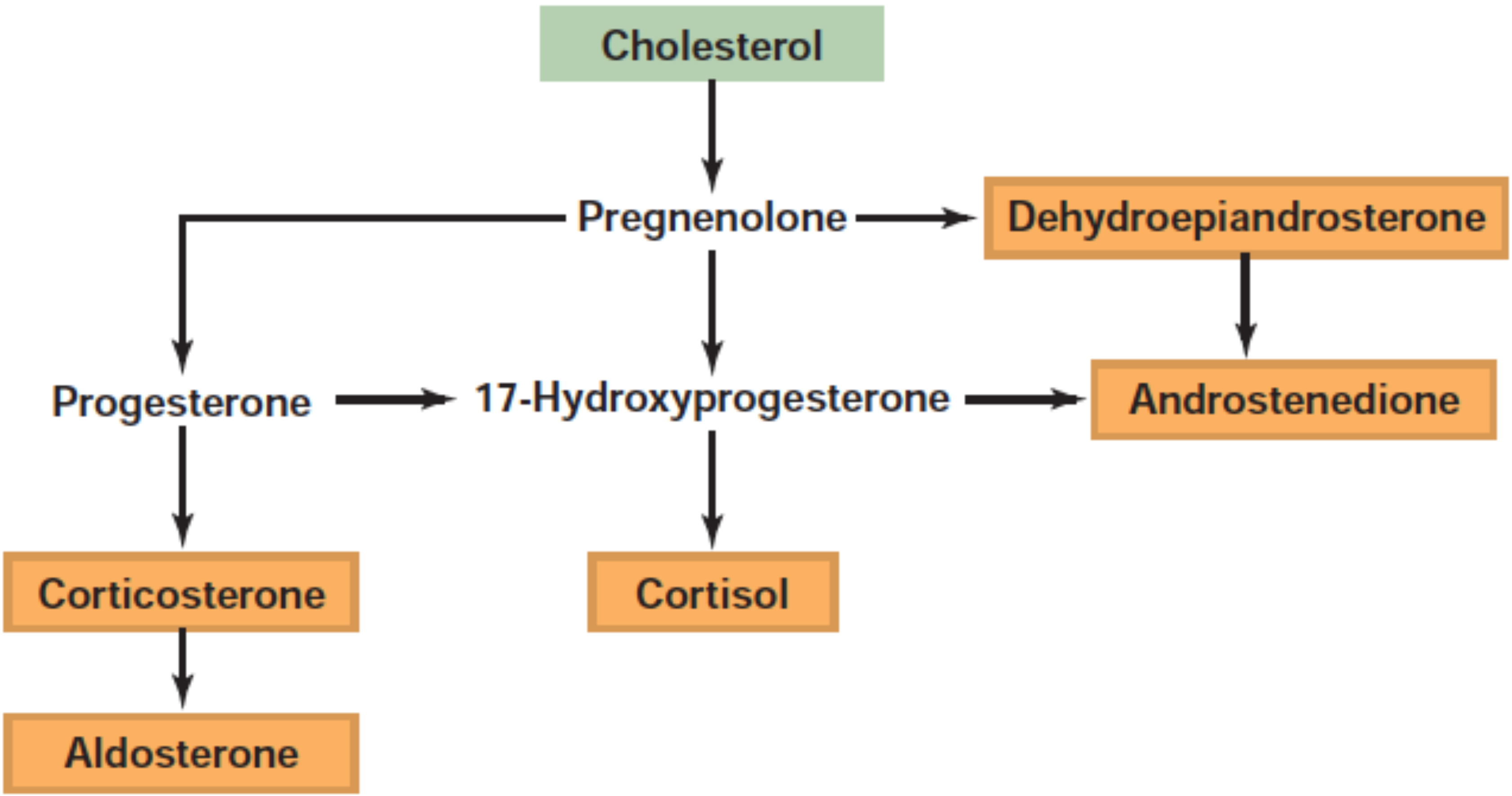


Steroid Hormone Biosynthesis

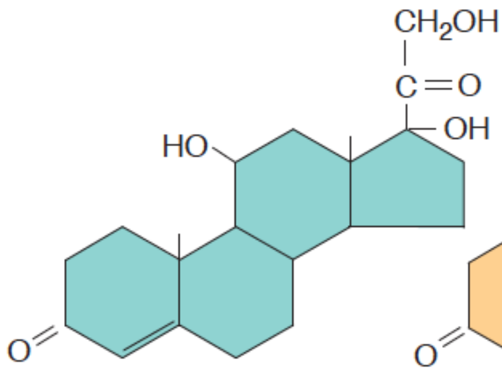


Maria I. New, and Robert C. Wilson PNAS
1999;96:12790-12797

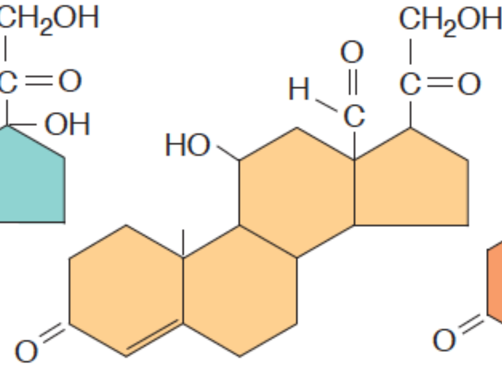
Steroid Hormone Synthesis



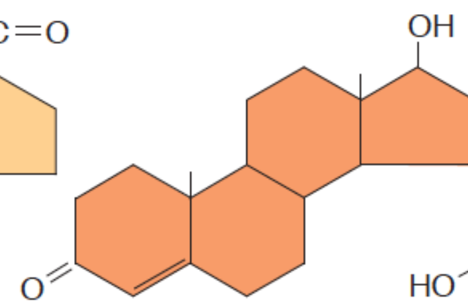
Steroid Hormones Released From Adrenal Medulla



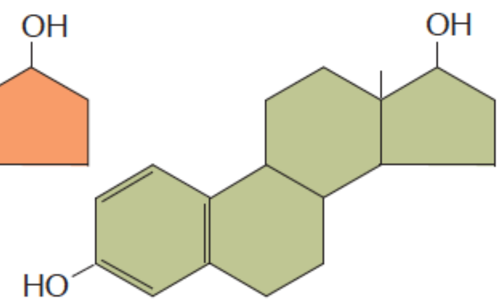
Cortisol



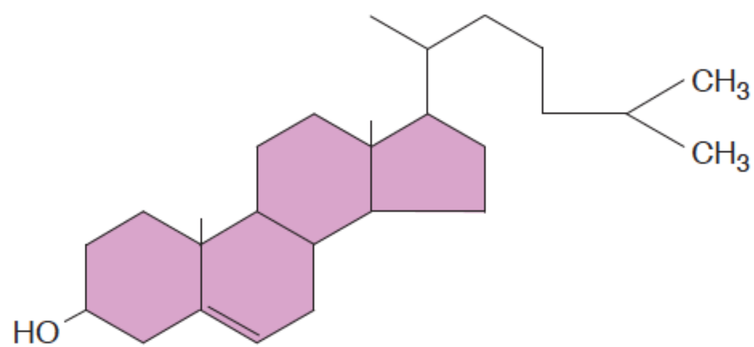
Aldosterone



Testosterone

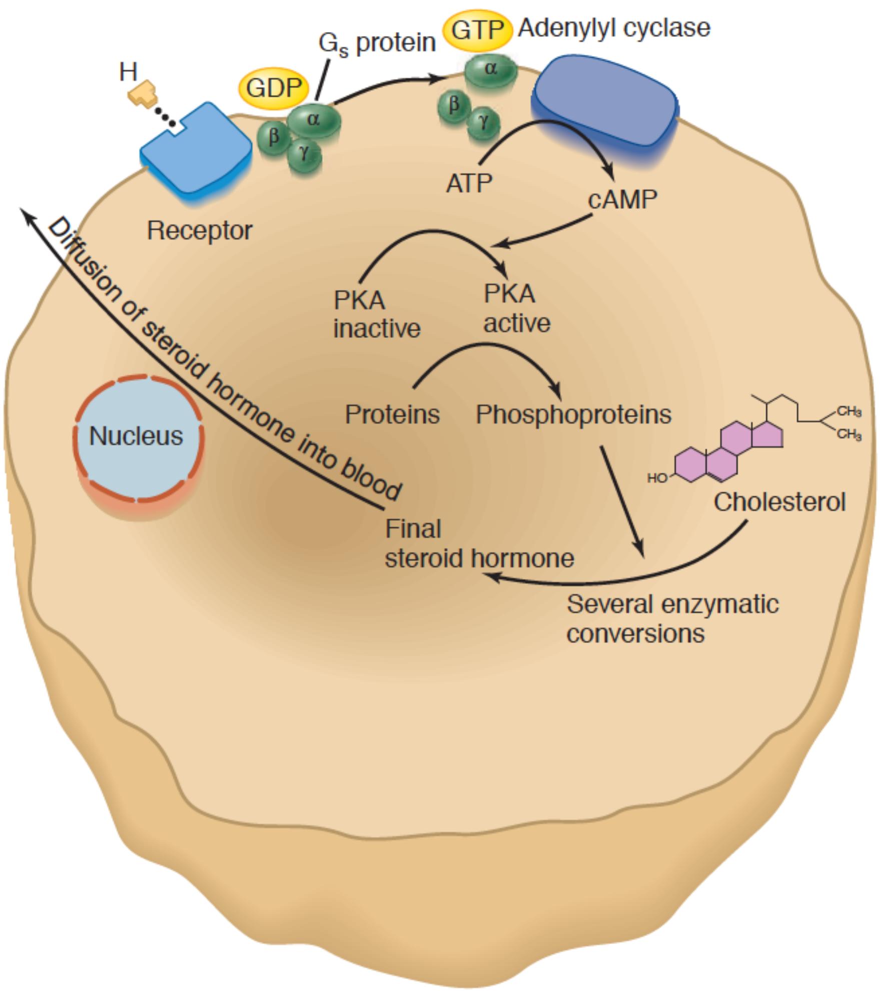


Estradiol



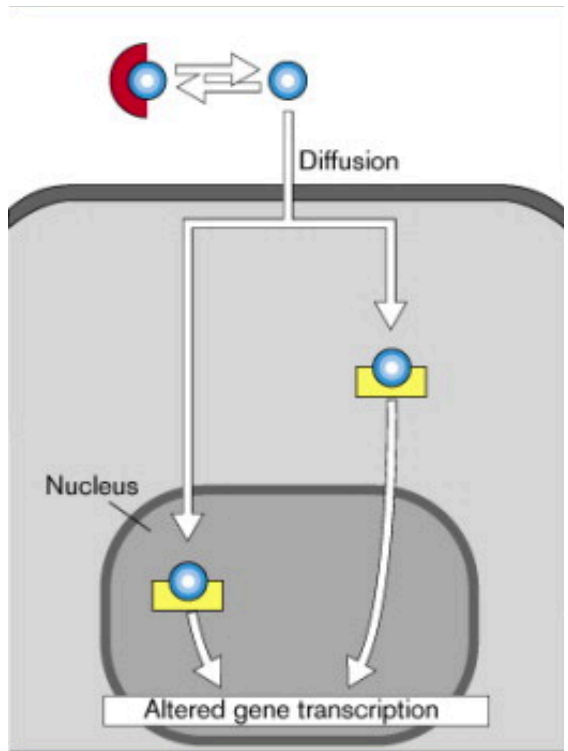
Cholesterol

Adrenal Steroid Hormone Synthesis Mechanisms



Signal	Receptor	Hormone
ACTH	MC2R (GPCR - Gs)	Cortisol
Angiotensin II	AGTR1 (GPCR – Gq)	Aldosterone

Both Aldosterone and Cortisol Function Through Nuclear Hormone Signaling

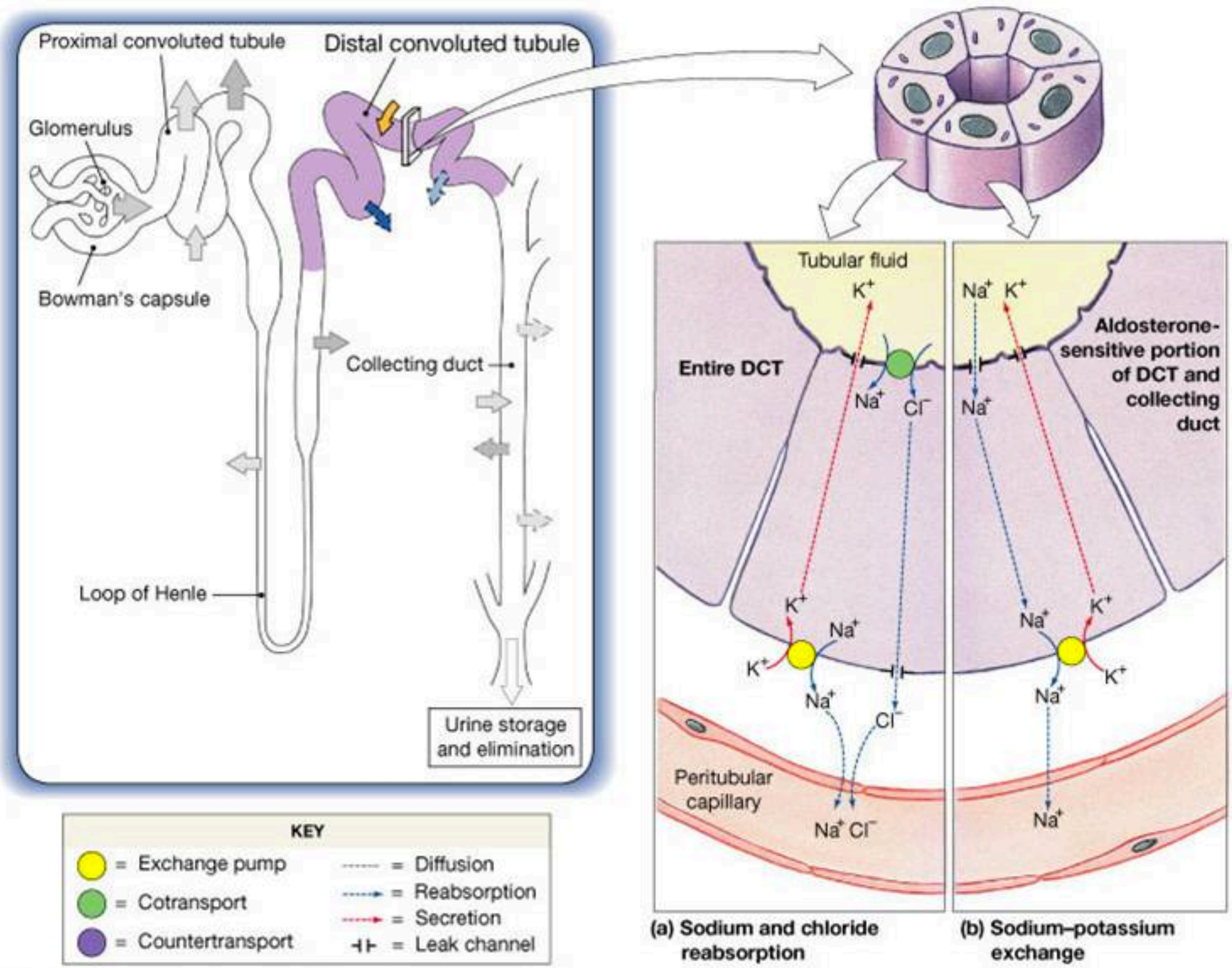


ALDOSTERONE REGULATES MINERAL BALANCE

Aldosterone Summary

What chemical type	Steroid hormone	
Where is it made?	Adrenal Cortex (Zona glomerulosa)	
What causes its release?	Angiotensin II Signaling (GPCR –Gq) and to a lesser extent ACTH	
What are its receptors?	Mineralcorticoid Receptor	
What tissues does it affect?	Kidneys (Collecting Ducts and Distal Convoluted Tubule)	ENAc, Na/K Transporter/SGK
How does it get turned off?	Receptor desensitization, less ATII signaling, 11BHSD2	

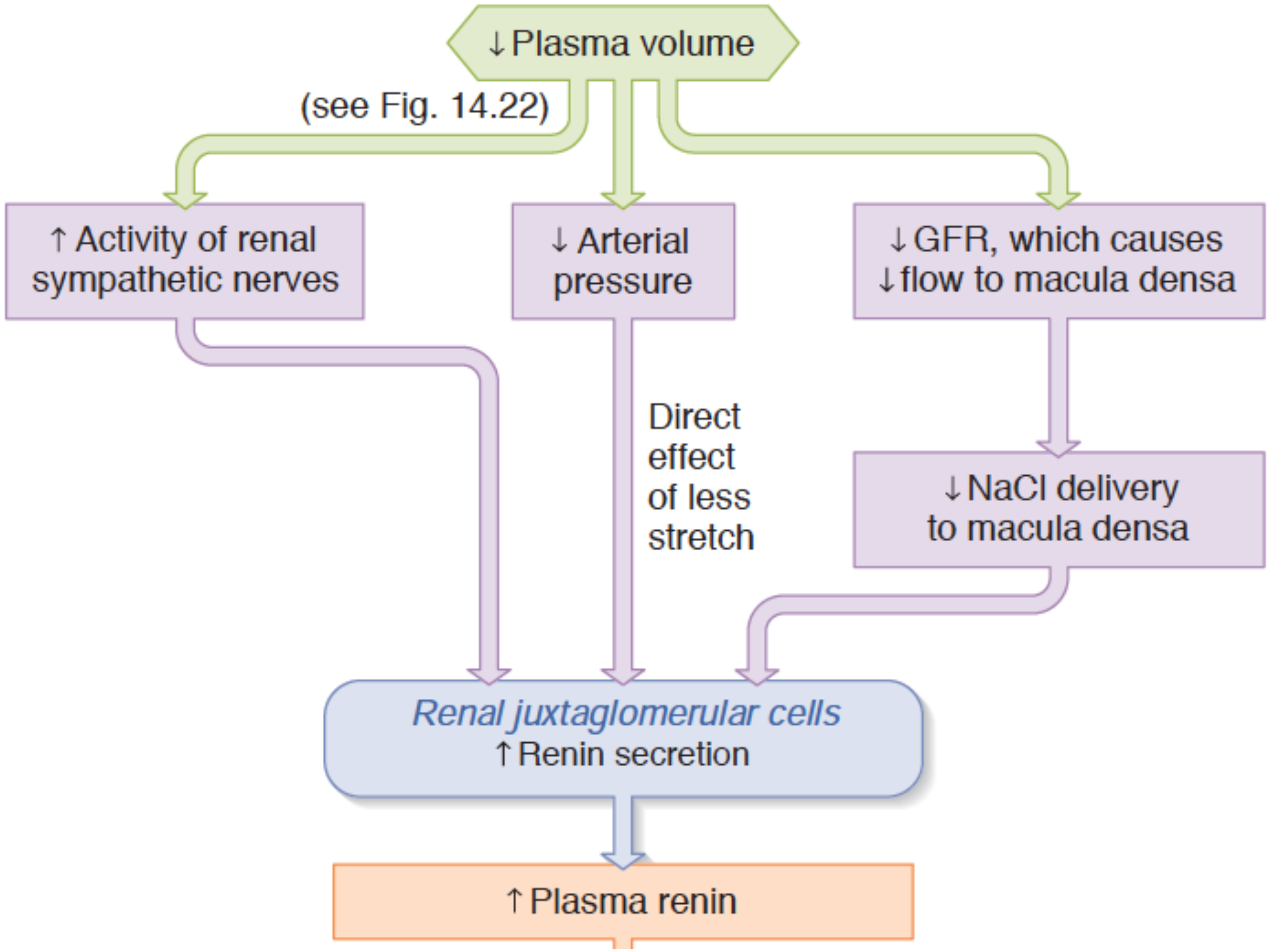
Key Aldosterone Effectors



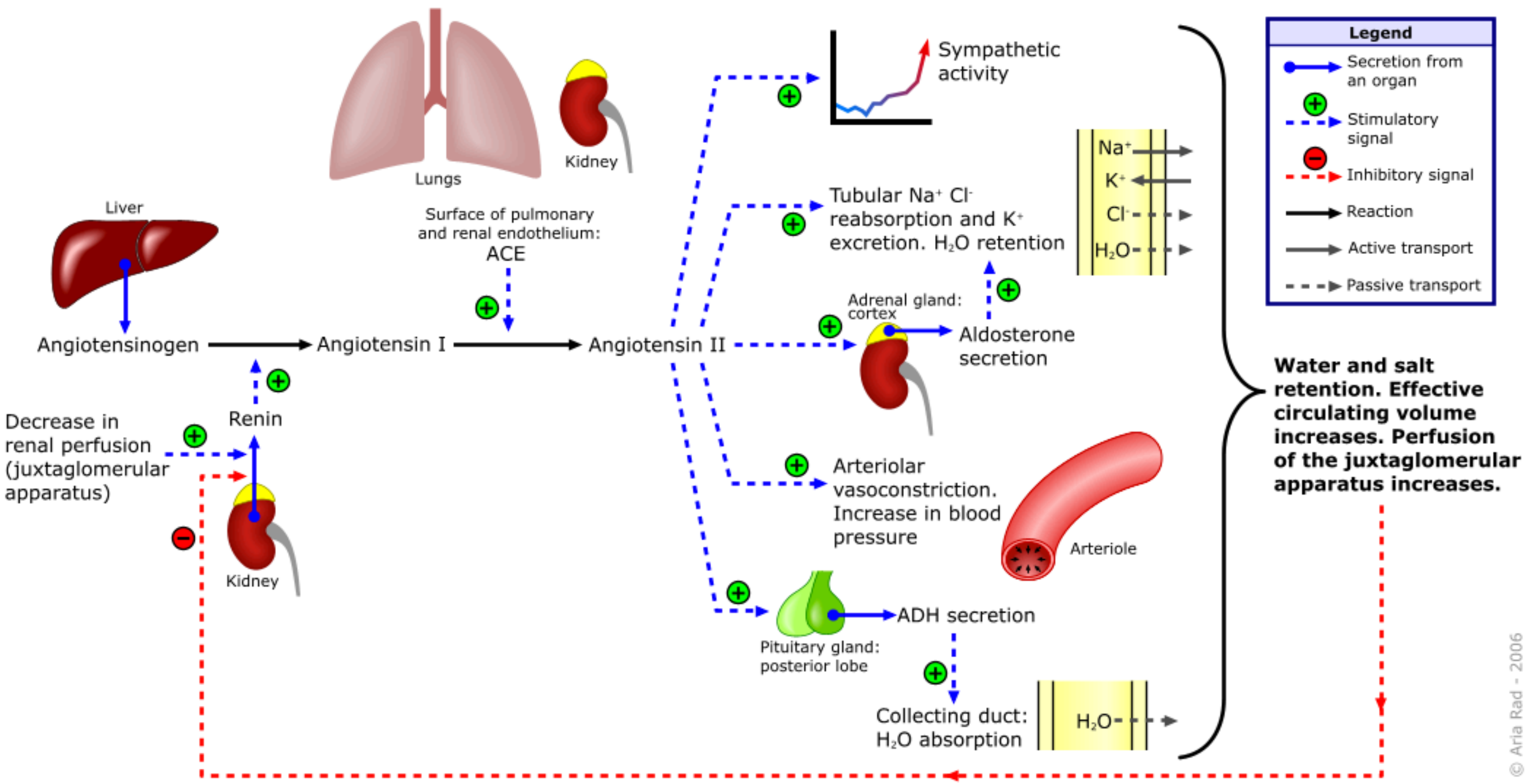
ENac

Na/K

Renin as a Volume/Pressure Sensor



The Renin/Angiotensin System

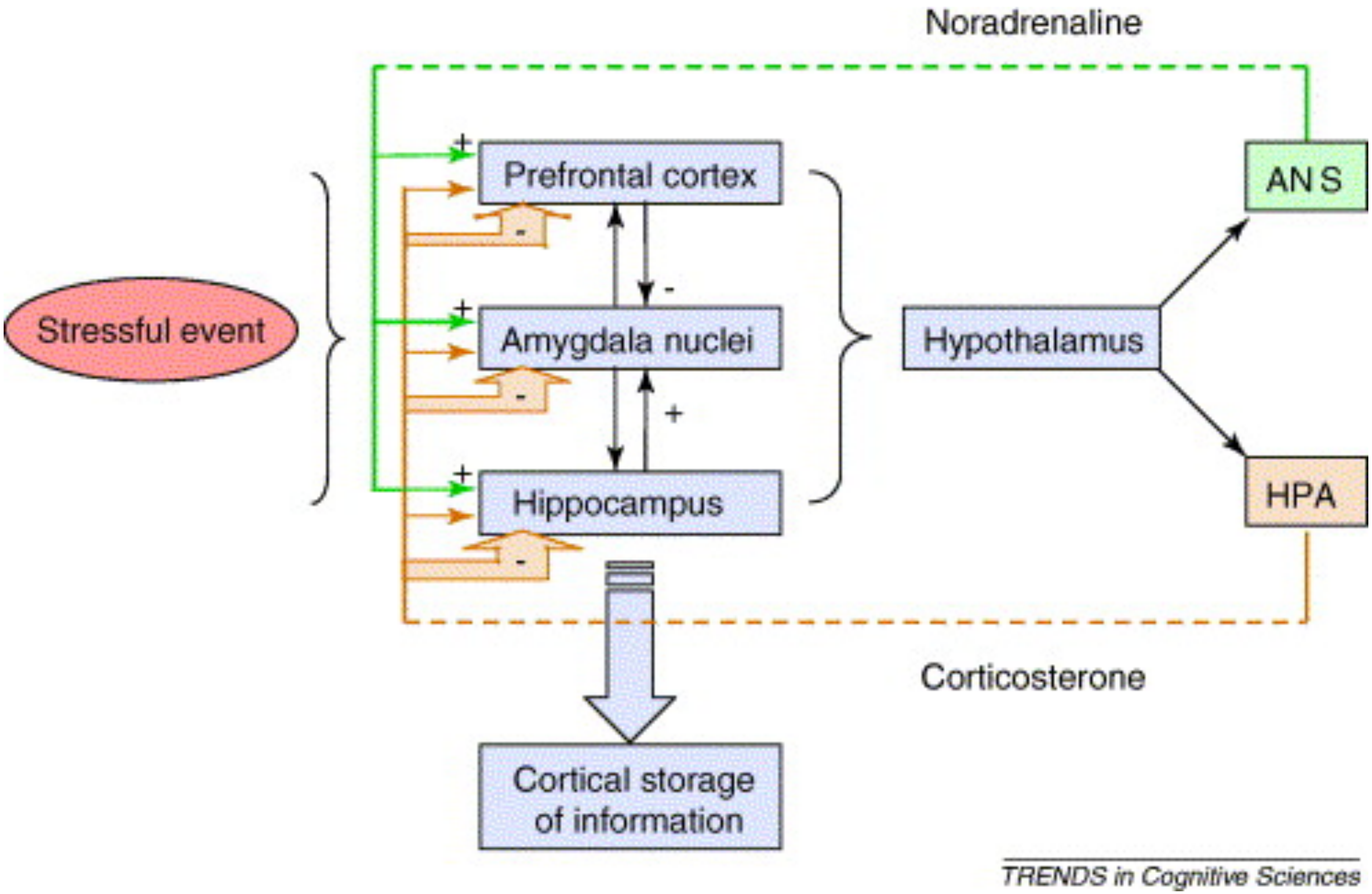


STRESS RESPONSIVE HORMONES

Two Types of Stress Response

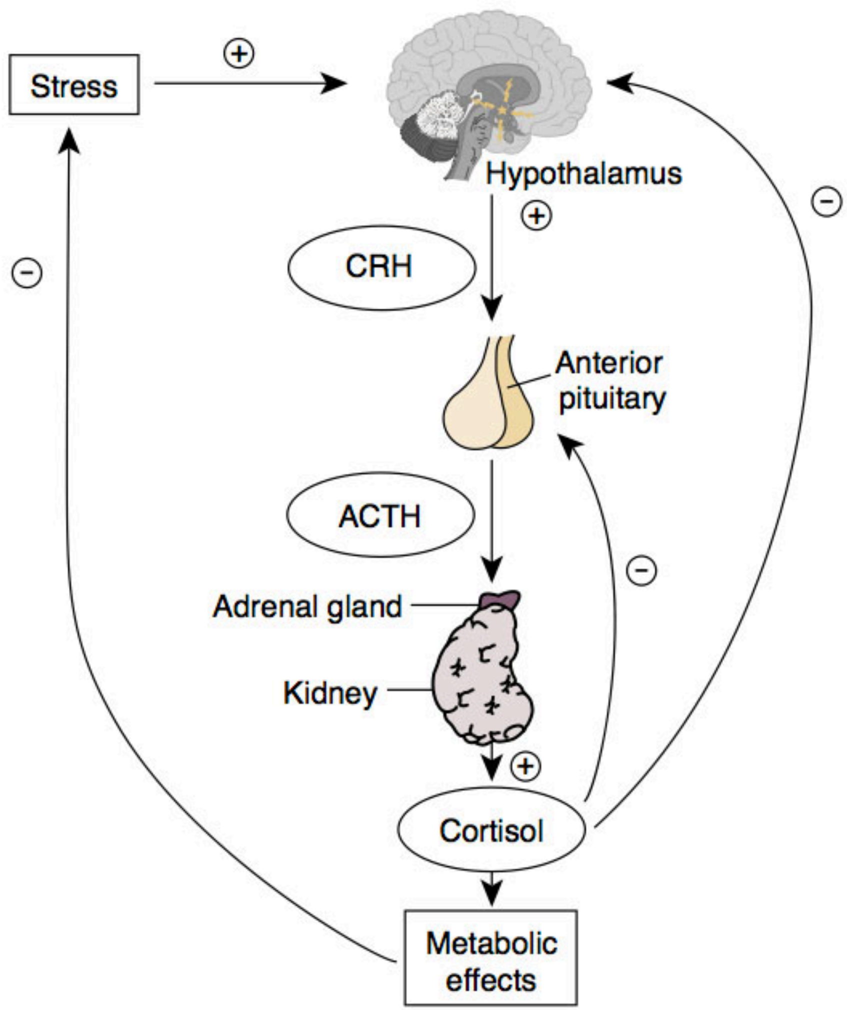
- Adrenaline
- Cortisol

CRH Release



Noradrenaline
Prefrontal cortex
Stressful event
Amygdala nuclei
Hippocampus
Hypothalamus
AN S
HPA
Corticosterone
Cortical storage of information
TRENDS in Cognitive Sciences

HPA Axis



Stress
+
Hypothalamus
+
CRH
Anterior
pituitary
ACTH
−
Adrenal gland
Kidney
+
Cortisol
Metabolic
effects
−
−

Corticotropin Releasing Hormone

Where is it made?	Hypothalamus (PVN)	
What causes its release?	Stress (Synaptic Inputs)	
What are its receptors?	CRHR1/2 (Gs)	
What tissues does it affect?	Corticotropes in the Anterior Pituitary	ACTH Release
How does it get turned off?	Receptor desensitization, Cortisol Negative Feedback to Hypothalamus, 11BHSD2	

ACTH

Where is it made?	Corticotropes of the Anterior Pituitary	
What causes its release?	CRH into the hypophysial portal system	
What are its receptors?	ACTHR (Gs - GPCR)	
What tissues does it affect?	Adrenal Cortex	Cortisol synthesis
How does it get turned off?	Receptor desensitization, Cortisol Negative Feedback to Hypothalamus, Cortisol Negative Feedback to Hypothalamus 11BHSD2	

Cortisol Summary

Where is it made?	Adrenal Cortex (Zona fasciculata)	
What causes its release?	ACTH (GPCR –Gs)	
What are its receptors?	Glucocorticoid Receptor	
What tissues does it affect?	Muscle	Protein Catabolism
	Adipose	Increased Lipolysis, Adipogenesis
	Liver	Increased Gluconeogenesis
	Brain	Less Food Intake
	Immune System	Reduced Th2 Activation
How does it get turned off?	Receptor desensitization, Negative Feedback to Pituitary, Negative Feedback to Hypothalamus, 11BHSD2	

CRH In Response to Stress

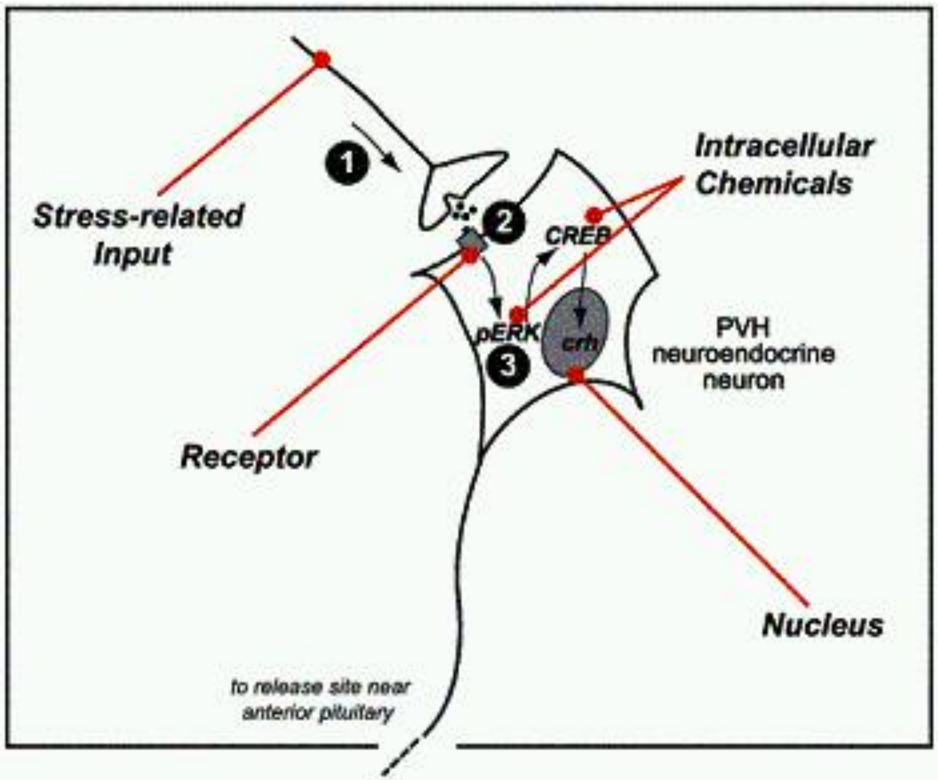
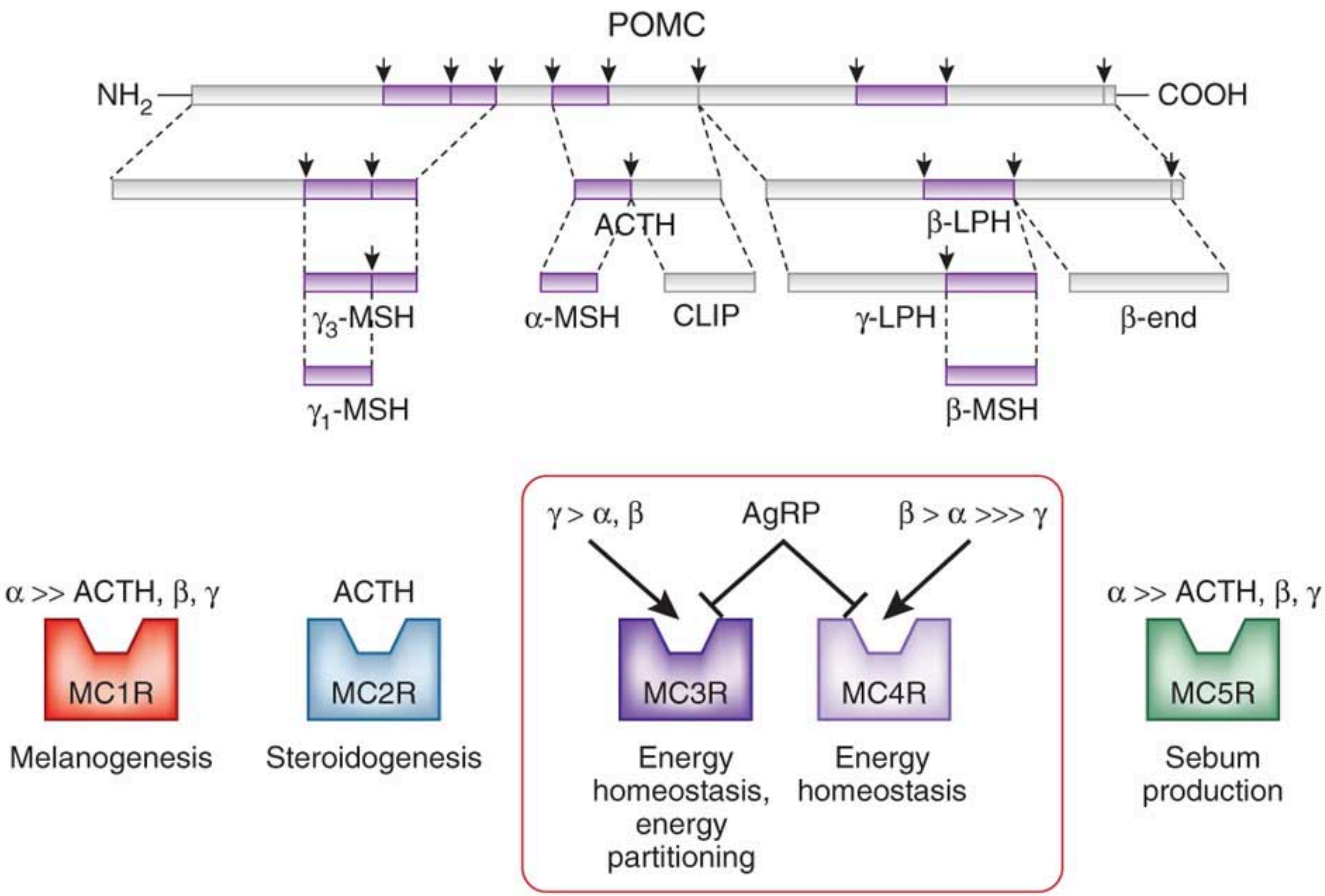
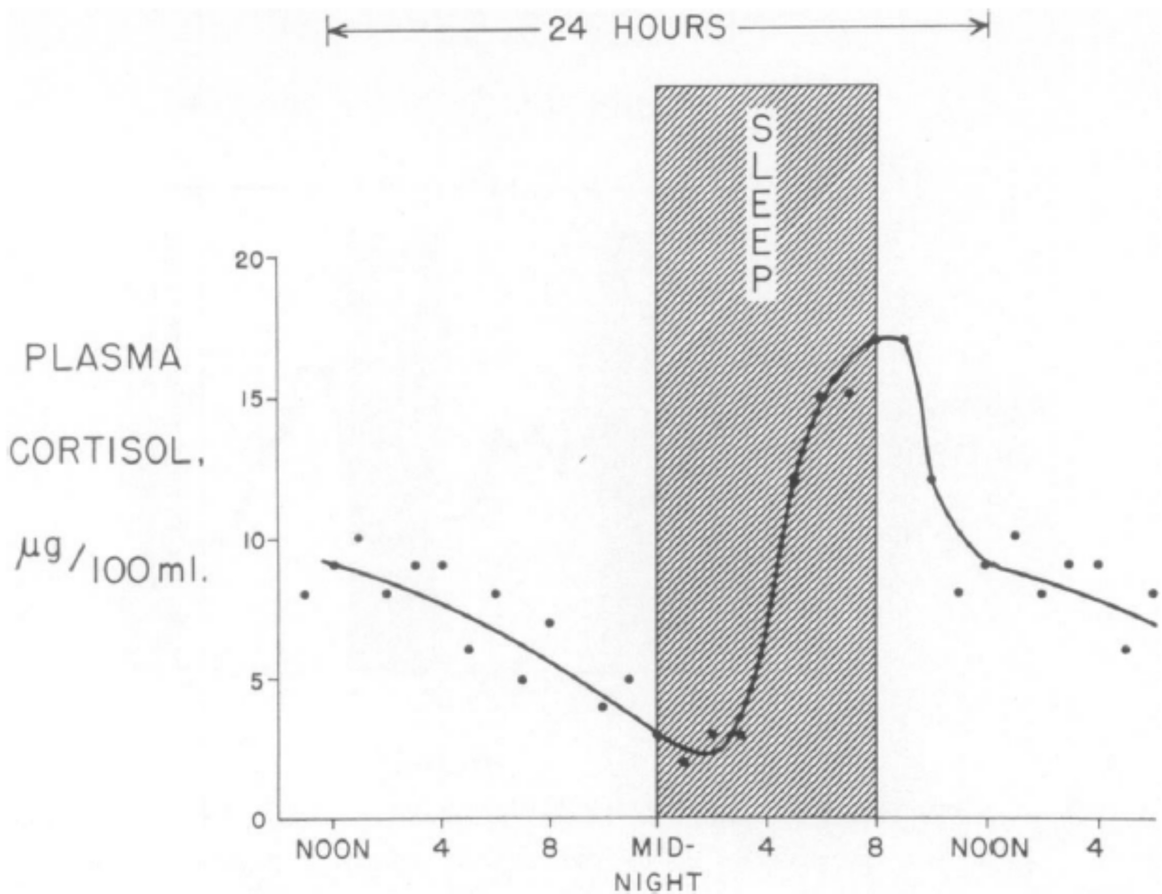


Figure 1. Activation of the CRH gene in the nucleus of a CRH neuroendocrine neuron in response to stress.

ACTH and other Hormones are Generated from POMC Transcripts

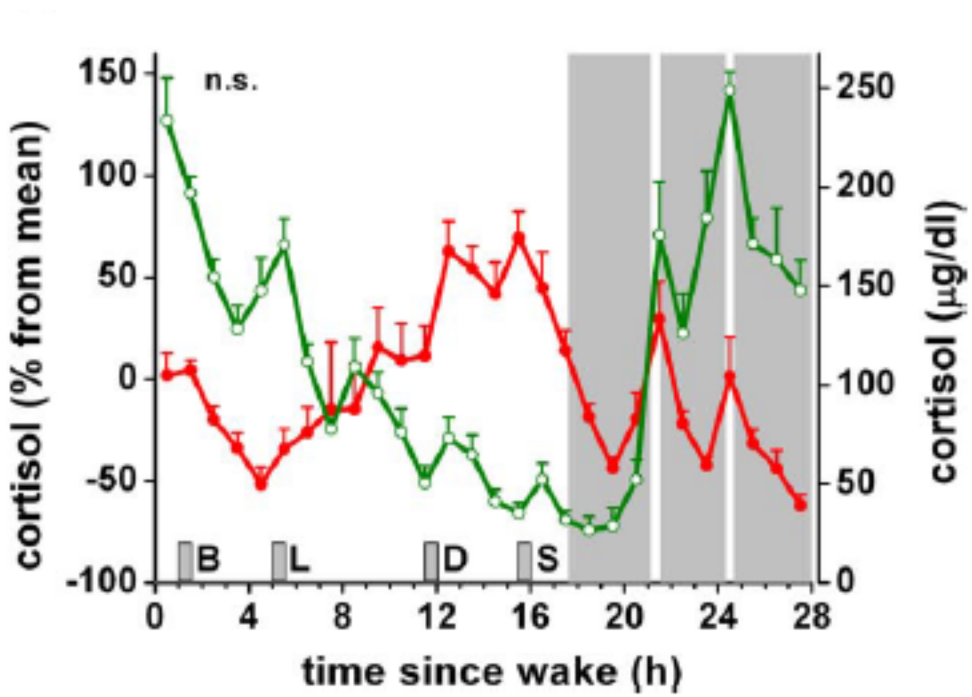


Daily Rhythms of Cortisol Release



Liddle GW (1966) An analysis of circadian rhythms in human adrenocortical secretory activity. Trans Am Clin Clim Assoc 77: 151–160.

Night Time Workers



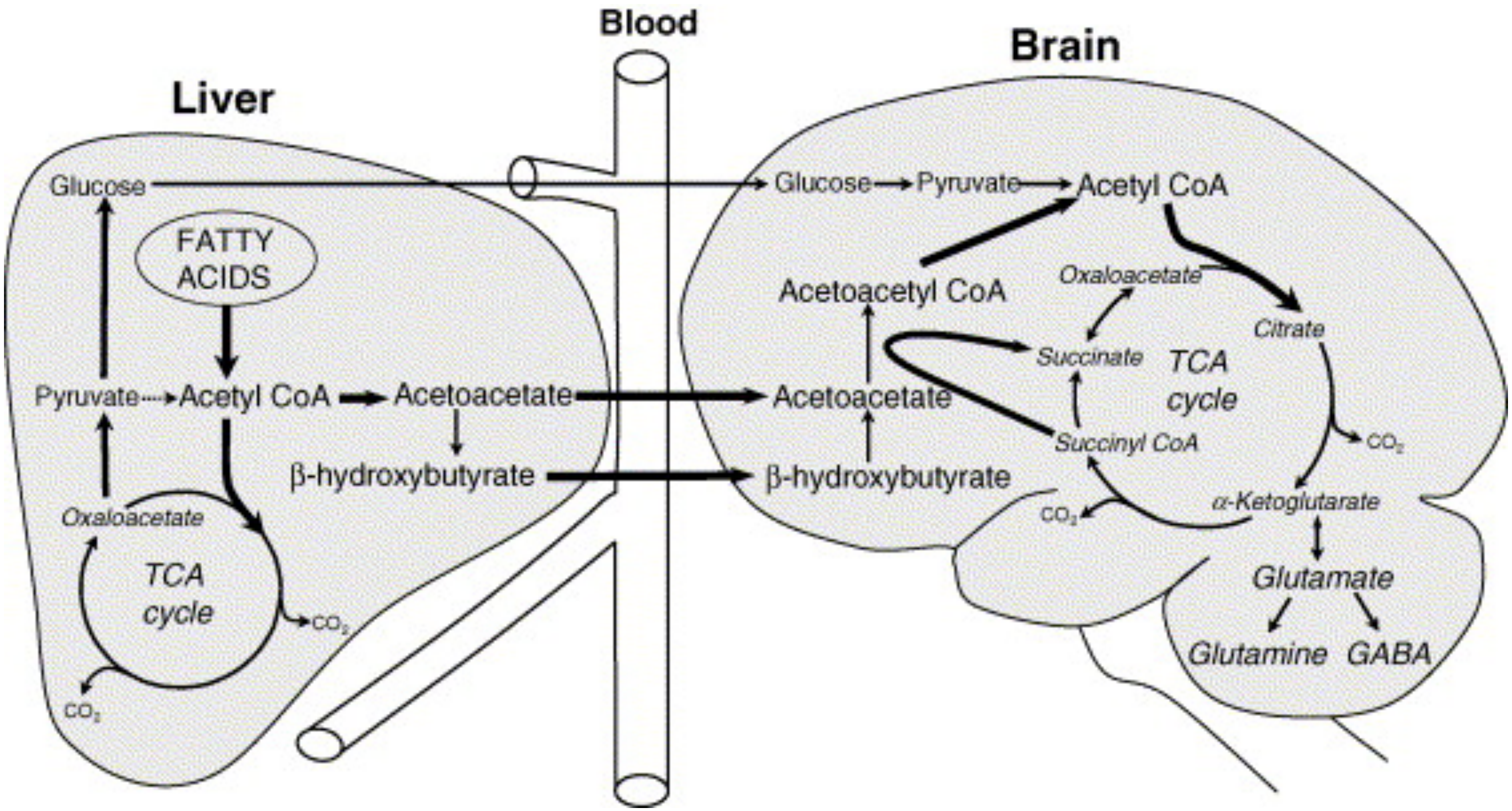
Normal
Sleep disrupted

Scheer F AJL, Hilton MF, Mantzoros CS, Shea S A (2009) Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 106: 4453–4458. doi: 10.1073/pnas.0808180106.

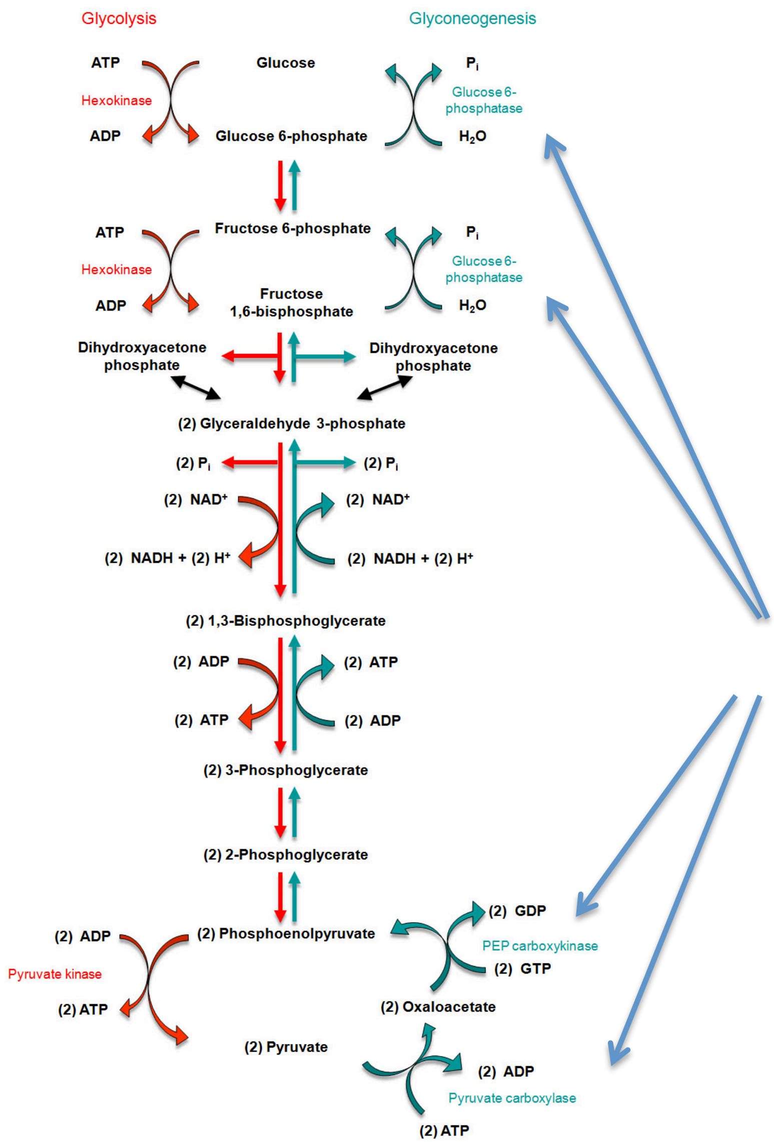
Major Chronic Responses to Stress

- Shift resources (mainly glucose) towards essential functions
- Suppress non-essential functions
  - Immune system
  - Reproductive system
  - Growth

Brain Requires Glucose Supply

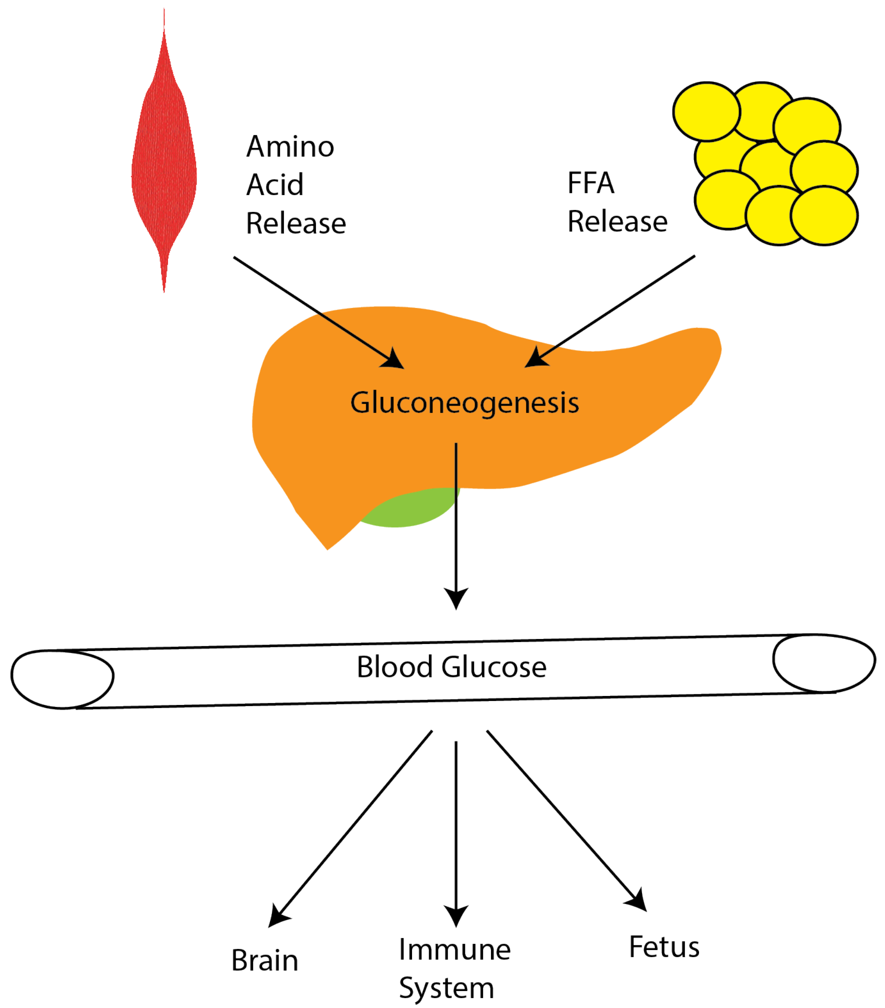


Regulation of Gluconeogenesis



Activation of mRNA transcription by glucocorticoids in the liver

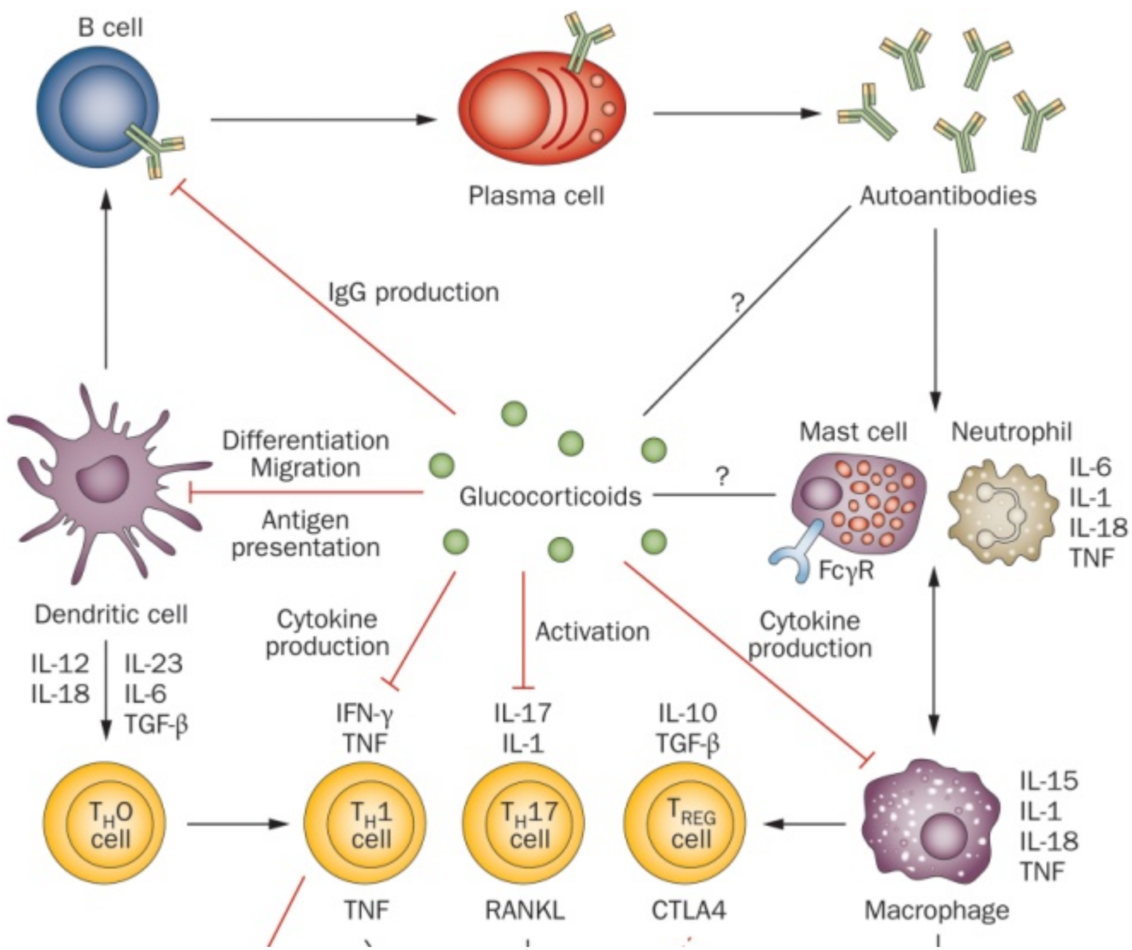
Cortisol Maintains Blood Glucose Levels



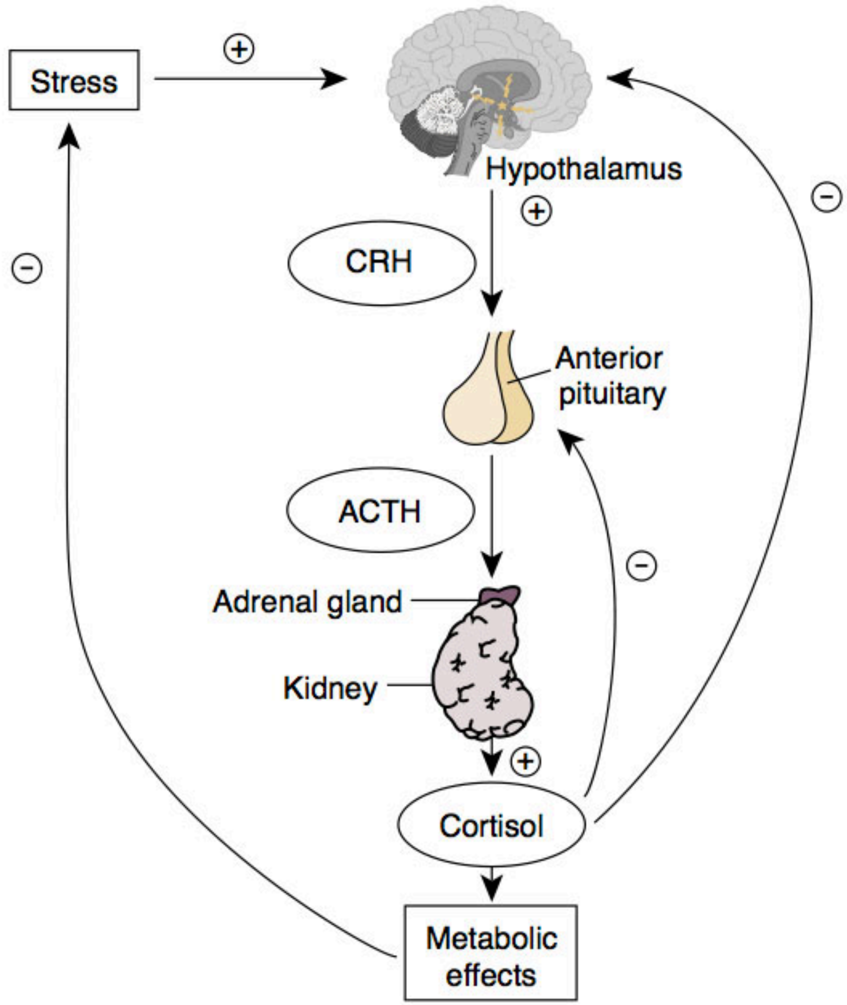
Three Mechanisms to Maintain Blood Glucose Levels

1. Promote gluconeogenesis (liver)
2. Provide substrates for gluconeogenesis (muscle/fat)
3. Prevent glucose uptake (muscle/fat)

Effects of Cortisol on Immune Function

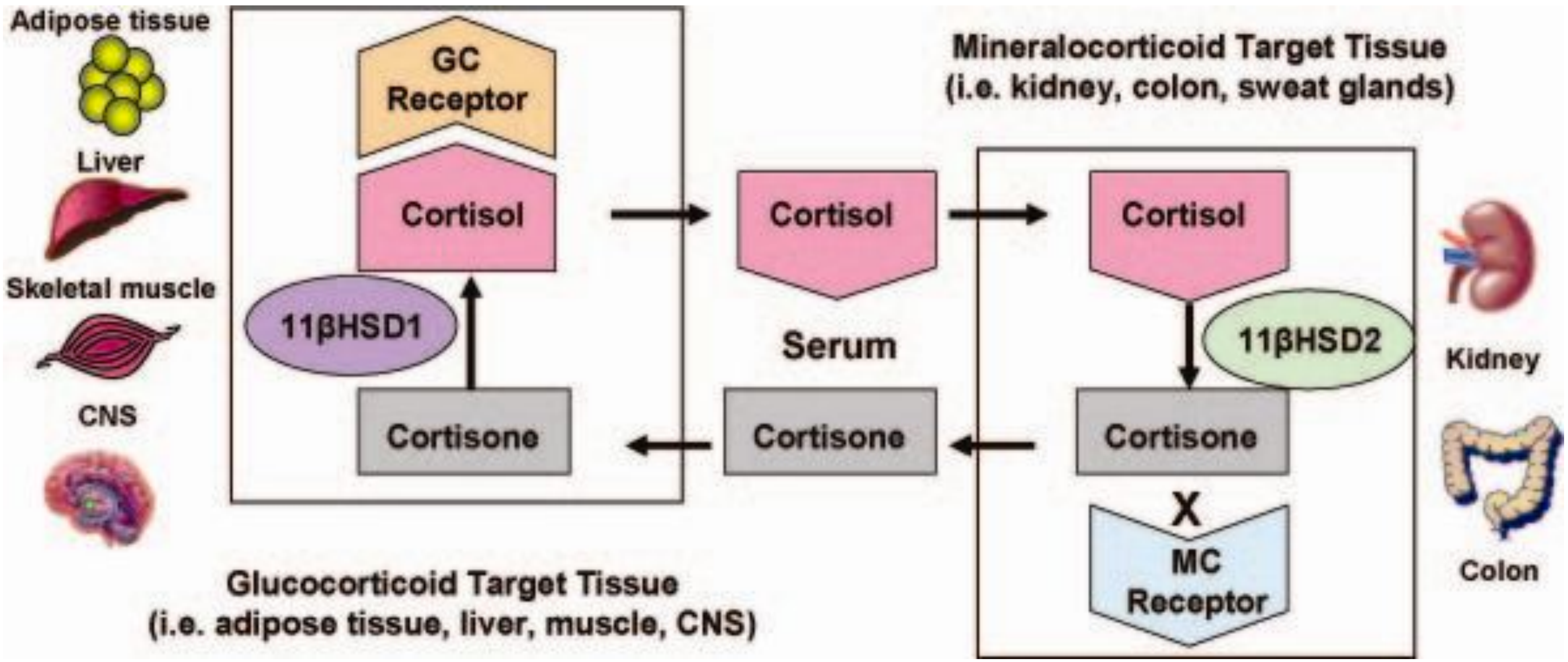


HPA Axis



Stress
+
Hypothalamus
+
CRH
Anterior
pituitary
ACTH
Adrenal gland
Kidney
+
Cortisol
Metabolic
effects
−
−
−

11β-HSD 2 and Local Concentrations of Glucocorticoids



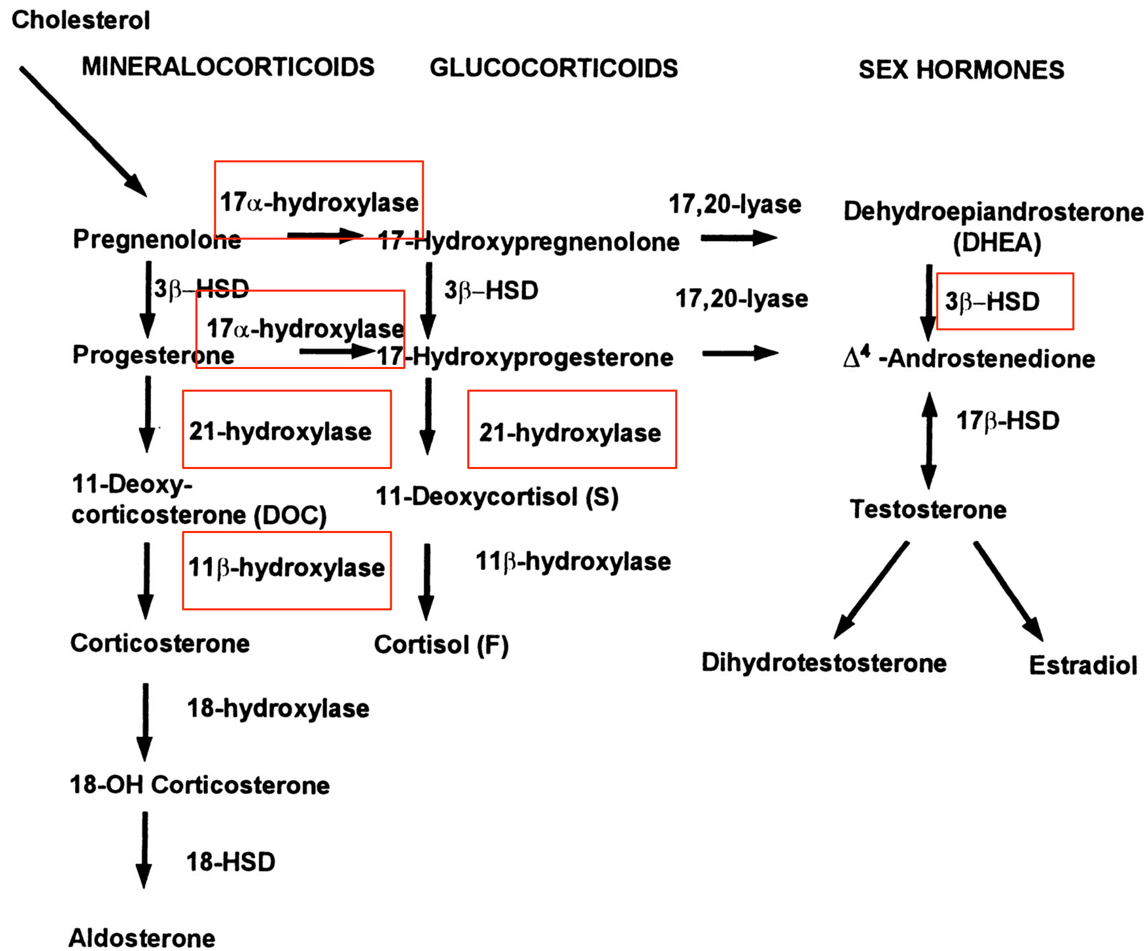
In off target tissues,
or to desensitize normal tissues

ADRENAL STEROID HORMONE DISFUNCTION

Main Types of Endocrine Disfunction

1. Congenital (Mutations in Hormone Production or Responses)
2. Tumors which secrete too much hormone
3. Immune destruction of hormone secreting cells

Common CAH Mutations



Maria I. New, and Robert C. Wilson PNAS 1999;96:12790-12797

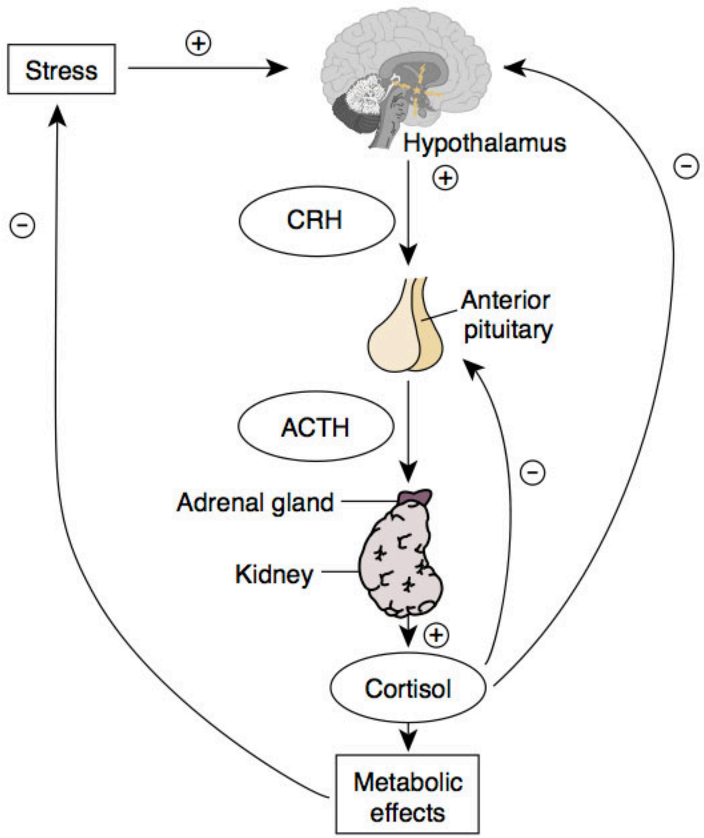
Discuss

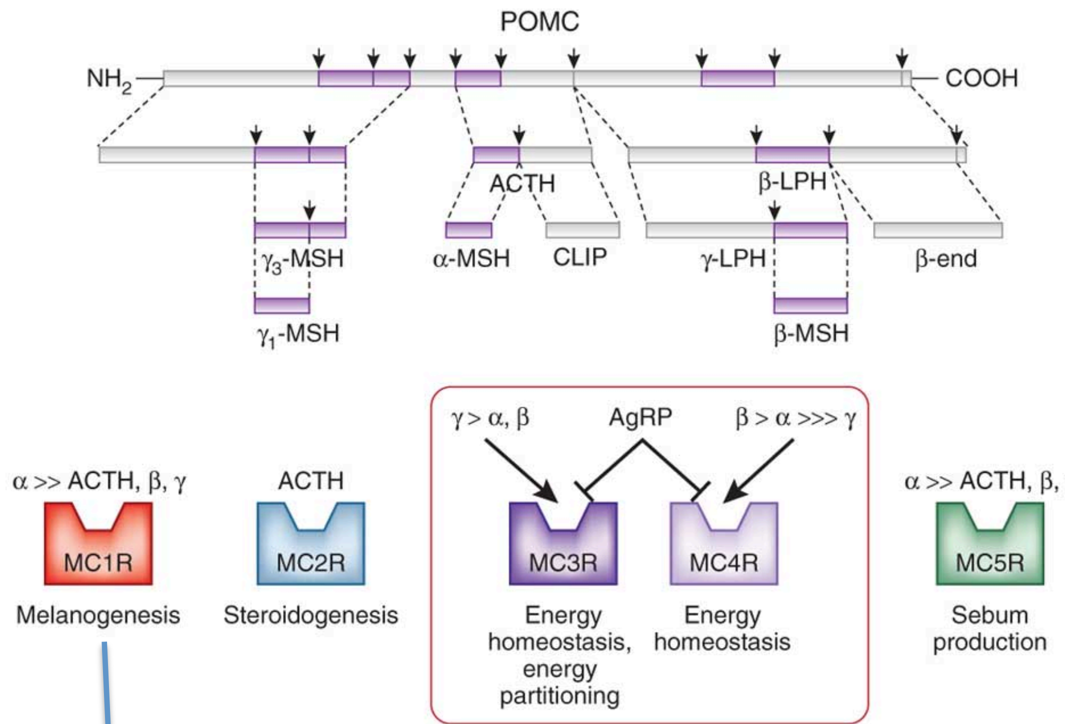
- Congenital Adrenal Hyperplasia (aka adrenogenital syndrome)
- Imagine mutations in genes involved early in the biosynthesis of cortisol/aldosterone
- What would be the effects on
  - Sex hormone production
  - Salt balance
  - Adrenal size

Addison's Disease

- Autoimmune destruction of adrenal gland
- How would this anatomically differ from CAH?
- Why would blood pressure be low?
- Why would there be a risk of hypoglycemia?

Hyperpigmentation in Addison's





Hyperpigmentation

Tumors Affecting Adrenal Function

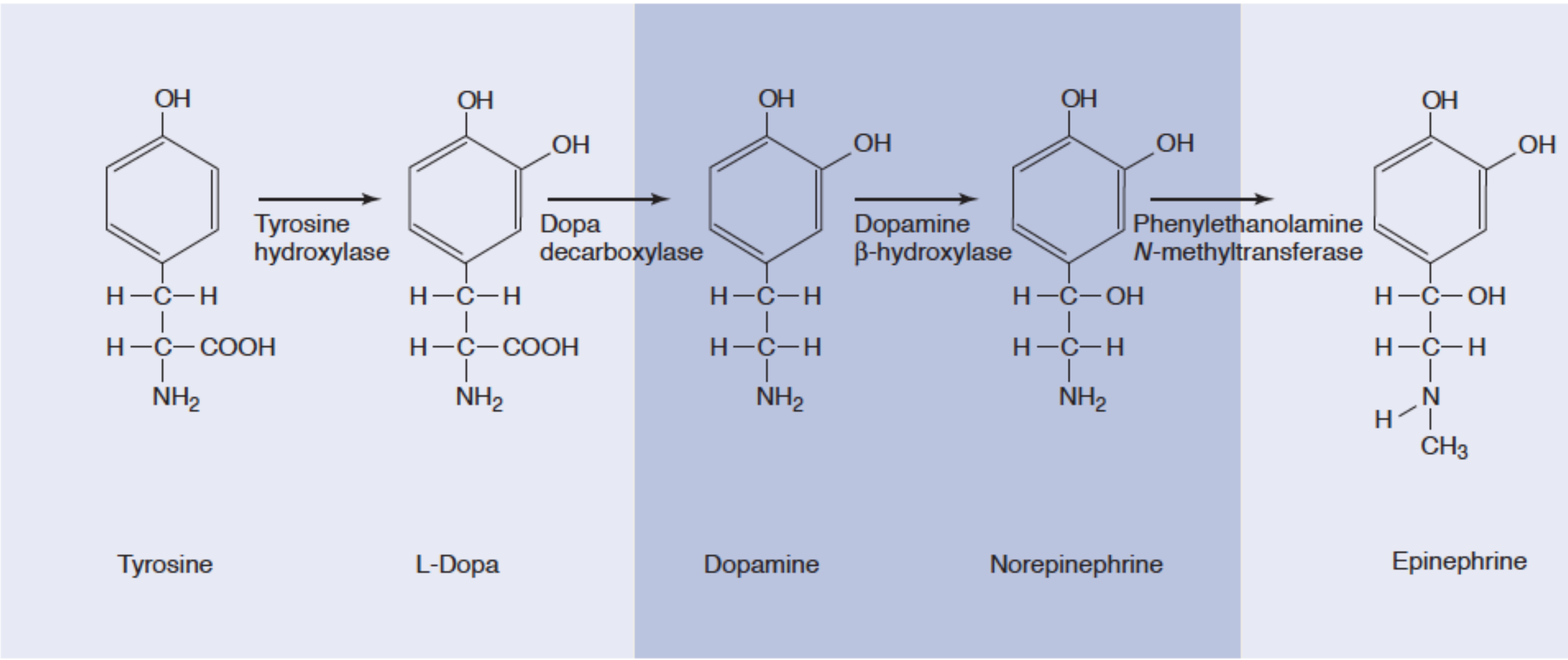
- Conn’s syndrome (adenoma of zona glomerulosa)
- Cushing’s syndrome
  - pituitary adenoma (ACTH releasing) or
  - adenoma of zona fasciculata

ADRENALINE MEDIATES SHORT-TERM STRESS RESPONSES

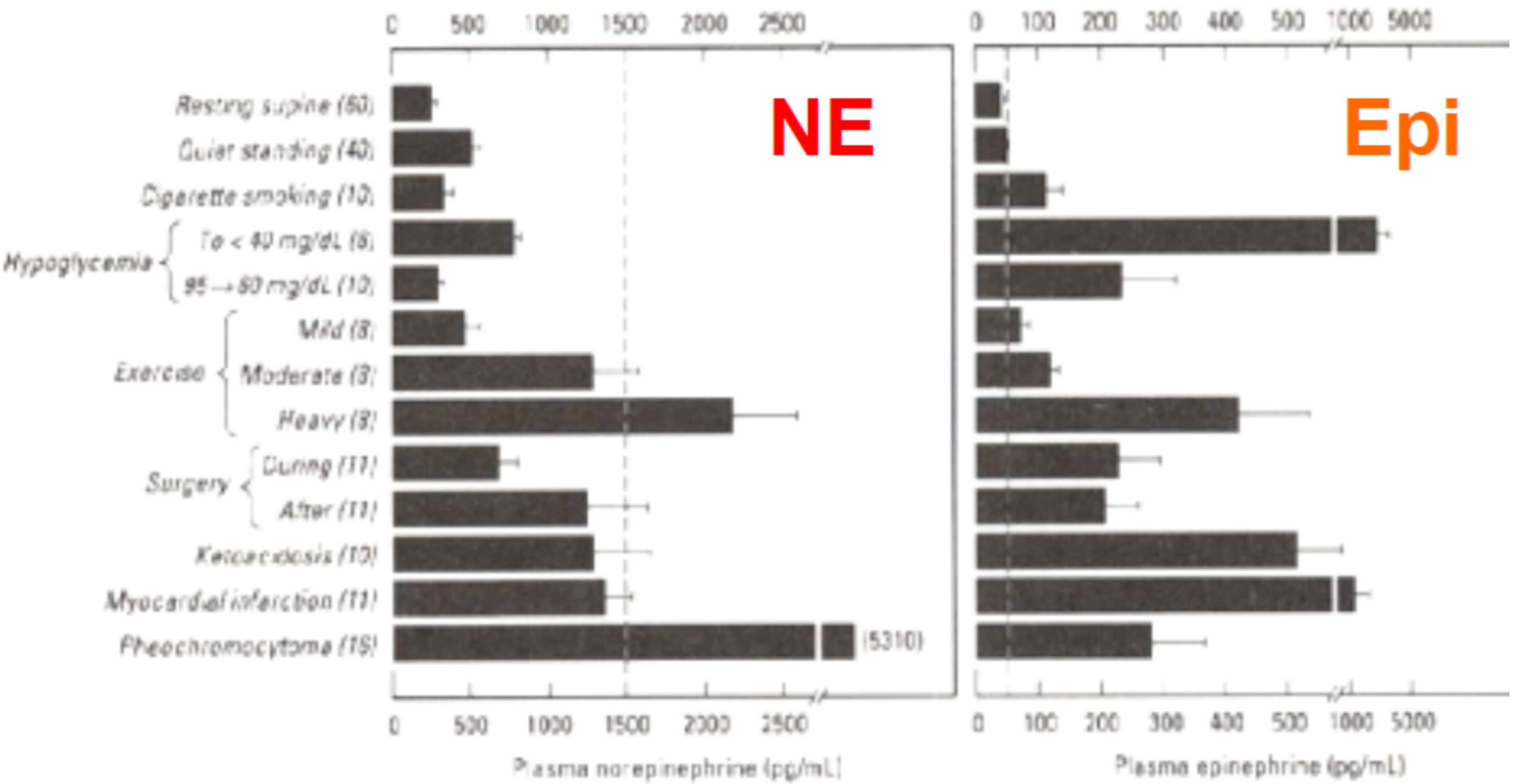
Epinephrine Summary

Where is it made?	Adrenal medulla	
What causes its release?	Sympathetic nervous stimulation	
What is its receptor?	Alpha/Beta-Adrenergic Receptors (5 subtypes)	GPCR -> Gs and Gi
What tissues does it affect?	Heart	Increased heart rate
	Lungs	Increased respiration
	Vasculature	Vasoconstriction (smooth muscle), vasodilation (skeletal muscle)
	Liver	Glycogenolysis
	Fat	Lipolysis
	Skeletal Muscle	Contraction
How does it get turned off?	Sympathetic signal stops, Receptor desensitization	

Epinephrine and Norepinephrine

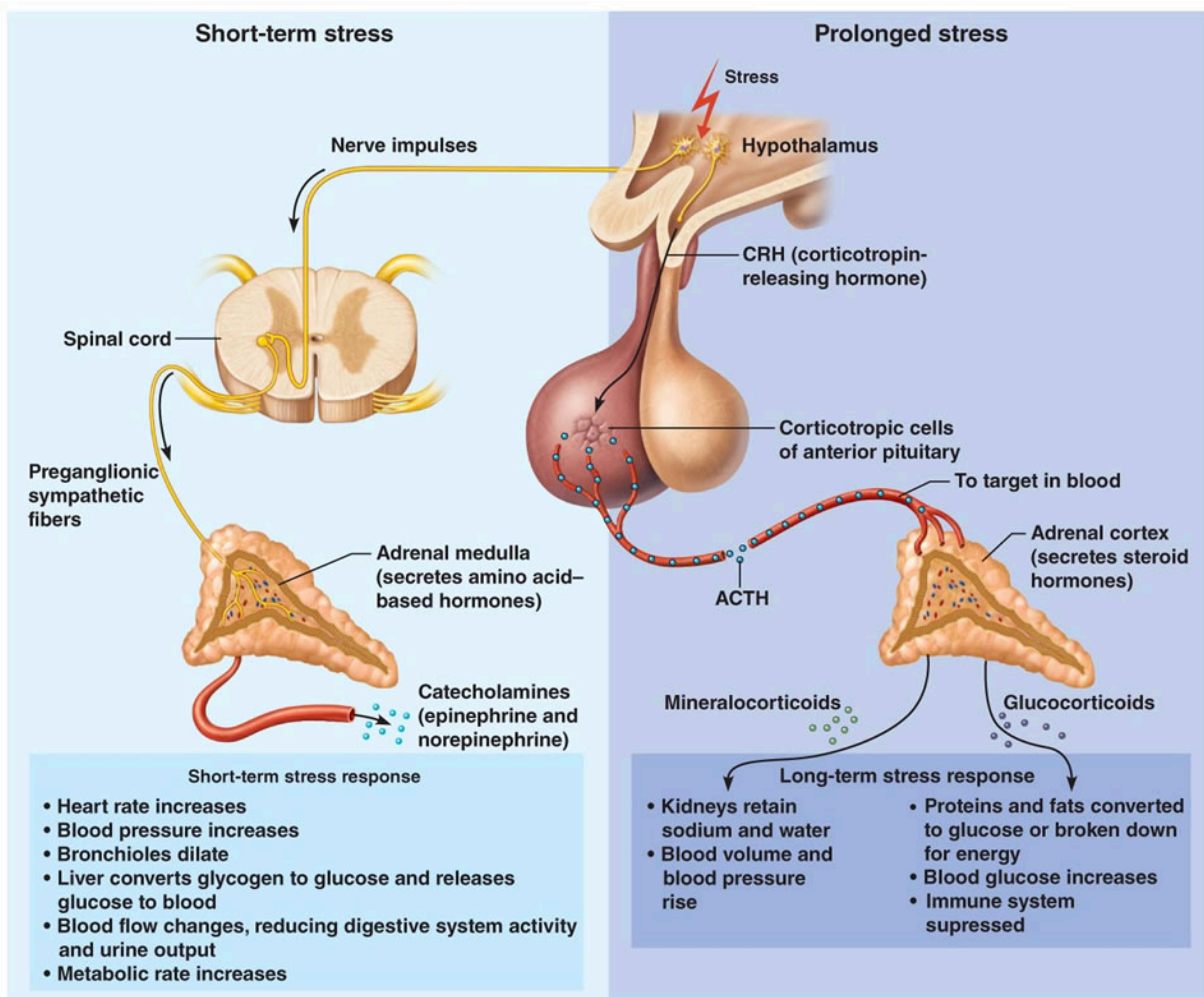


Epinephrine vs Norepinephrine

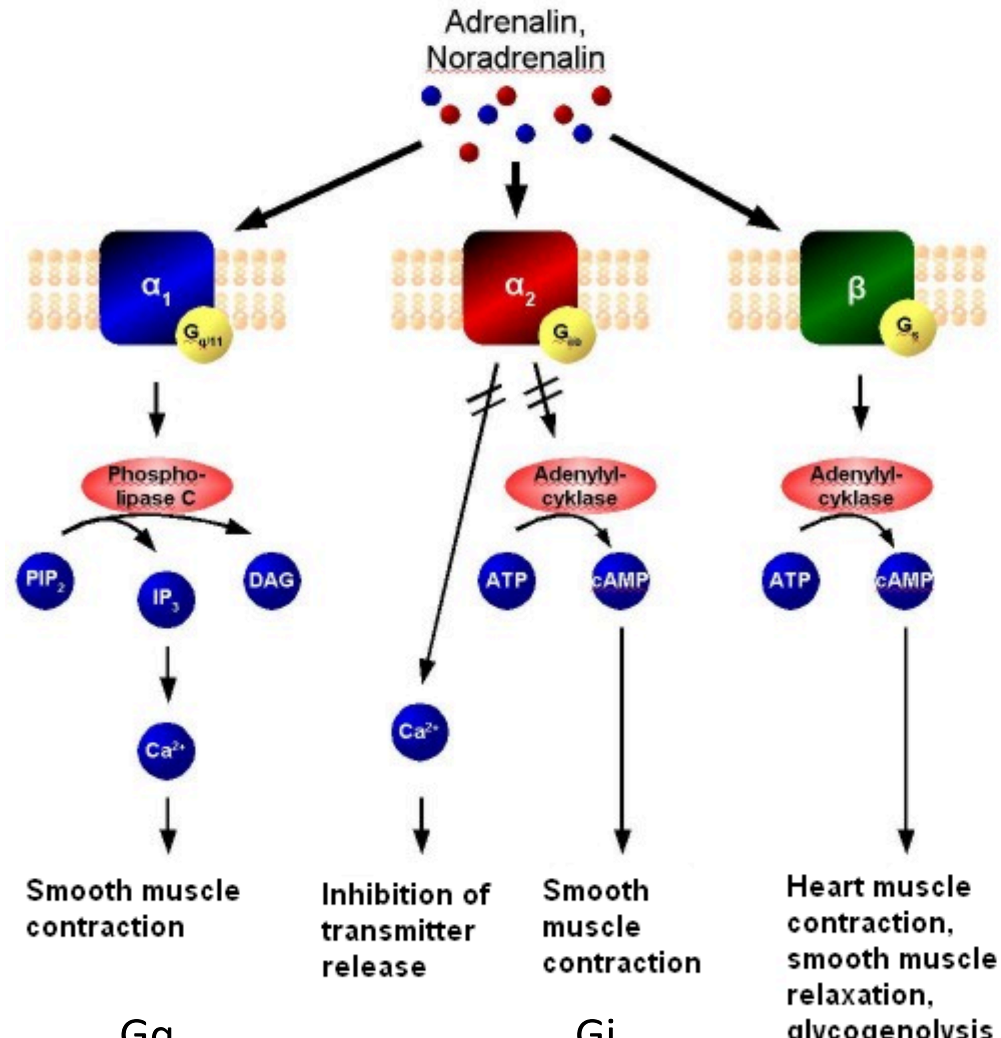


Dashed line is level in circulation needed to elicit a physiological response

Adrenaline vs Cortisol Release



Cardiovascular Roles of Epinephrine

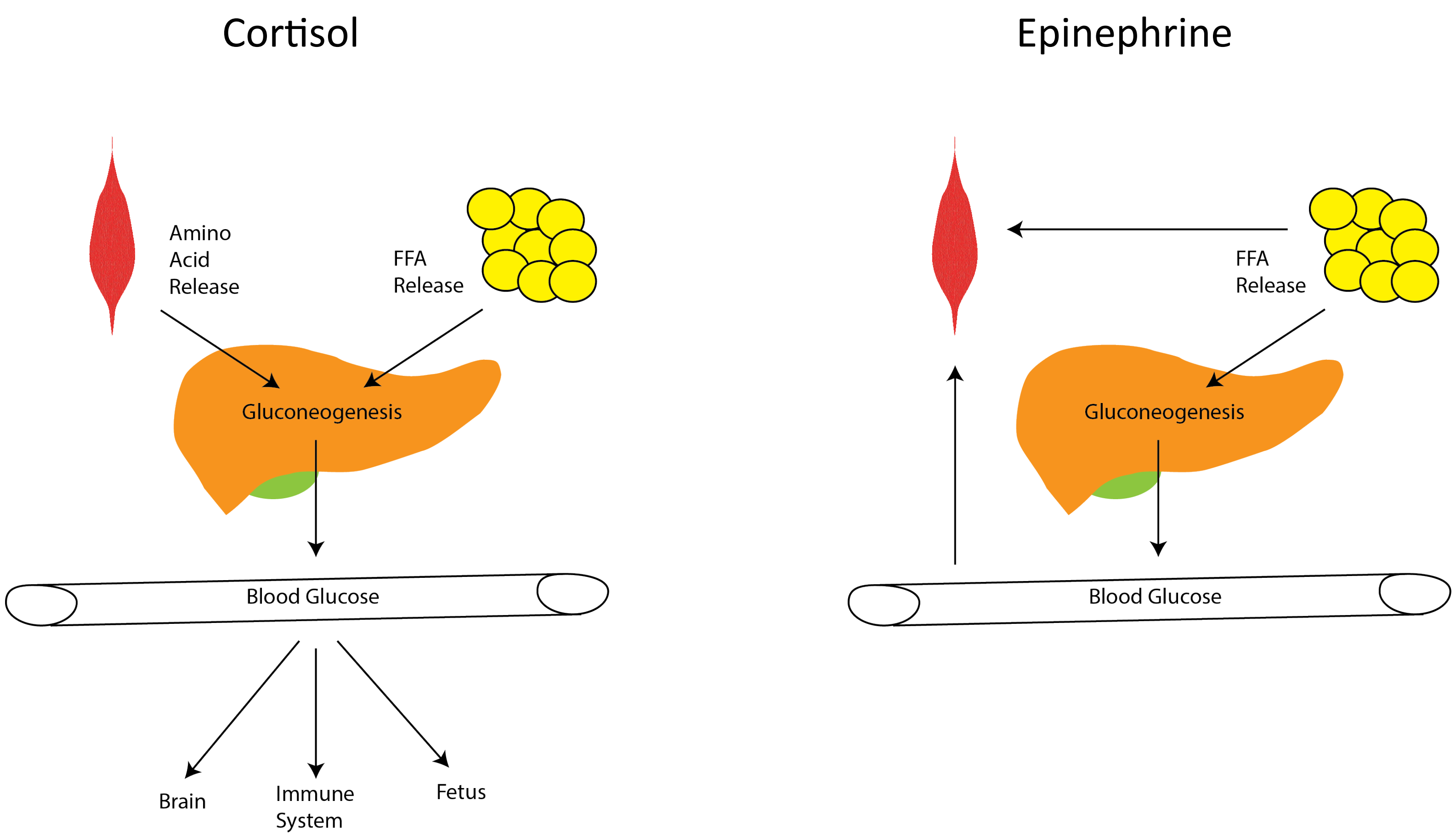


Gq

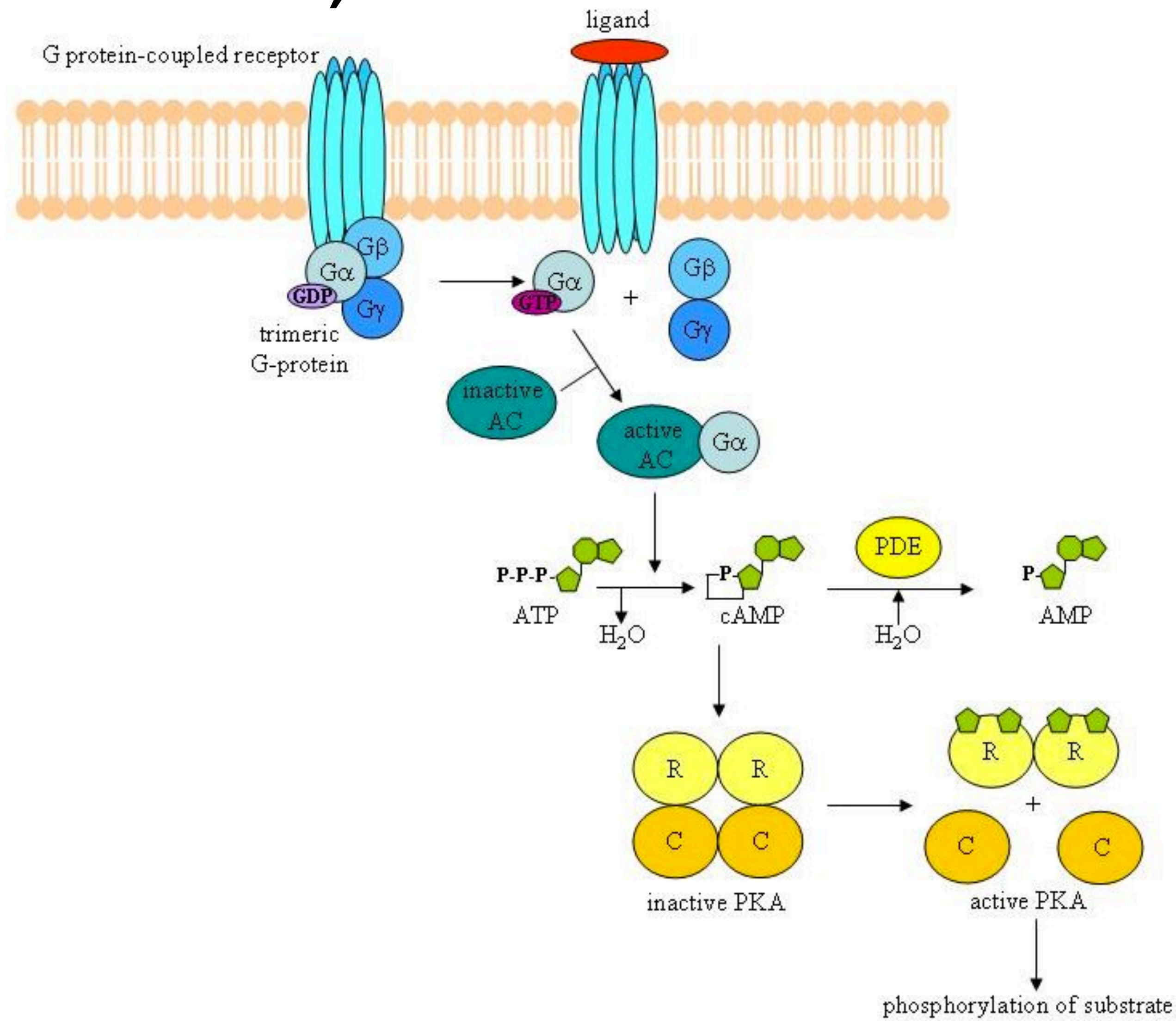
Gi

Gs

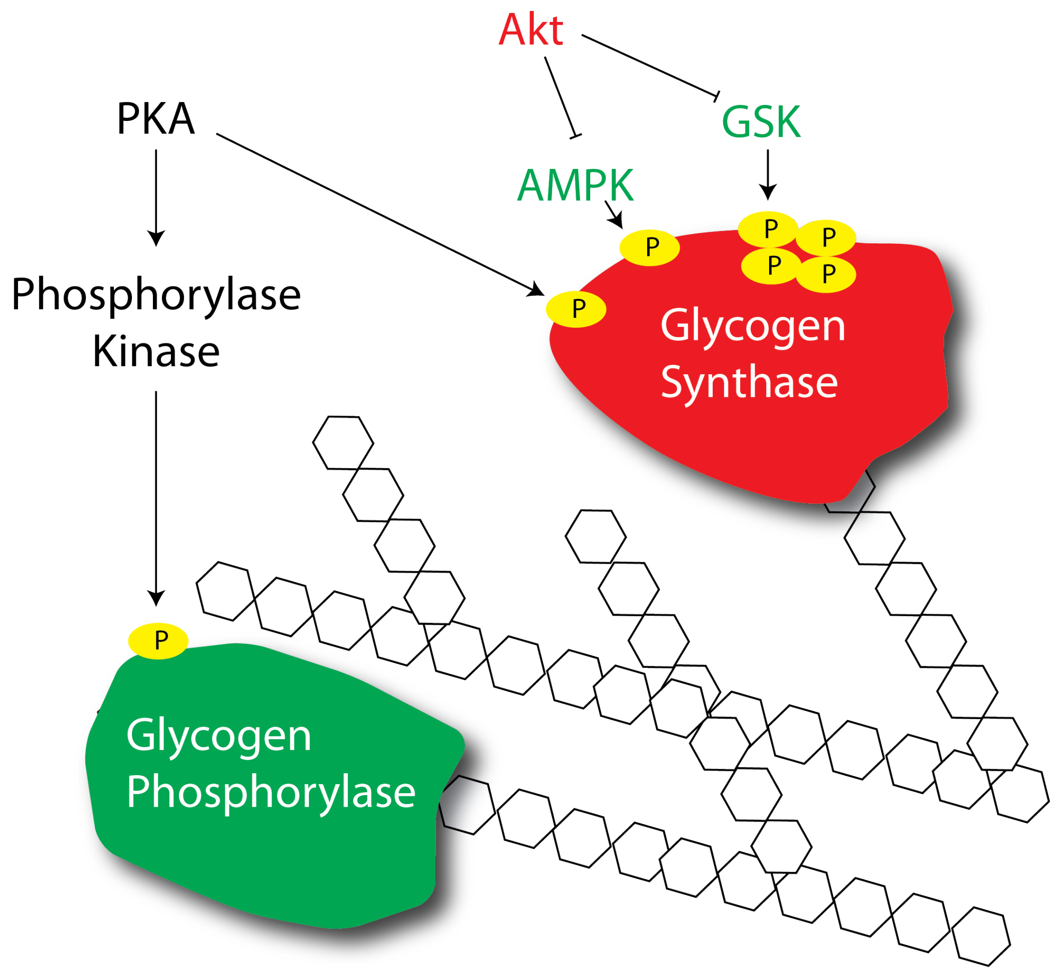
Metabolic Roles of Epinephrine



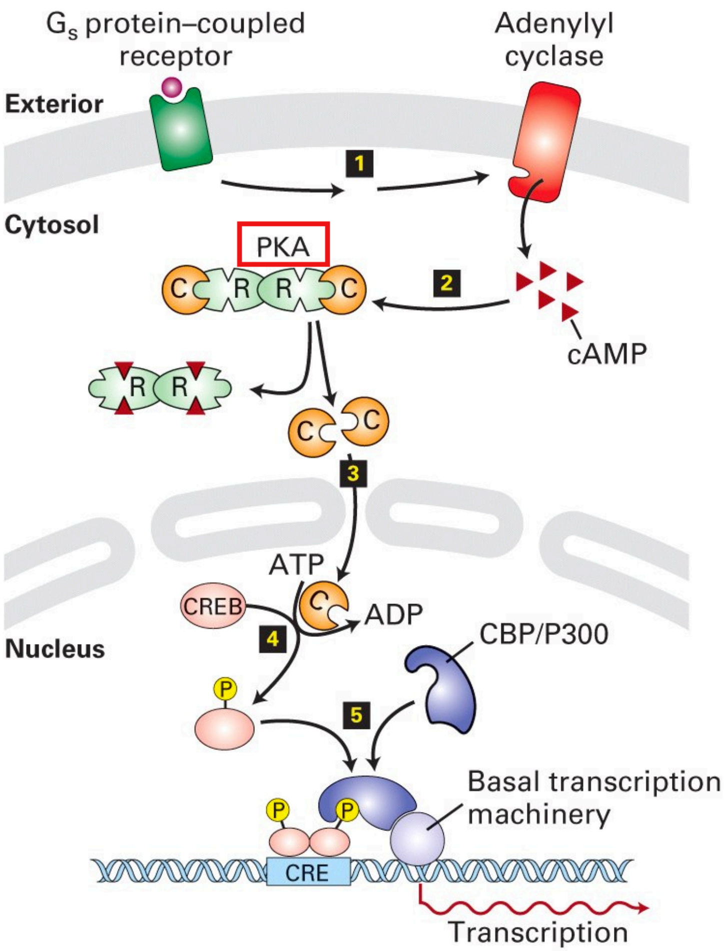
Epinephrine Binds B-AR/Gs in Skeletal Muscle, Liver and Fat Tissue



Epinephrine Mediated Activation of Glycogenolysis



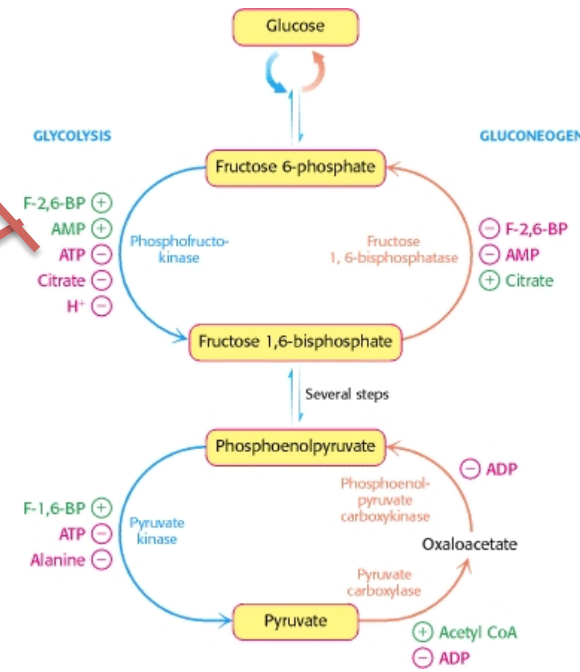
Dual Effects of Epinephrine on Gluconeogenesis in the Liver



Gluconeogenic Gene Transcription

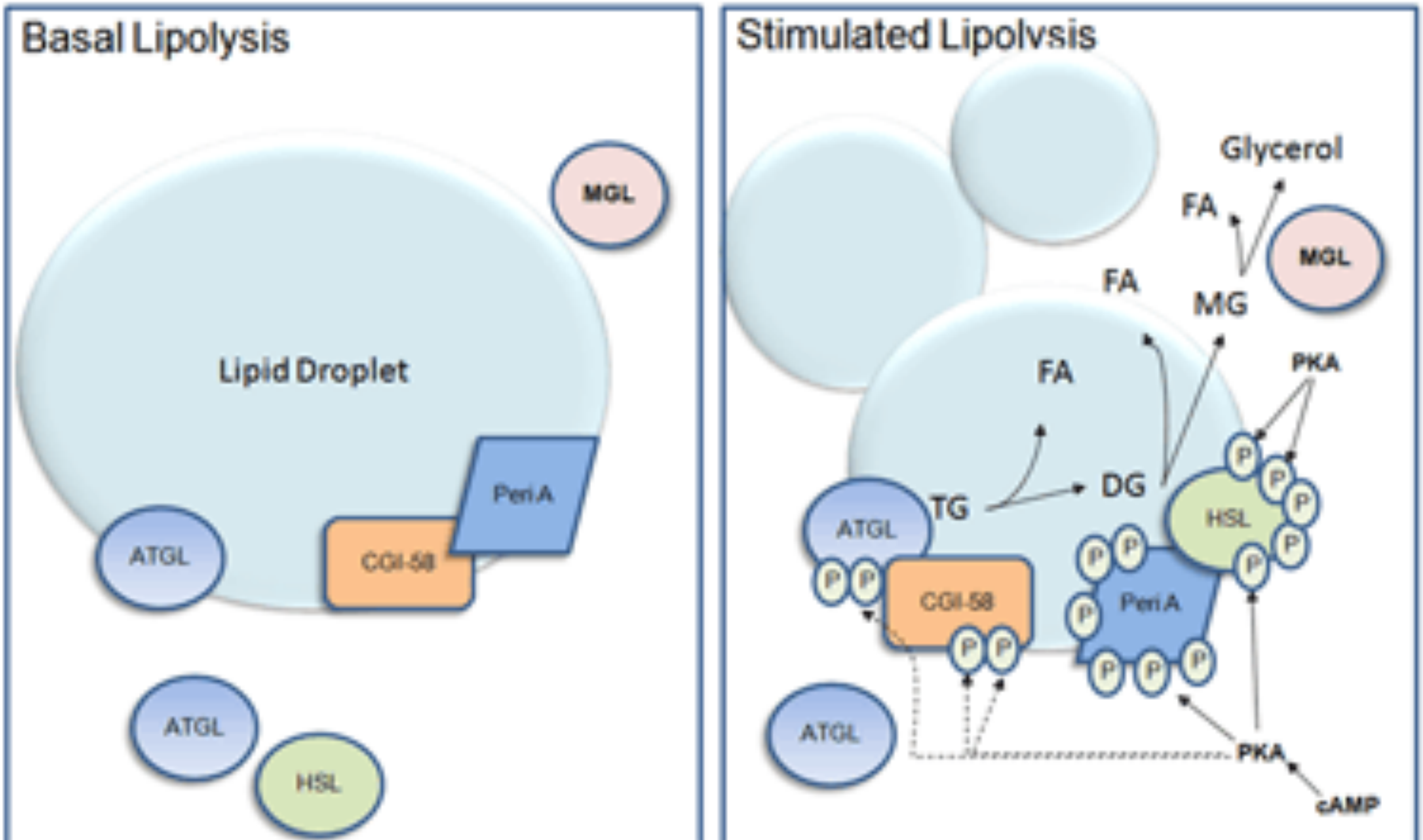
PKA

PFK-2



Post-Translational Induction of Gluconeogenesis

Effects of Epinephrine on Lipid Breakdown

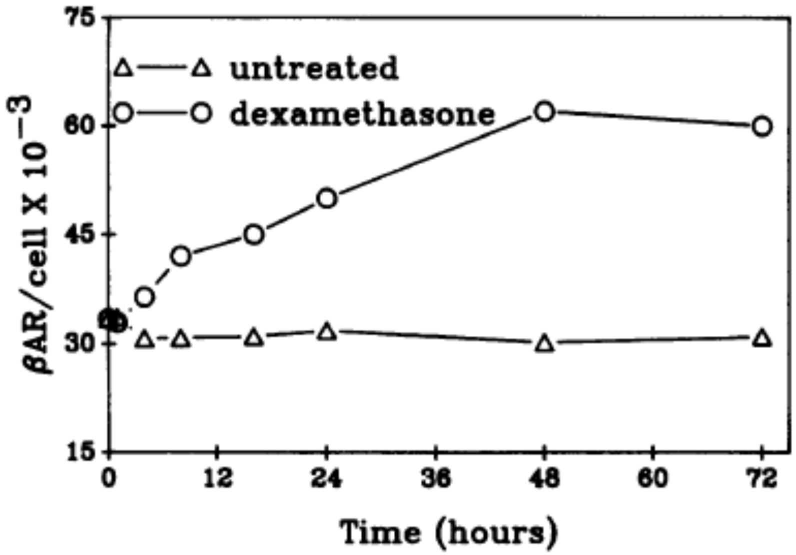


Short Term and Long Term Stress

Chronic Stress

Cortisol

Glucocorticoid Receptor



Elevated Transcription of Beta-Adrenergic Receptors

Acute Stress

Epinephrine

Higher sensitivity towards epinephrine

Hadcock JR, Malbon CC (1988) Regulation of beta-adrenergic receptors by "permissive" hormones: glucocorticoids increase steady-state levels of receptor mRNA. Proc Natl Acad Sci U S A 85: 8415–8419. doi:10.1073/pnas.85.22.8415.

Pheochromocytoma

- Tumor that constitutively secretes adrenaline or noradrenaline
- What cardiovascular and molecular phenotypes would this person have?
- How could you treat this person?

Learning Objectives

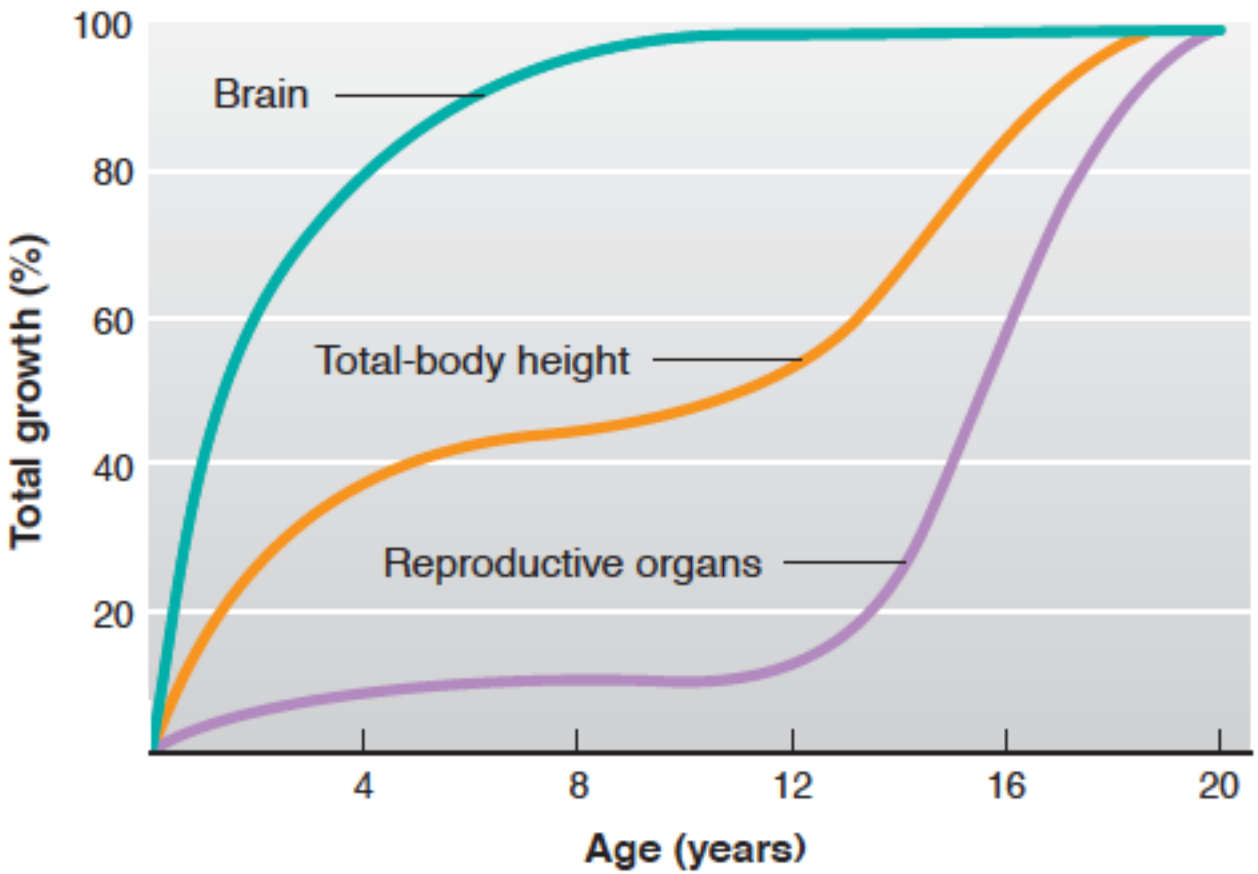
- Name three zones in the adrenal cortex and major regulator(s) of each zone.
- Name three steroidogenesis pathways and their major products.
- Explain briefly the physiological mechanism of adrenogenital syndrome.
- Describe the physiological actions and roles of aldosterone.
- Explain briefly the renin-angiotensin system.
- Describe the negative feedback regulation of aldosterone and its relationship to blood volume/blood pressure homeostasis.
- Describe hepatic and extrahepatic metabolic actions of glucocorticoids. Discuss their relationship.
- State the major findings caused by adrenal hypersecretion of mineralocorticoids.
- State the major findings caused by adrenal hypersecretion of glucocorticoids.
- Name the major hormones secreted from the adrenal medulla. Discuss the differences of epinephrine (epi) and norepinephrine (NE) in cardiovascular actions (physiological levels).
- List the major metabolic actions of catecholamines.
- Contrast the thresholds for actions vs. plasma levels of epi and NE under common conditions, like exercise, and in the disease pheochromocytoma

Endocrine Control of Growth

Learning Objectives

- List the hormones important for growth at key times in a person's life.
- Describe the functions of human growth hormone on growth (bones and soft tissues), and on metabolism, and the regulation of its secretion. Explain what 'rhGH' means.
- State the "dual effector hypothesis" for GH actions, and the relative roles of GH and IGF-1 in growth control.
- Describe the interactions among all the key growth-regulating hormones at key times of a person's life: in utero, neonatally, childhood, puberty, adulthood, and senescence.
- Describe the daily regulation of GH levels and the physiological relevance of these cycles.

Human Organ Growth



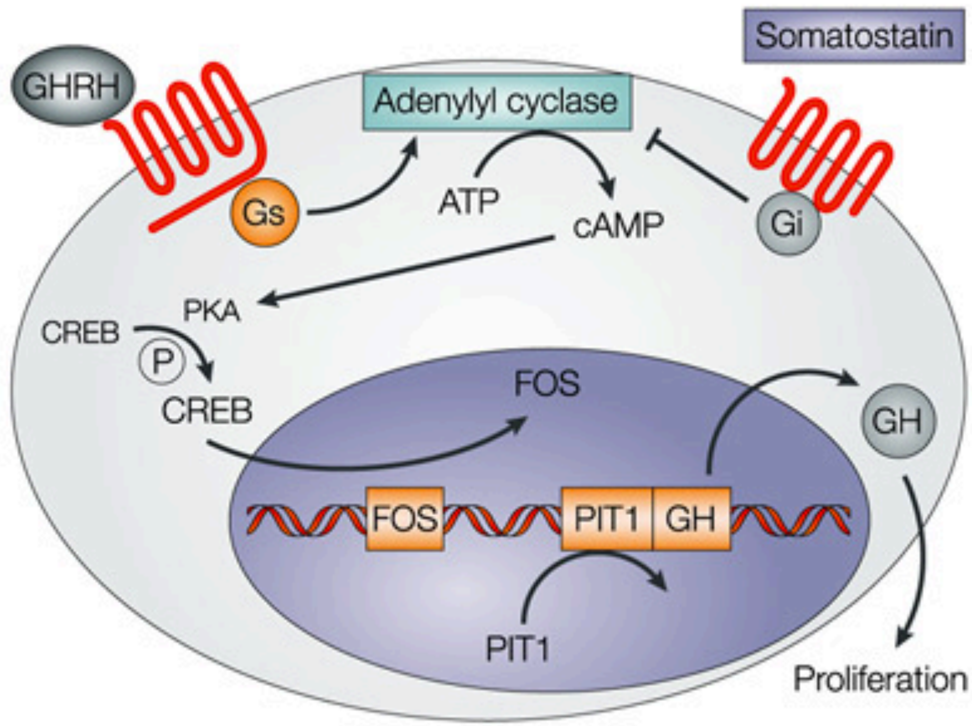
Hormones During Growth

Stage	Age	Hormonal Requirements
Prenatal	(9 months)	Insulin
Infantile	0-1	Insulin
Juvenile	1-12 years	GH, Insulin, T3, Vitamin D
Adolescent (Pubertal)	10-14 (F) 12-16 (M)	GH, insulin, T3, Vitamin D and Sex Steroids
Adult	Puberty – 100	Normally limited growth

Growth Hormone Summary

What chemical type is it?	Protein	
Where is it made?	Somatotropes of Anterior Pituitary	
What causes its release?	GHRH release (also regulated by somatostatin)	
What is its receptor?	Growth Hormone Receptor	JAK/STAT
What tissues does it affect?	Liver	IGF-1 Release
	Bones	Growth
	Muscle	Protein Synthesis
	Adipose Tissue	Lipolysis
How does it get turned off?	IGF Negative Feedback to Pituitary and Hypothalamus. GH/IGF1 Stimulation of somatostatin and receptor desensitization	

Regulation of GH Release

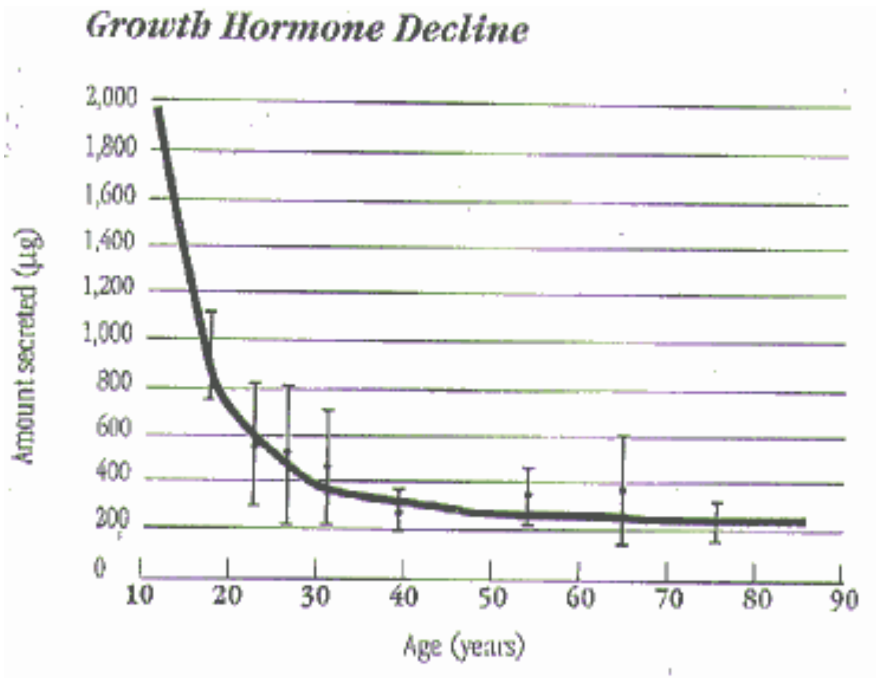


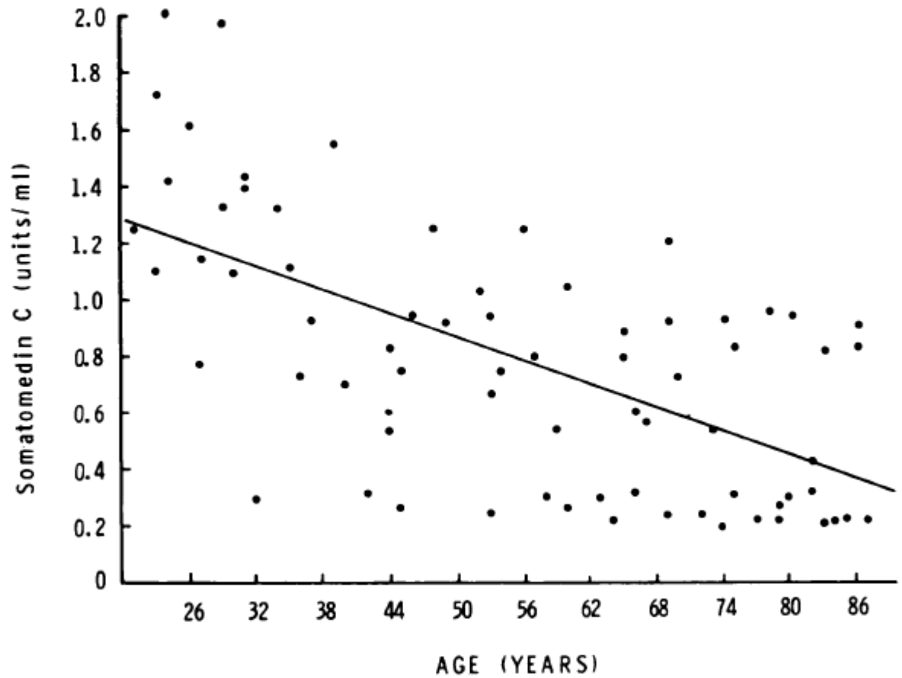
Nature Reviews | Cancer

GH Decreases with Aging

- Think of some possible mechanisms by which this could happen?
- Less GH synthesis
- Less GHRH responsiveness
- Less GHRH synthesis
- More SST synthesis
- More SST responsiveness

GH and Aging

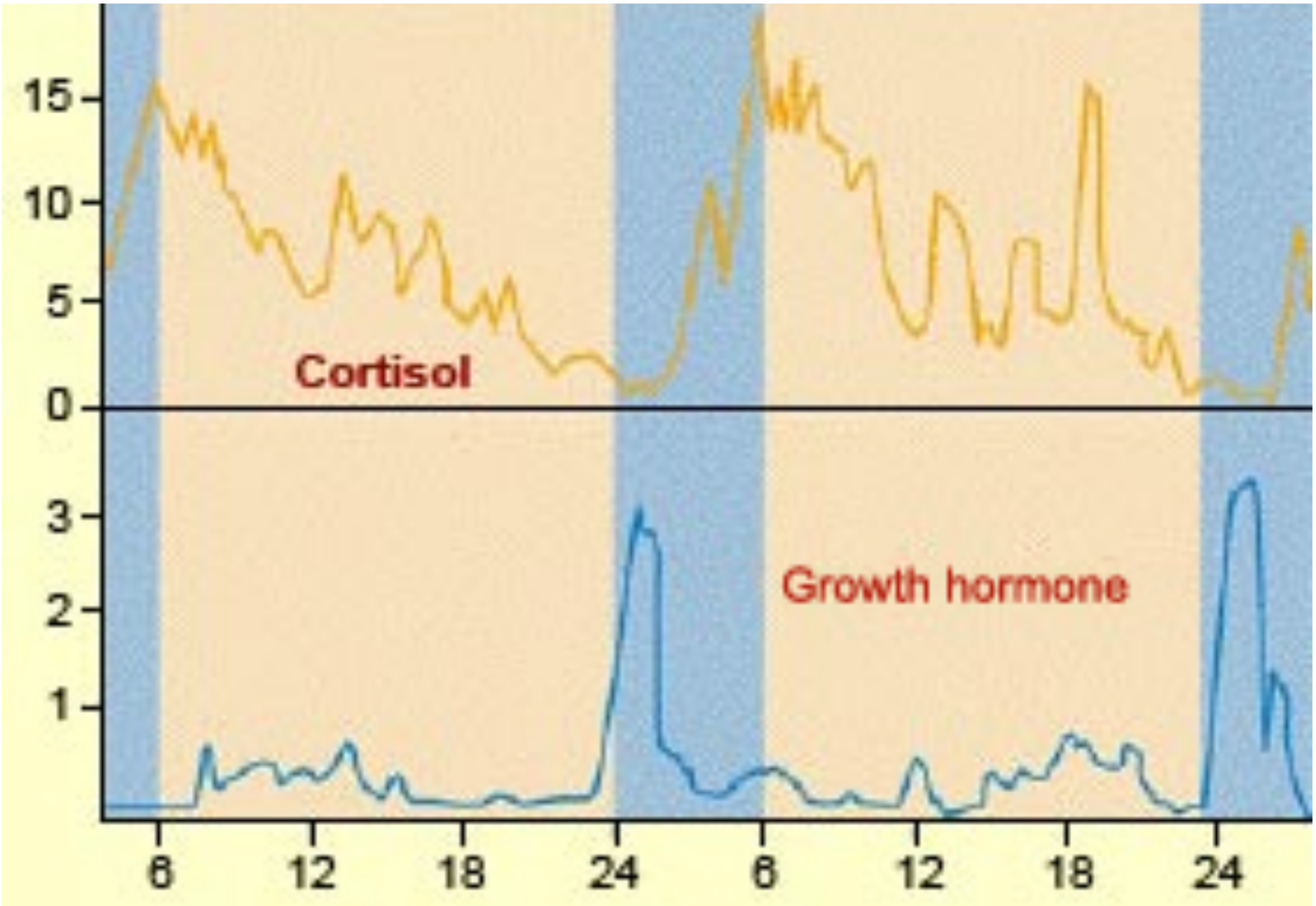




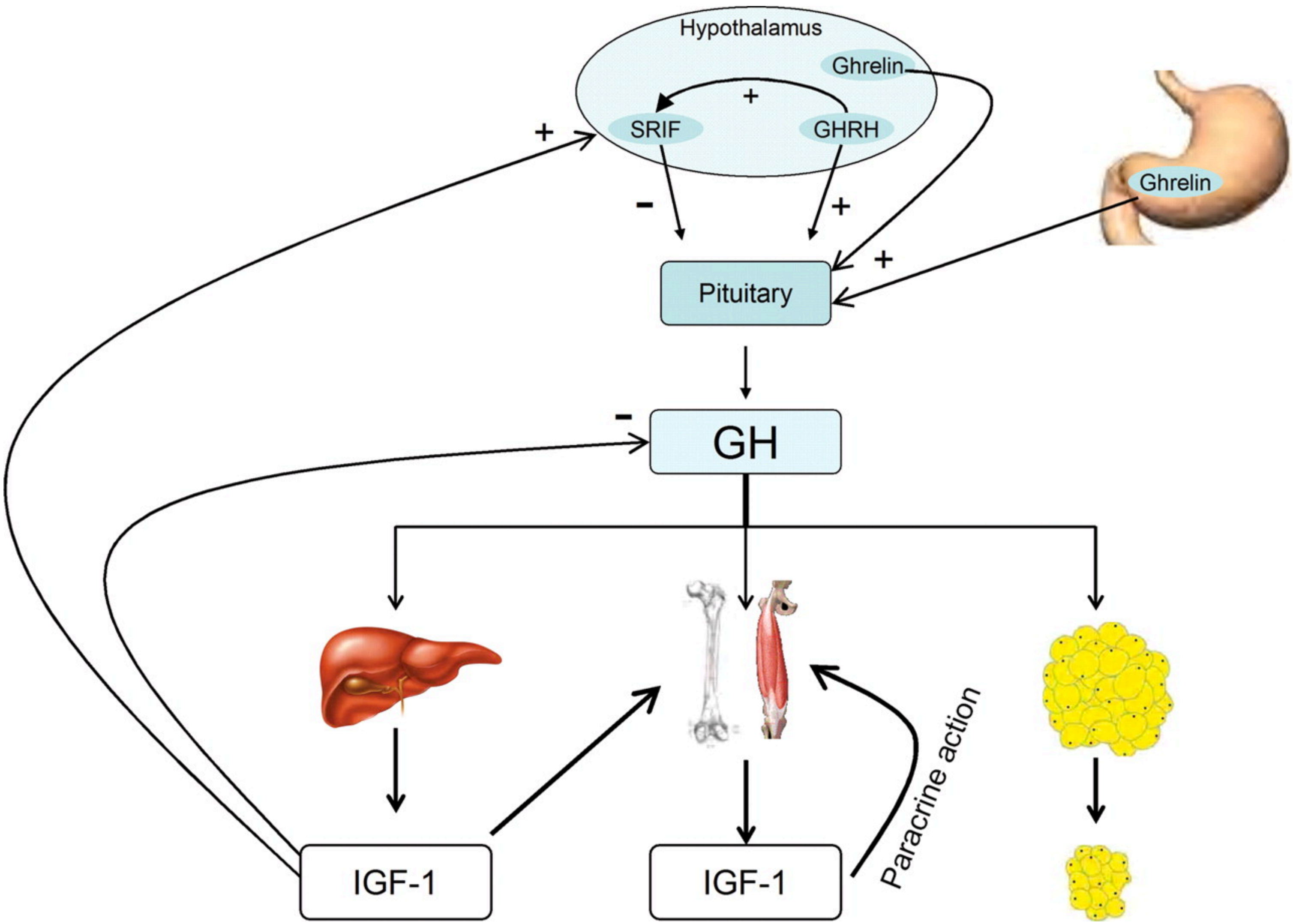
GHRH Levels

Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming G a., et al. (1981) Impaired growth hormone secretion in the adult population. Relation to age and adiposity. J Clin Invest 67: 1361–1369. doi:10.1172/JCI110164.

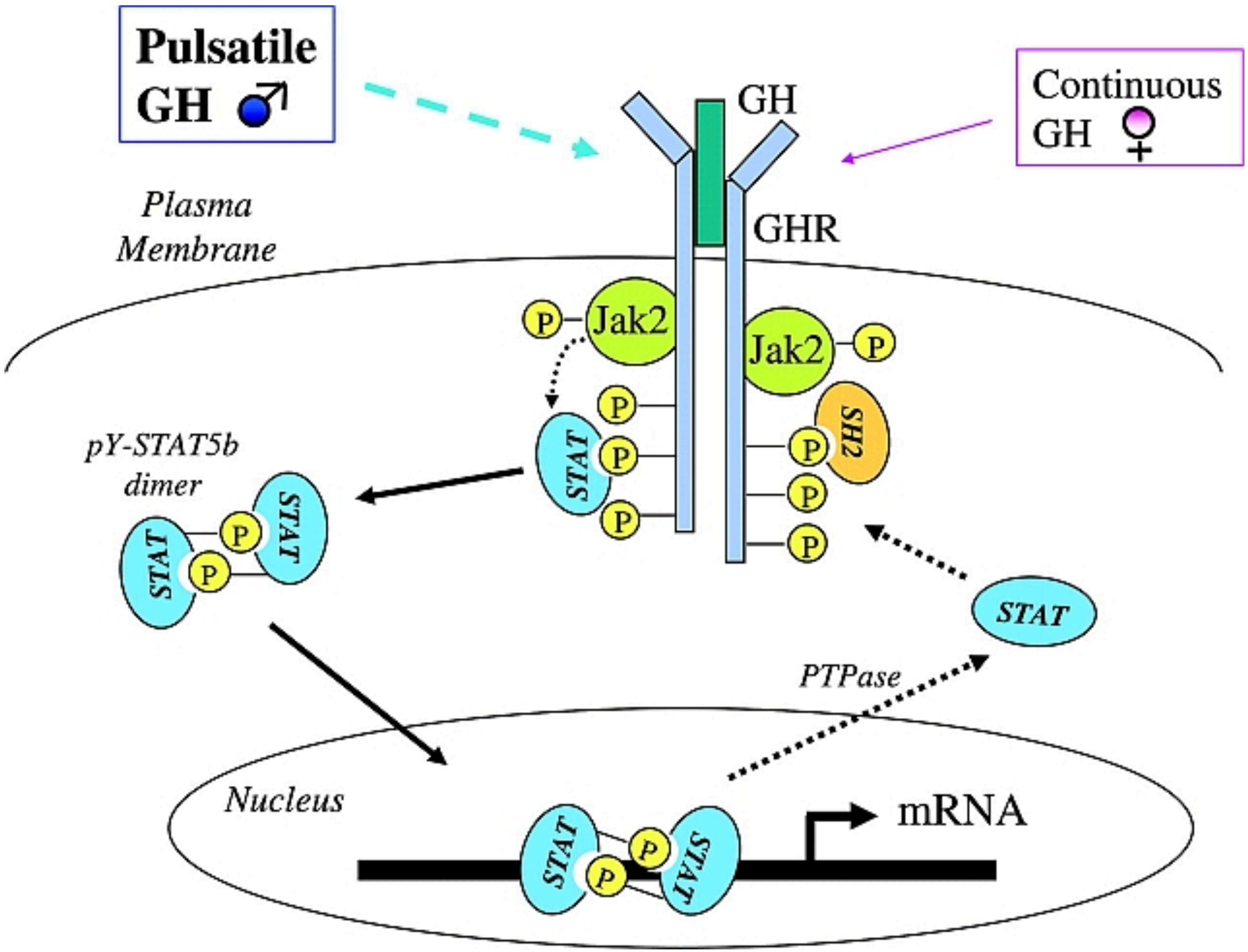
Diurnal Rhythms of GH Release



Growth Hormone Causes IGF-1 Release



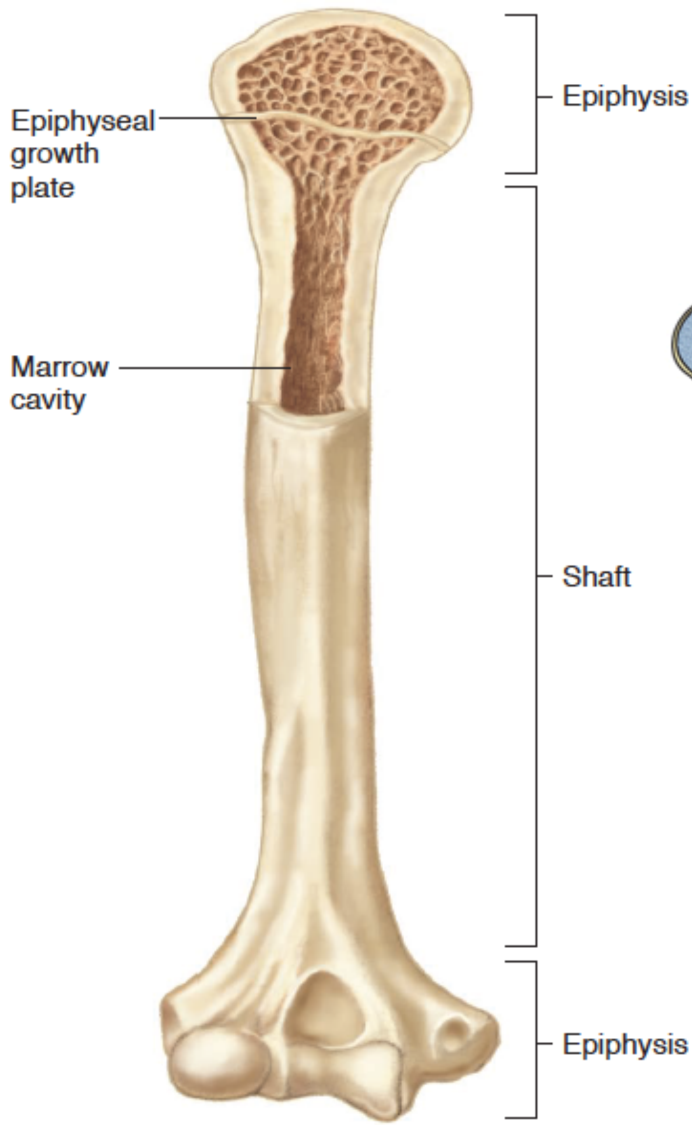
Growth Hormone Receptor

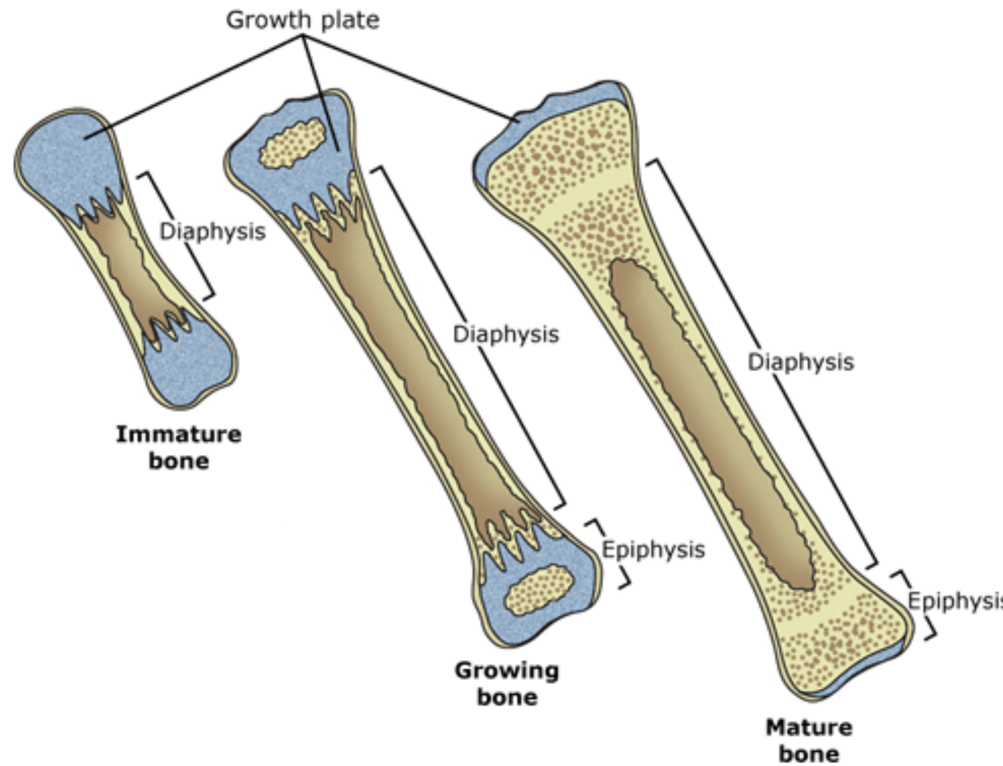


IGF-1 Summary

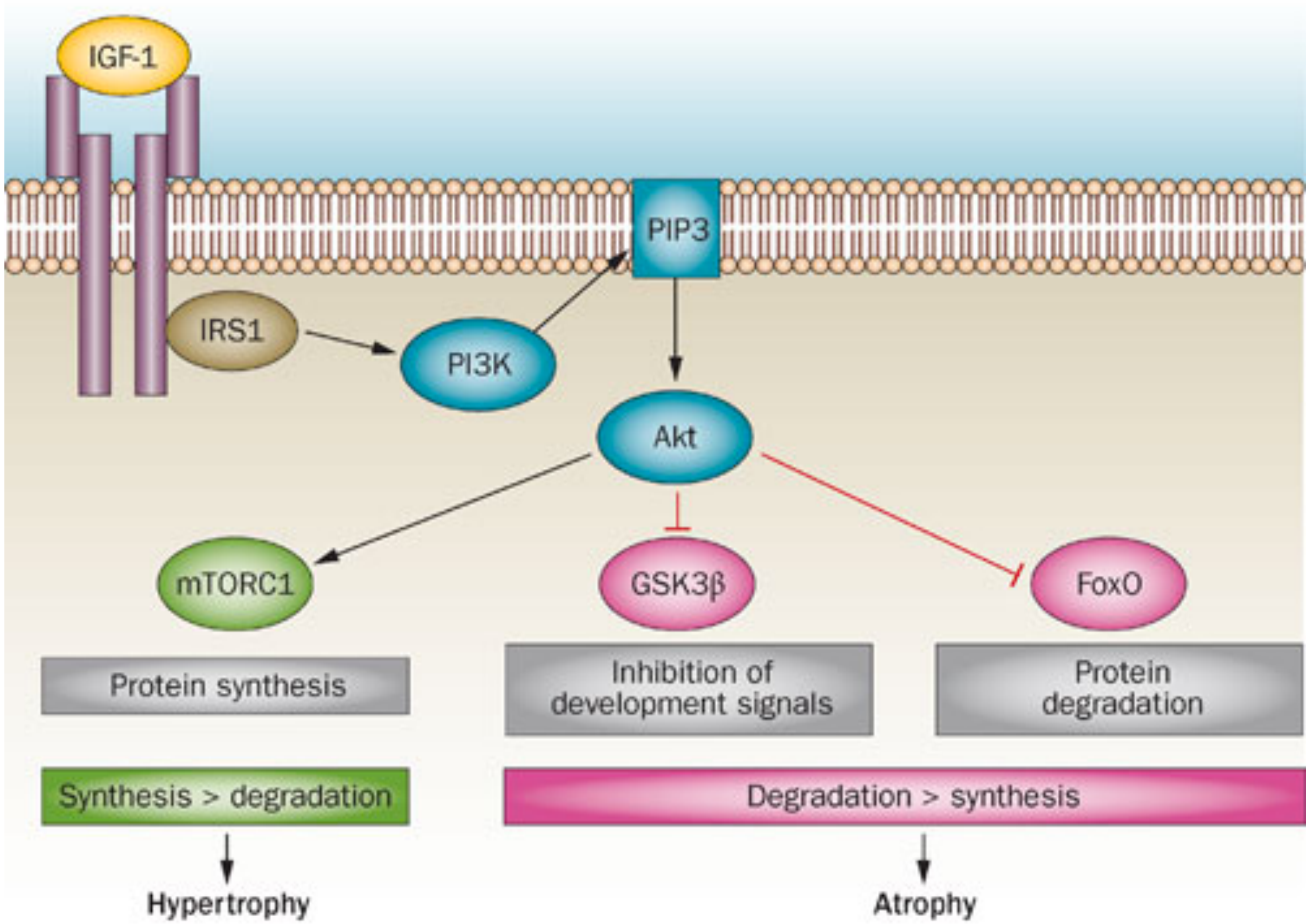
What chemical type is it?	Protein	
Where is it made?	Liver	
What causes its release?	GH Signaling	
What is its receptor?	IGF1R	Receptor Tyrosine Kinase
What tissues does it affect?	Liver	IGF-1 Release
	Bones	Chondrocyte replication
	Muscle	Protein Synthesis
How does it get turned off?	Receptor desensitization, Less GH production, IGF-1 degradation	

Regulation of Bone Growth

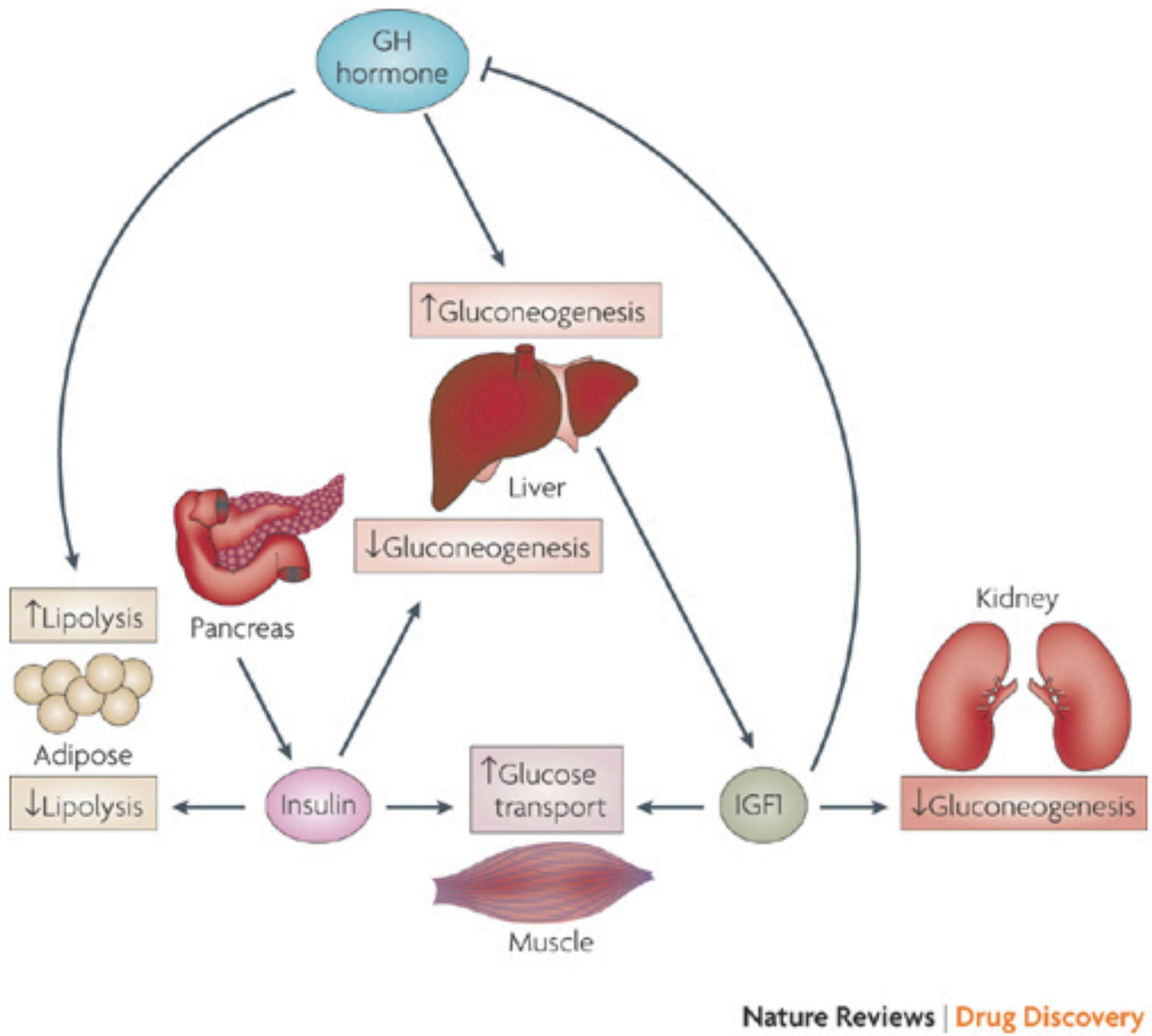




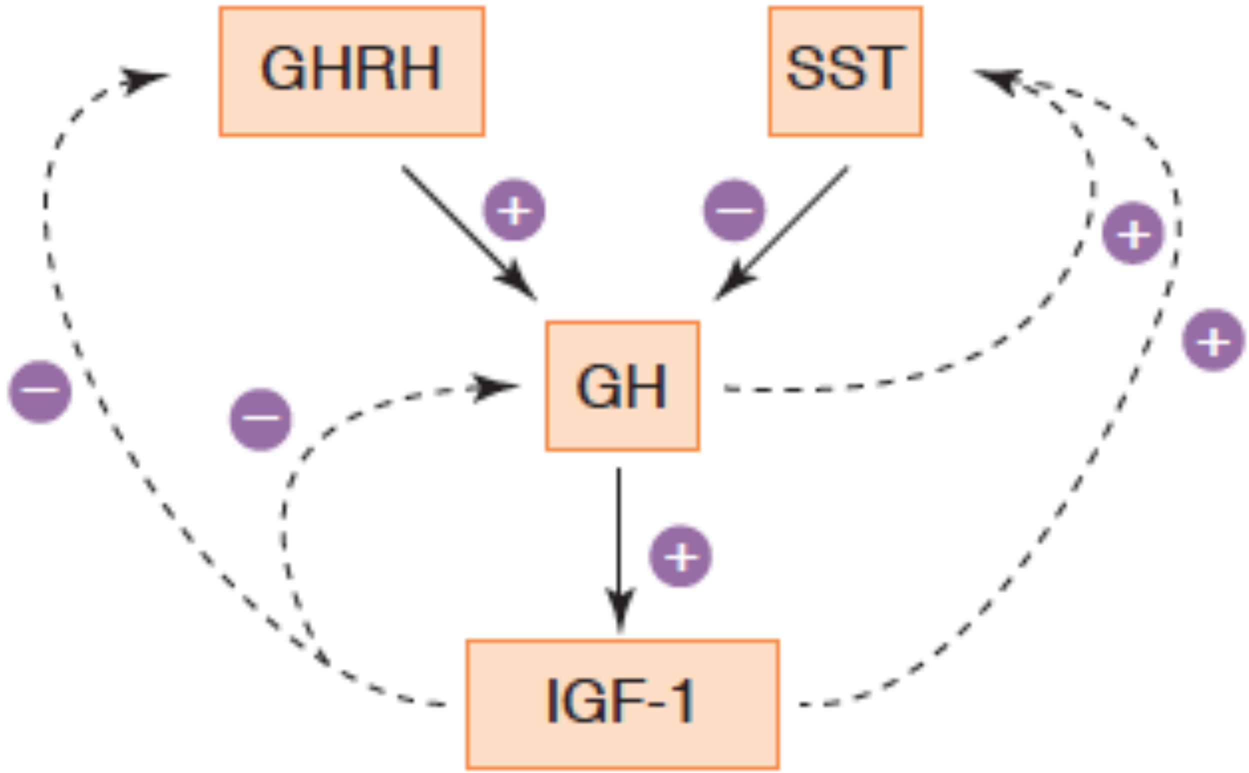
Regulation of Muscle Growth



Effects of GH/IGF1 on Metabolism



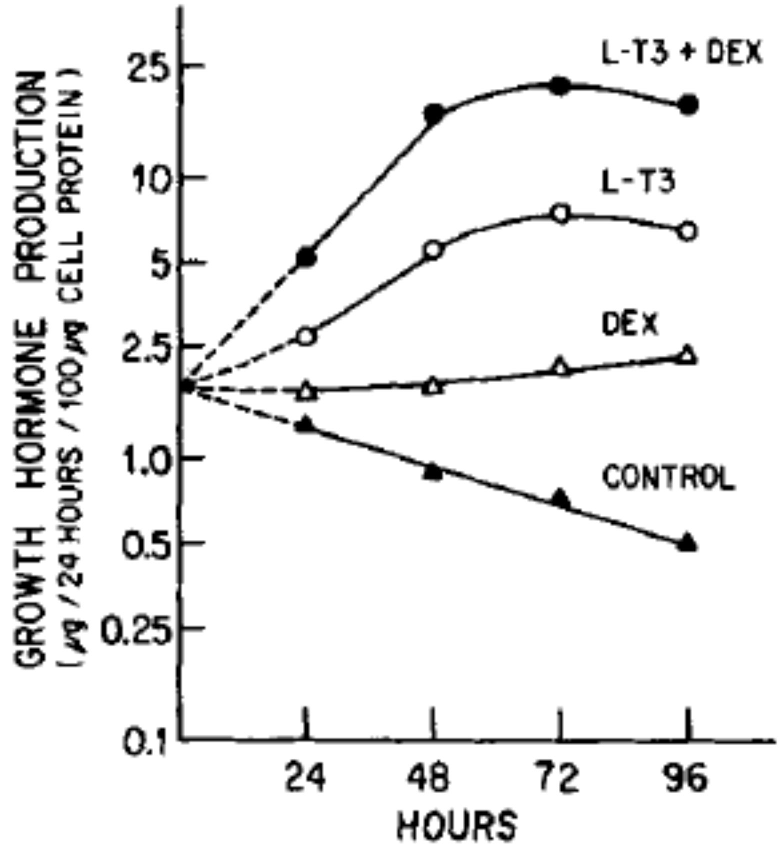
Negative Feedback of GH



Other Hormones Influencing Growth

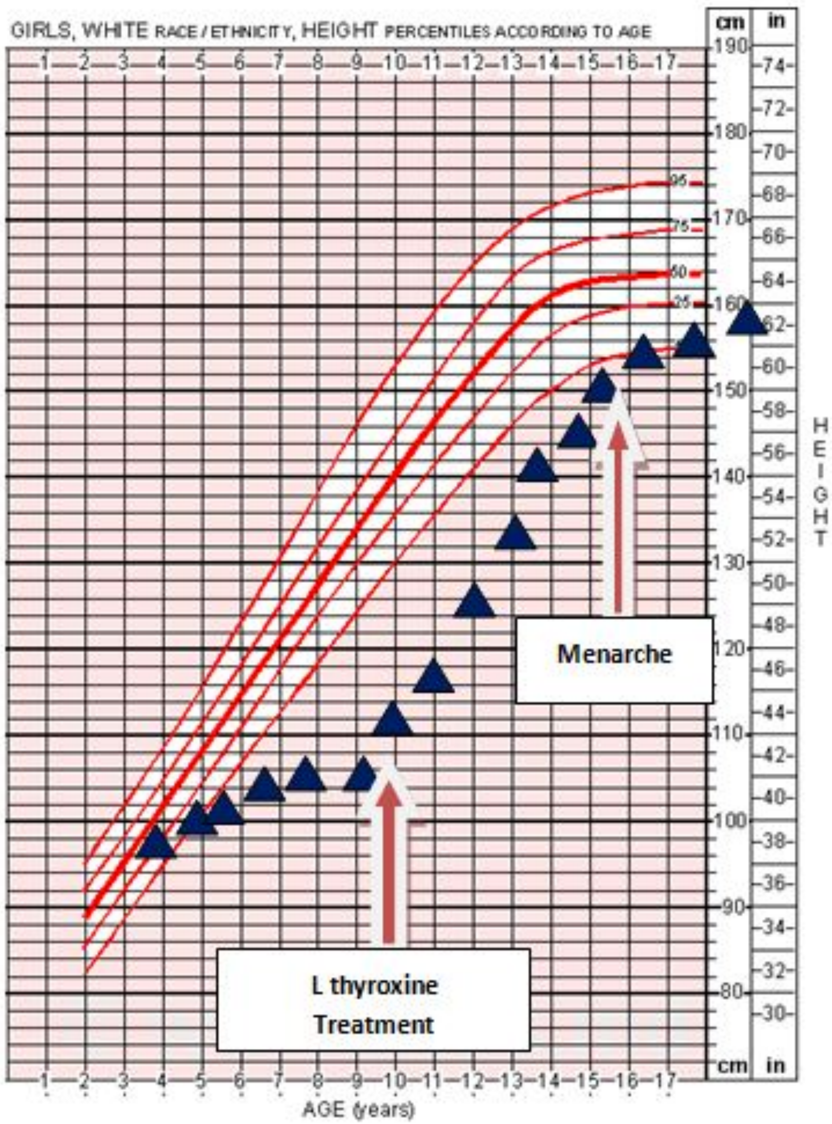
Insulin	Stimulates fetal growth Stimulates postnatal growth by stimulating secretion of IGF-1 Stimulates protein synthesis
Thyroid hormone	Permissive for growth hormone's secretion and actions Permissive for development of the central nervous system
Testosterone	Stimulates growth at puberty, in large part by stimulating the secretion of growth hormone Causes eventual epiphyseal closure Stimulates protein synthesis in male
Estrogen	Stimulates the secretion of growth hormone at puberty Causes eventual epiphyseal closure
Cortisol	Inhibits growth Stimulates protein catabolism

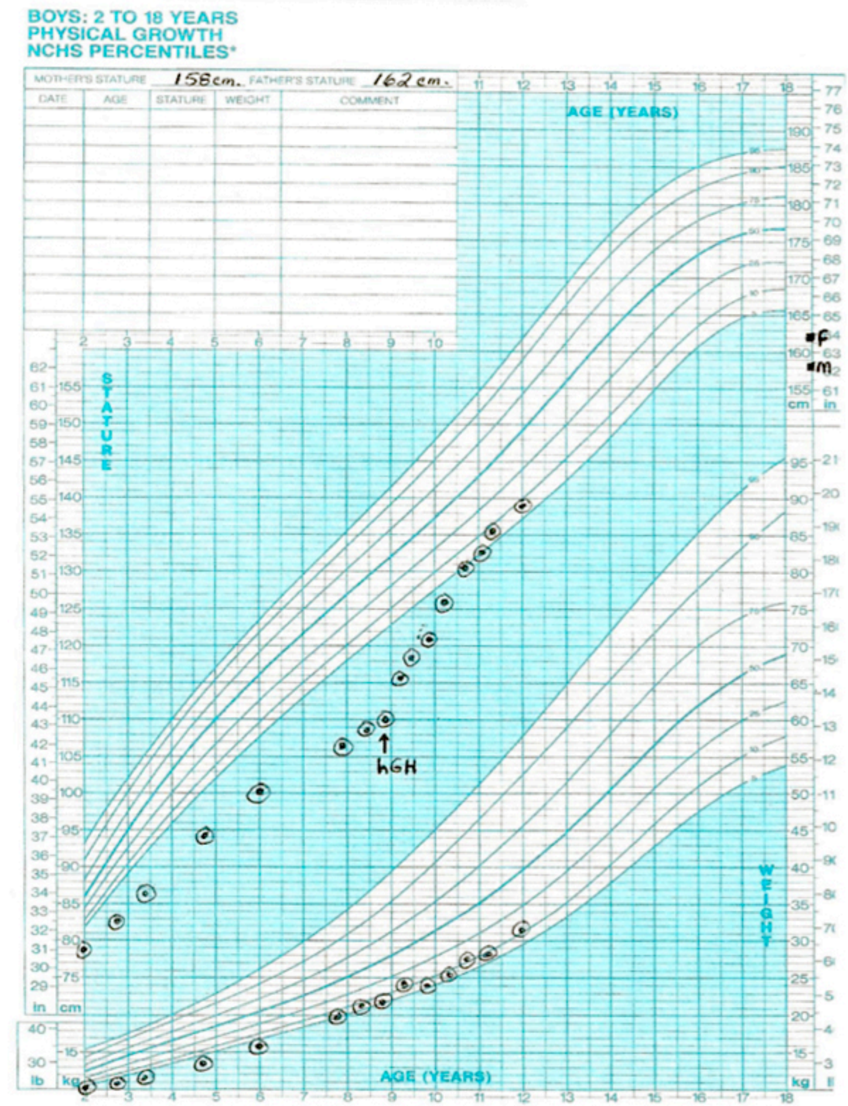
T3, Cortisol and GH Synthesis



Yaffes BM, Samuels HH (1984) Hormonal Regulation of the Growth Hormone Gene. J Biol Chem 259: 6284–6291.

Treatment of Hypothyroidism





Acromegaly

- Pituitary tumor of the somatotropes
- Overproduction of GH
- Clinical presentation
  - Bone growth
  - Protruding brow and jaw, spacing of teeth
  - Low body fat increased muscle
  - Insulin resistant/diabetic

Dwarfism/Growth Hormone Deficiency

- Congenital or immune destruction of somatotropes
- Can be GH deficiency or GH resistance
- Can be secondary to hypothyroidism
- Clinical features
  - Reduced height
  - Reduced muscle mass
  - Elevations in fat mass
  - Resistance to diabetes

Learning Objectives

- List the hormones important for growth at key times in a person's life.
- Describe the functions of human growth hormone on growth (bones and soft tissues), and on metabolism, and the regulation of its secretion. Explain what 'rhGH' means.
- State the "dual effector hypothesis" for GH actions, and the relative roles of GH and IGF-1 in growth control.
- Describe the interactions among all the key growth-regulating hormones at key times of a person's life: in utero, neonatally, childhood, puberty, adulthood, and senescence.
- Describe the daily regulation of GH levels and the physiological relevance of these cycles.