

# Any Questions about Tuesday's Learning Objectives

- Recall anatomical, biochemical, and functional evidence showing intimate relationships between hypothalamus and pituitary.
- Describe how hormones are sensed by the neurons of the hypothalamus, and the role that the blood brain barrier and transport mechanisms play.
- Recall how the central nervous system can integrate with the hypothalamus and modify both hormonal secretions and executive function.
- Describe the differences in how hypothalamic signals are passed to the posterior and anterior pituitary glands.
- List the known hypothalamic hormones which cause release (and release-inhibition) of anterior pituitary hormones, including their acronyms.
- Name two major posterior pituitary hormones, their chemical category, and succinctly describe their secretory mechanism.
- Describe cellular actions of vasopressin in terms of site of actions, receptors, and cellular signals.
- Discuss briefly aquaporin water channels and relation to vasopressin.
- Predict what the changes are expected in urine volume and osmolality and in ECF volume when vasopressin synthesis or secretion is severely impaired. Predict what will happen to water intake. Explain why there can be transient diabetes insipidus following a whiplash injury, and the rationale for therapy during this time.
- Describe the control of vasopressin release.
- Describe the function of oxytocin with respect to delivery and lactation.

# Discuss with Folks Nearby

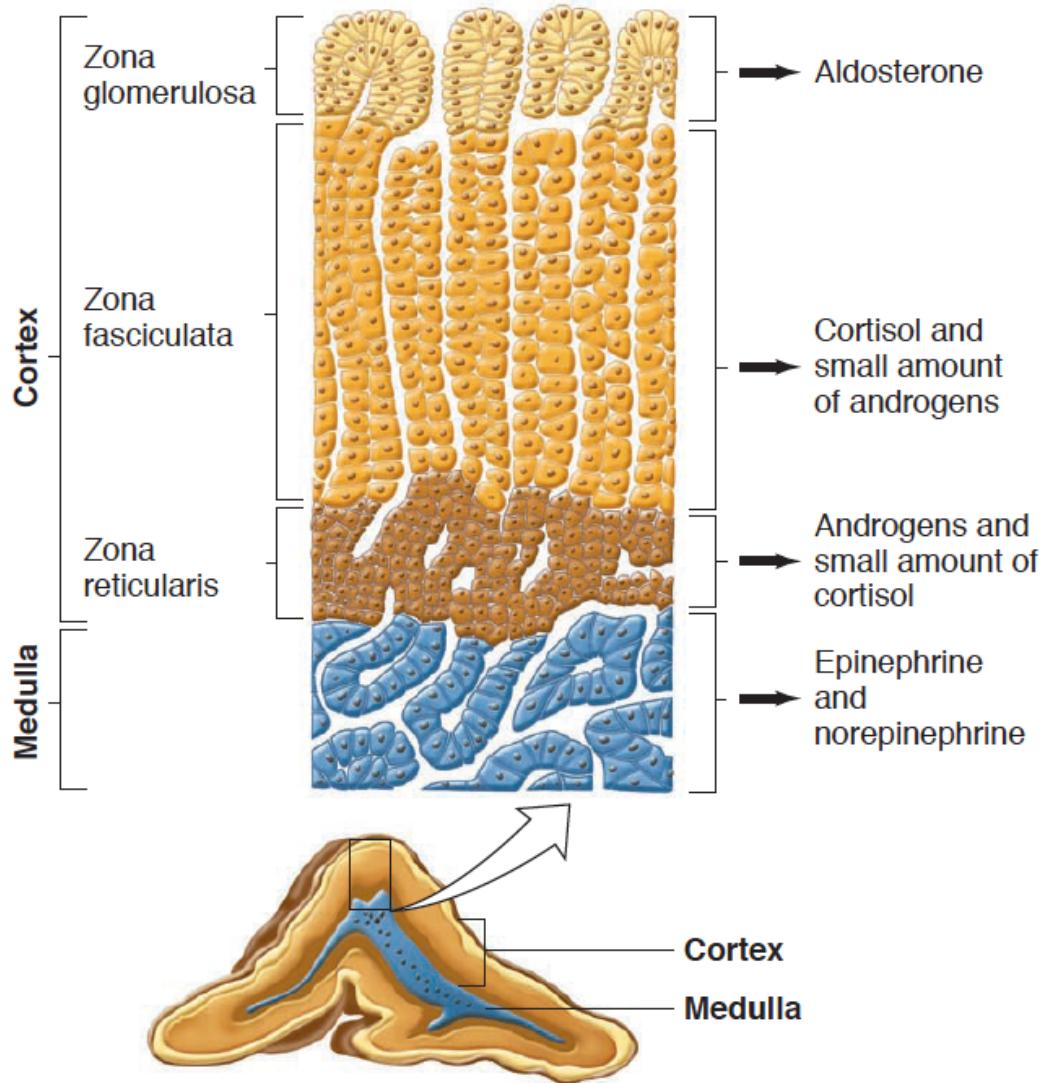
- How could whiplash cause diabetes insipidus?
- HINT: Relates to damage/severing of infundibulum

# Adrenal Gland and Stress Hormones

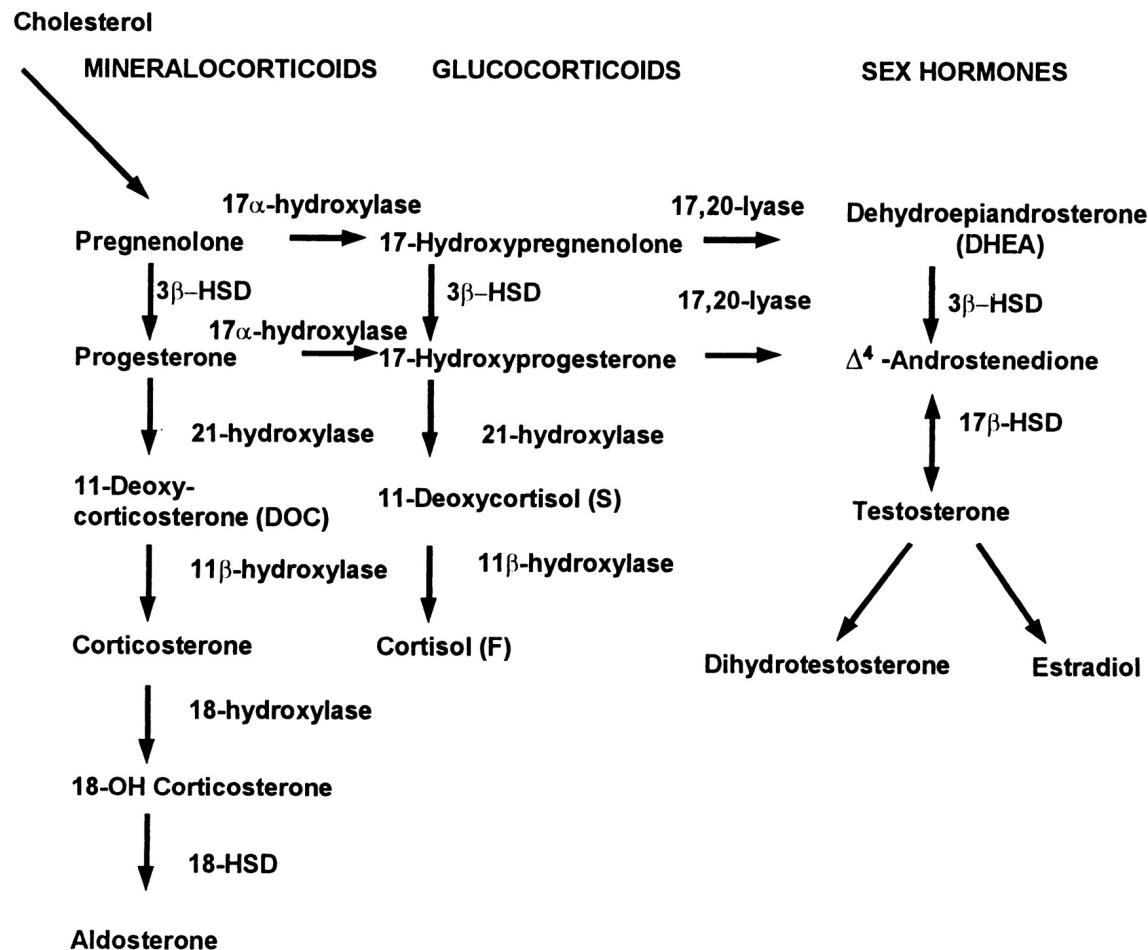
# Learning Objectives

- 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

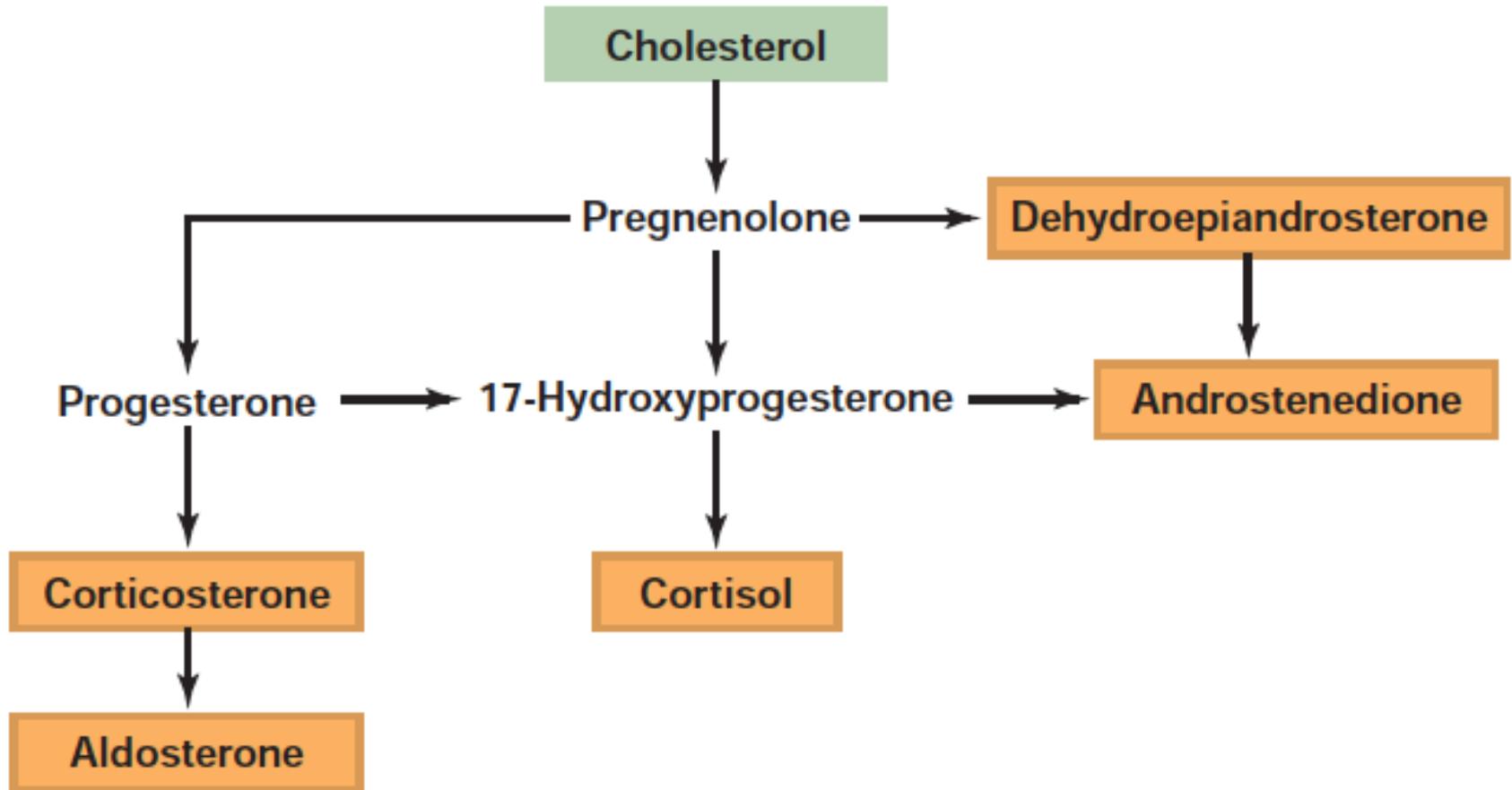


# Steroid Hormone Biosynthesis

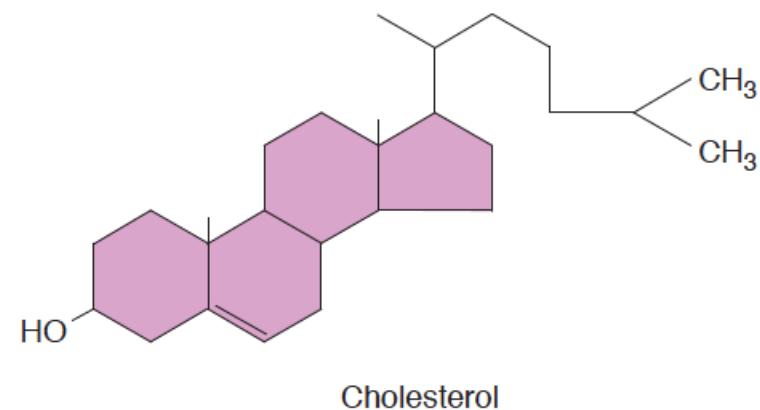
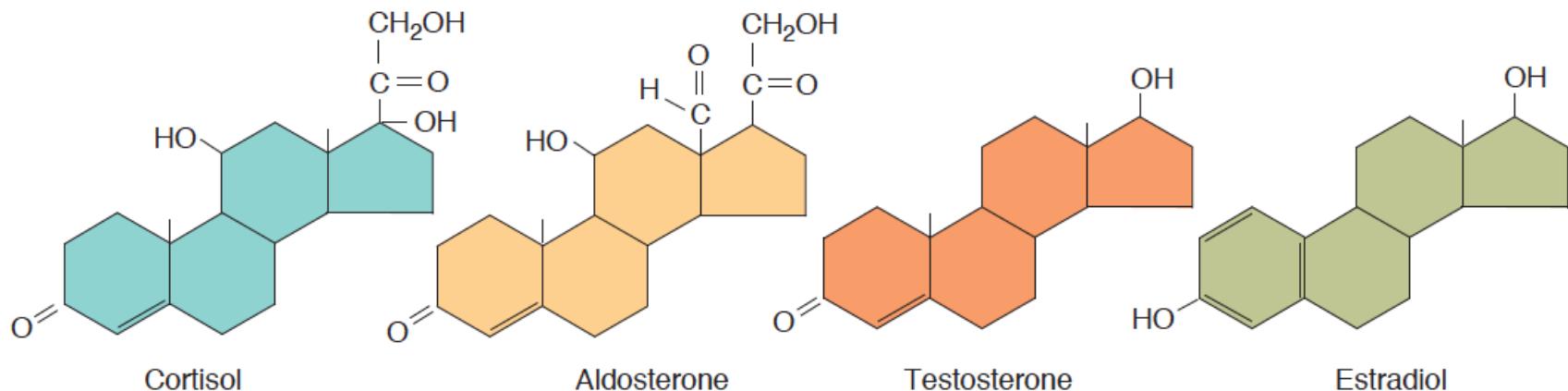


Maria I. New, and Robert C. Wilson PNAS  
1999;96:12790-12797

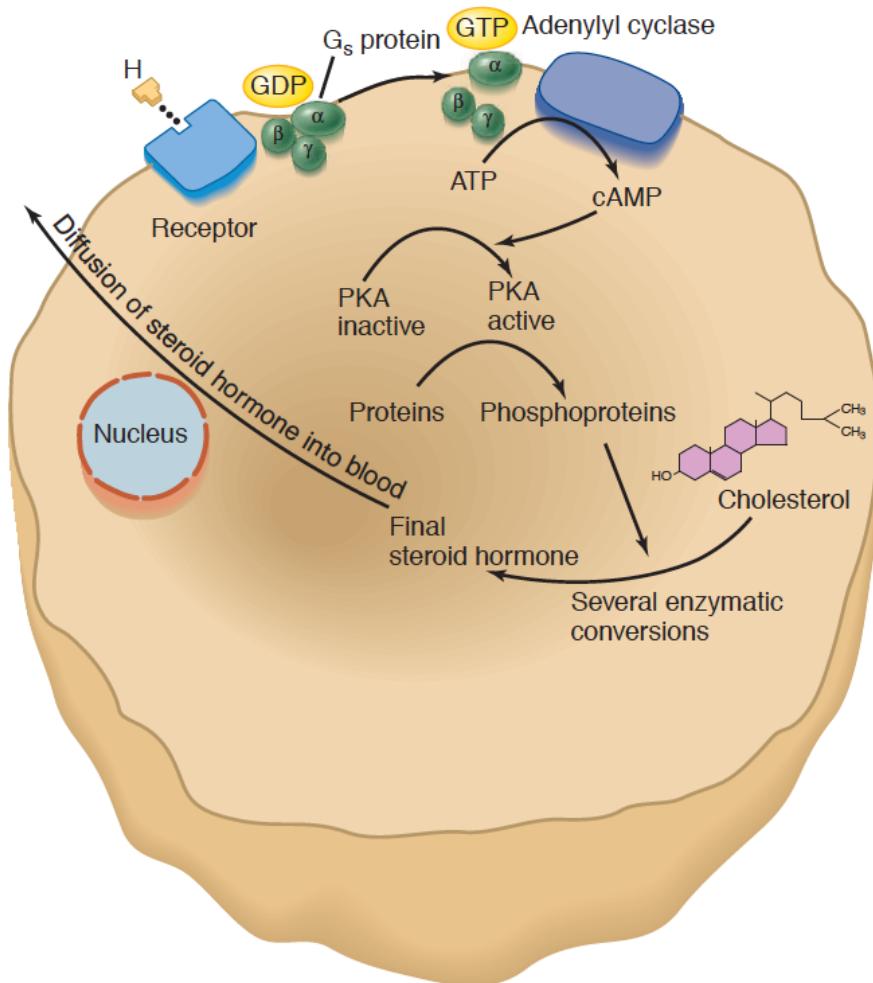
# Steroid Hormone Synthesis



# Steroid Hormones Released From Adrenal Medulla

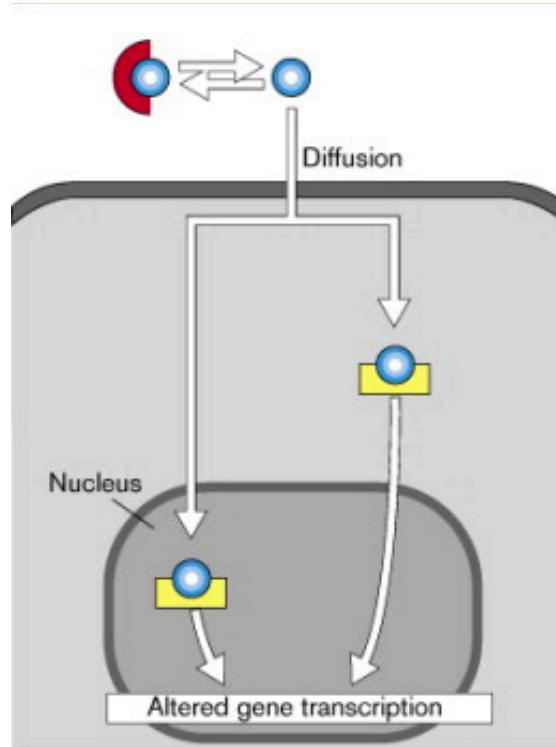


# Adrenal Steroid Hormone Synthesis Mechanisms



Signal	Receptor	Hormone
ACTH	MC2R (GPCR - G <sub>s</sub> )	Cortisol
Angiotensin II	AGTR1 (GPCR – G <sub>q</sub> )	Aldosterone

# Both Aldosterone and Cortisol Function Through Nuclear Hormone Signaling

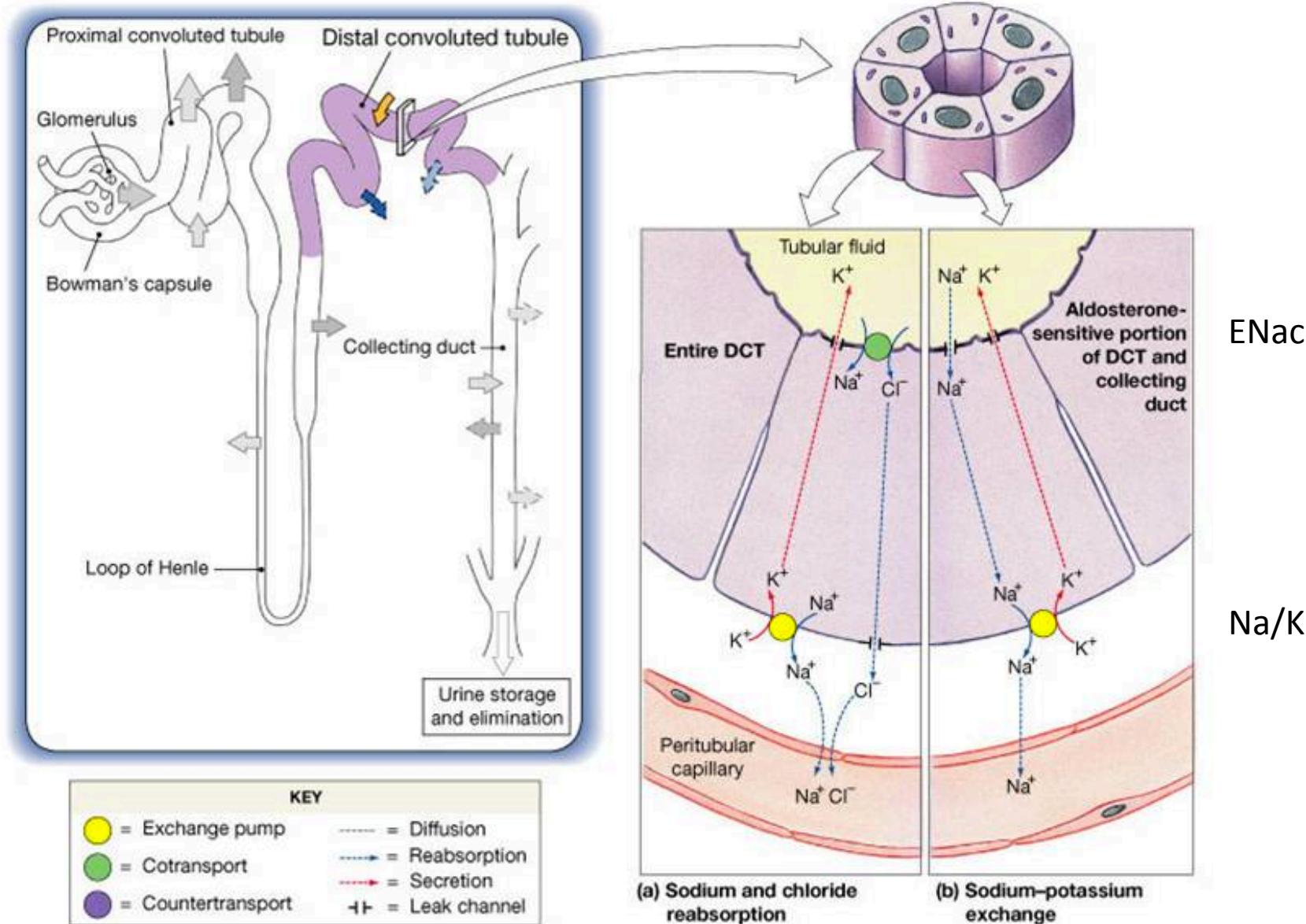


**ALDOSTERONE REGULATES  
MINERAL BALANCE**

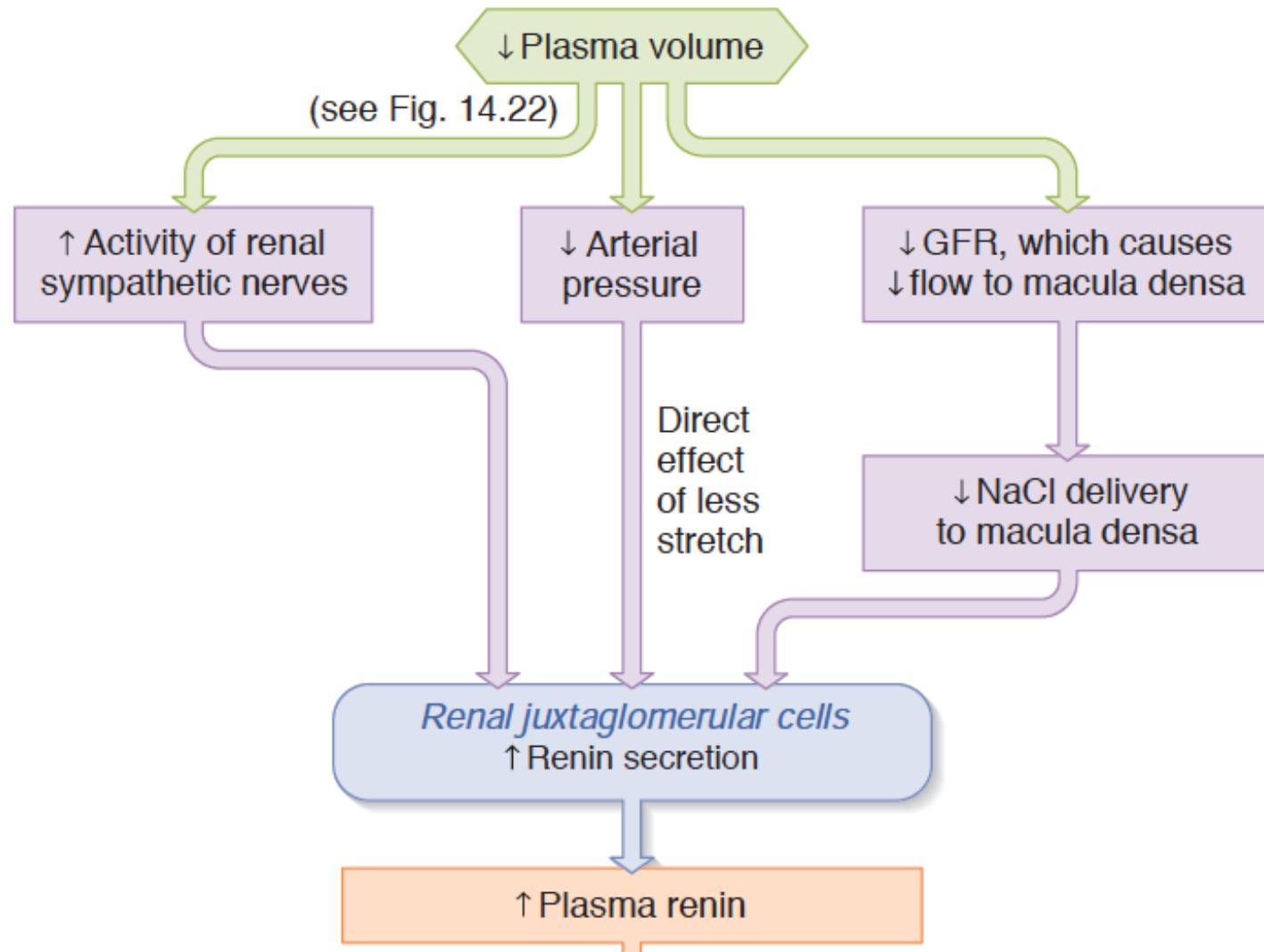
# Aldosterone Summary

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

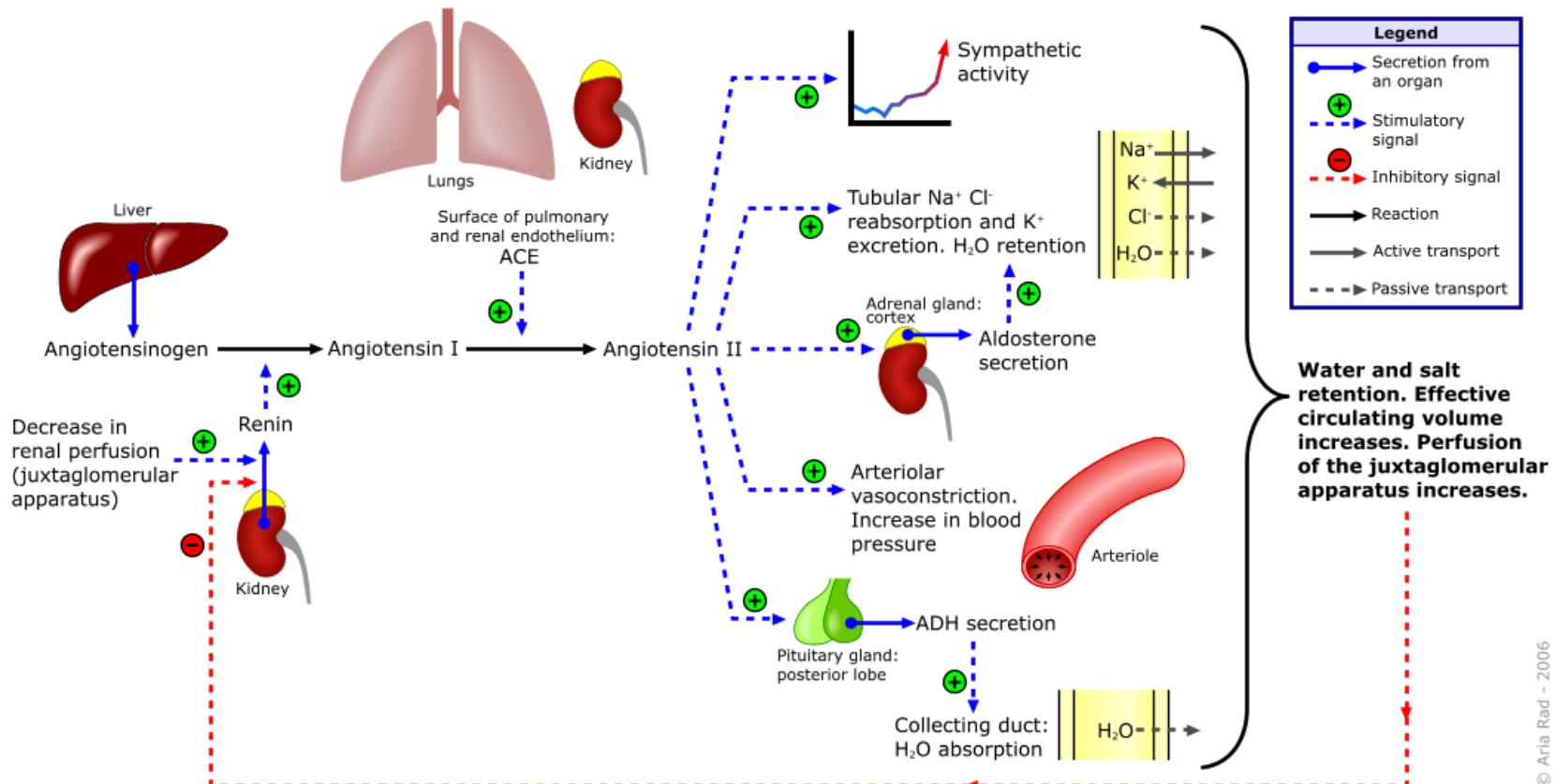
# Key Aldosterone Effectors



# Renin as a Volume/Pressure Sensor



# The Renin/Angiotensin System

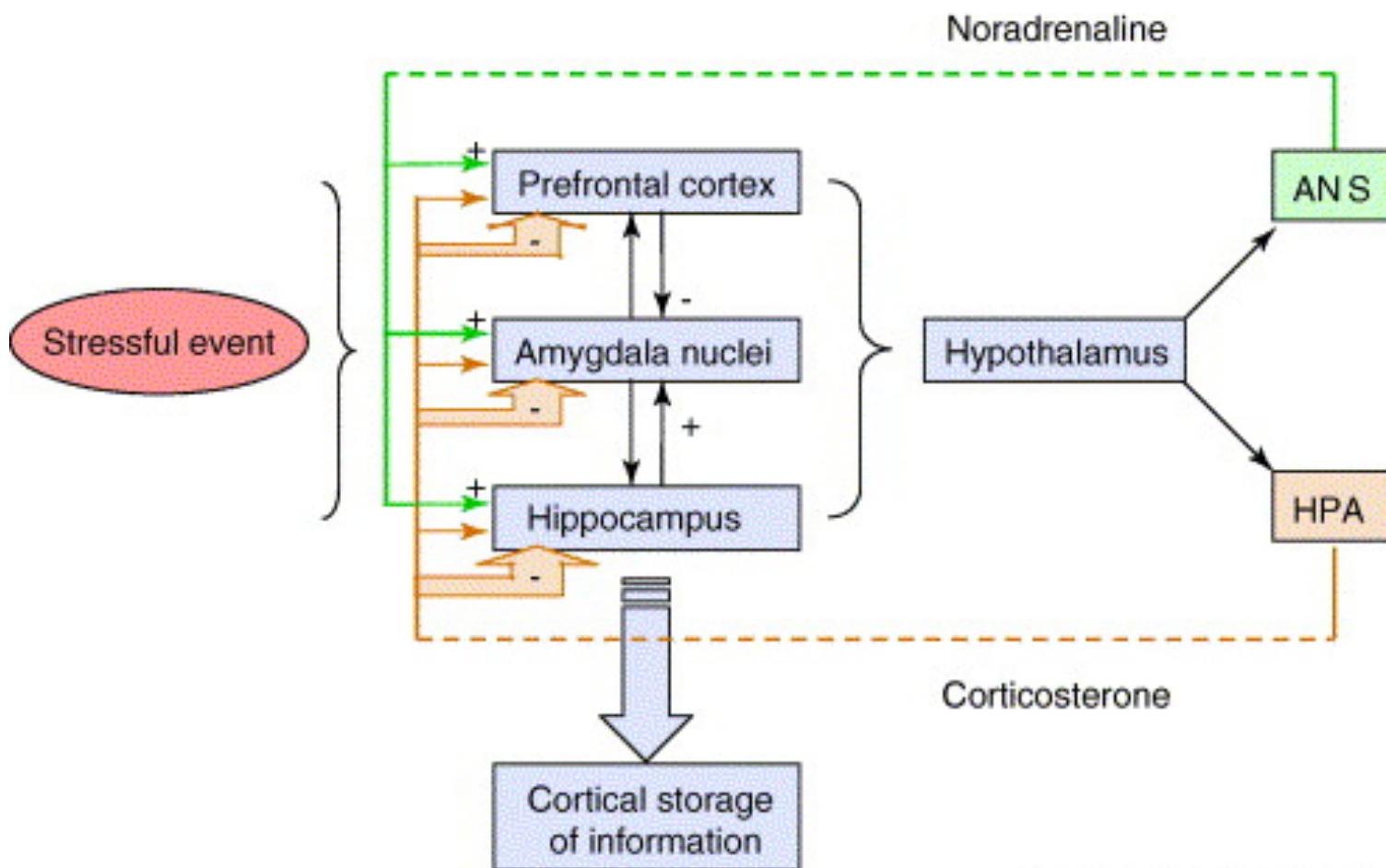


# **STRESS RESPONSIVE HORMONES**

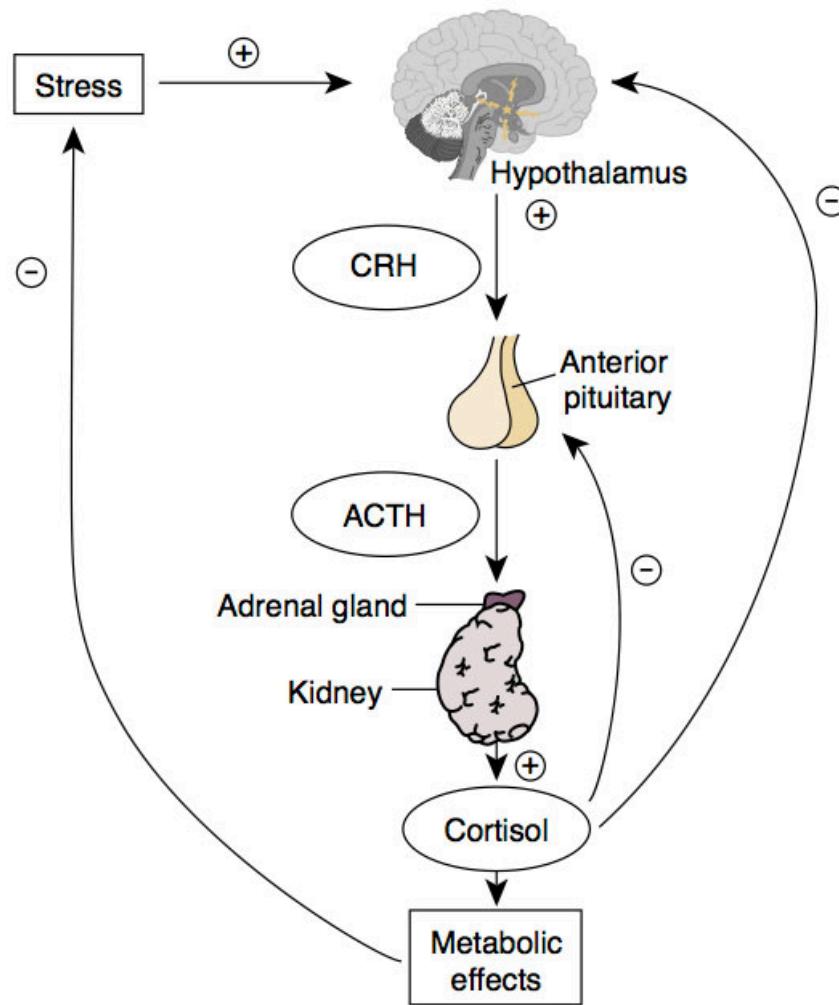
# Two Types of Stress Response

- Adrenaline
- Cortisol

# CRH Release



# HPA Axis



# Corticotropin Releasing Hormone

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

# ACTH

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

# Cortisol Summary

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

# CRH In Response to Stress

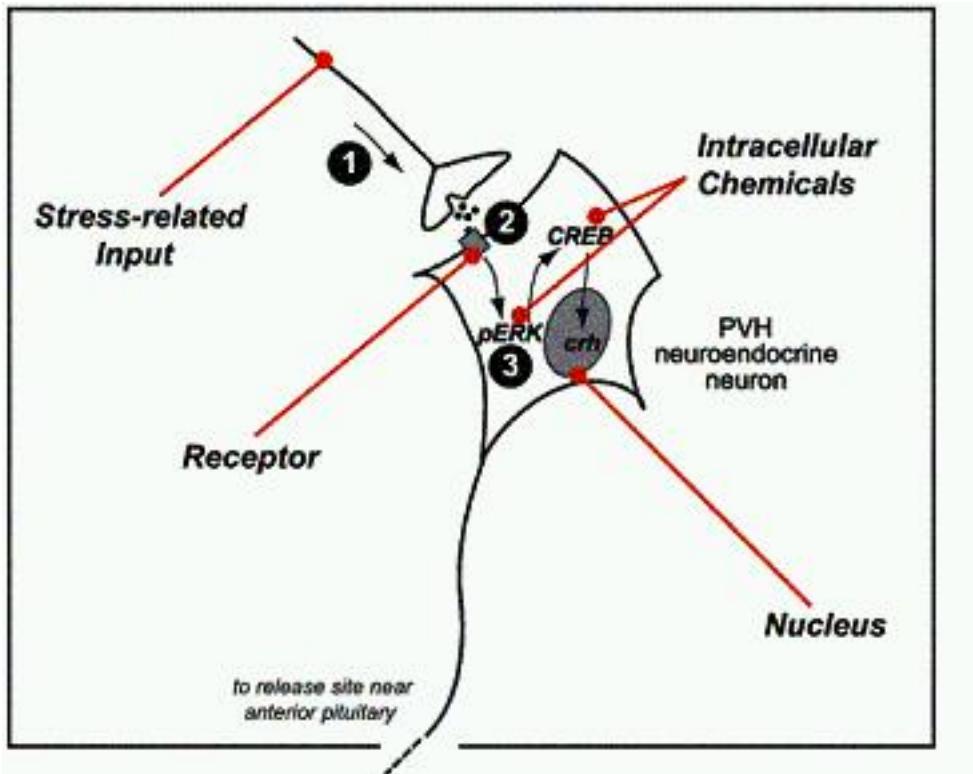
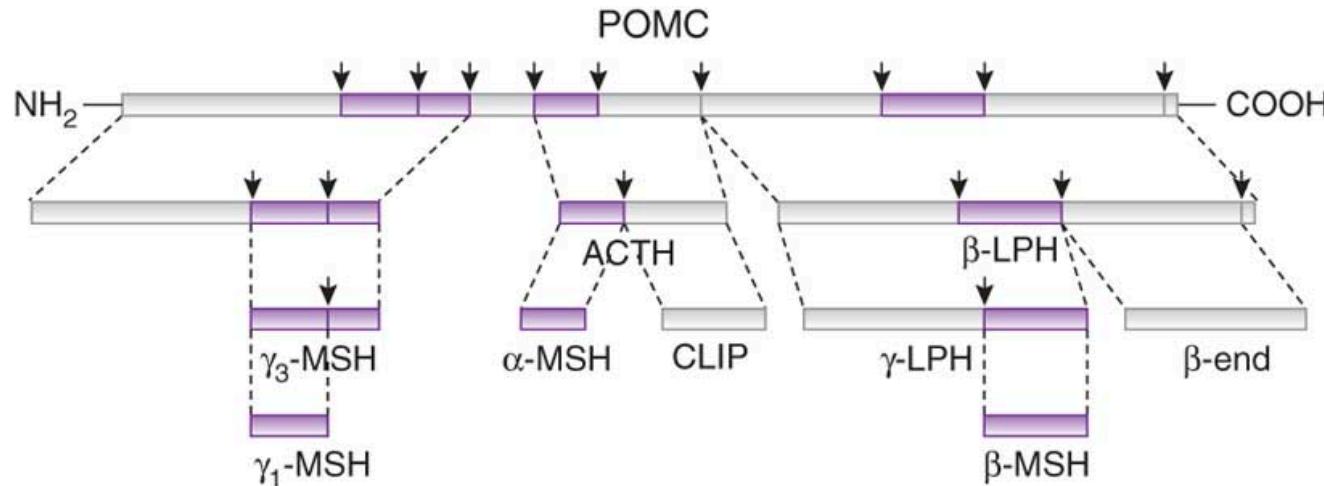


Figure 1. Activation of the CRH gene in the nucleus of a CRH neuroendocrine neuron in response to stress.

# ACTH and other Hormones are Generated from POMC Transcripts



α >> ACTH, β, γ



Melanogenesis

ACTH



Steroidogenesis

γ > α, β

AgRP

β > α >> γ

MC3R

Energy homeostasis, energy partitioning

MC4R

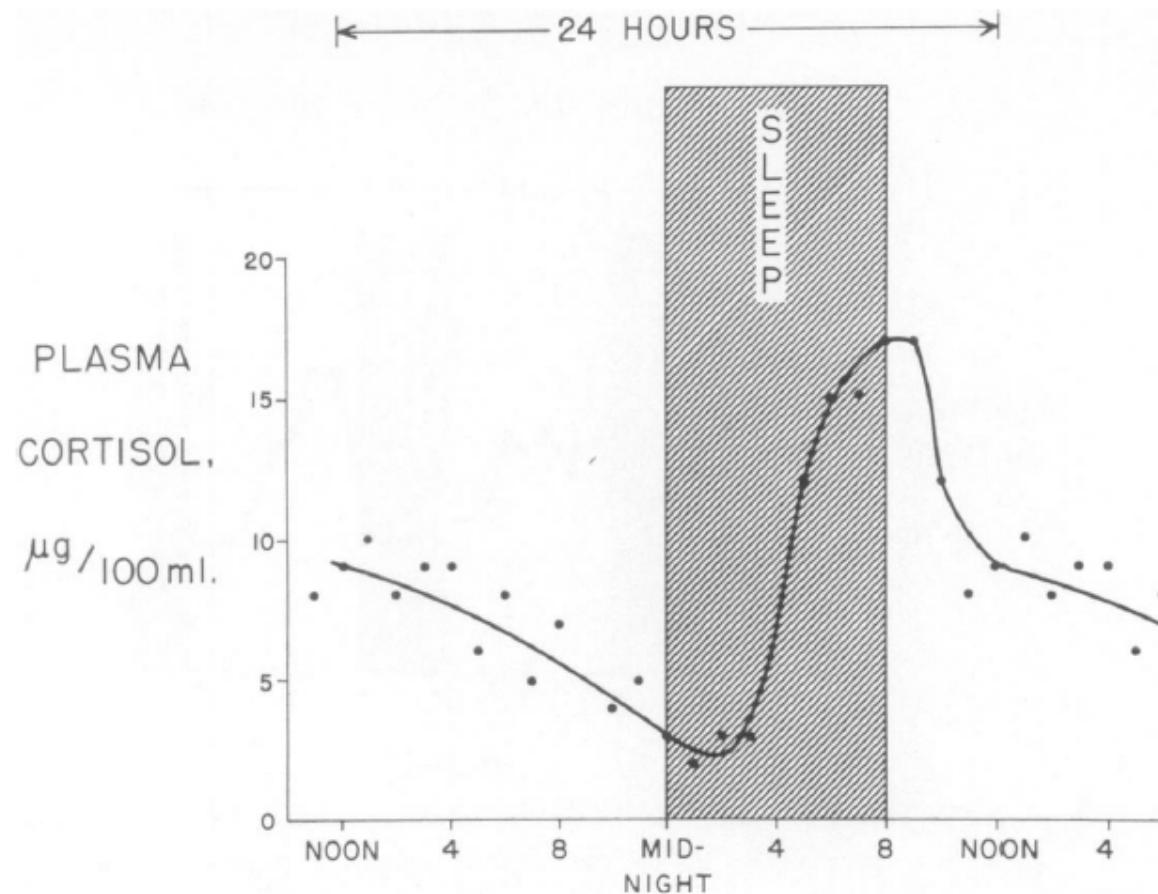
Energy homeostasis

α >> ACTH, β, γ



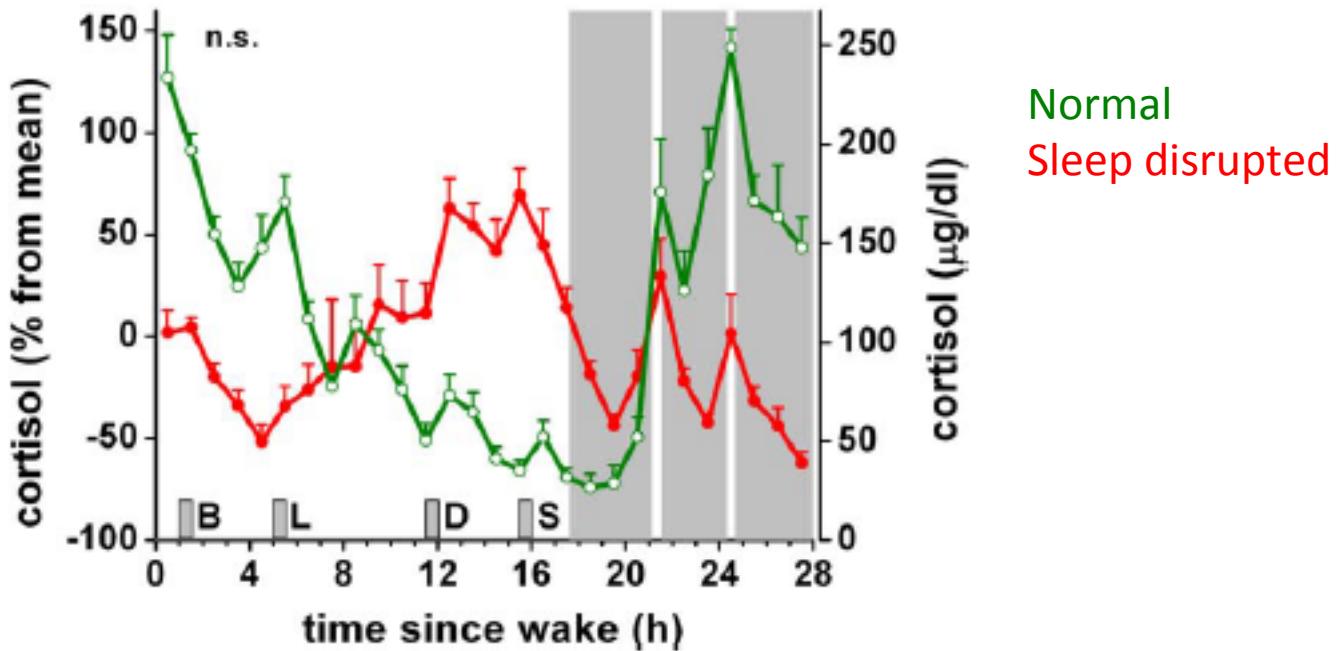
Sebum production

# 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

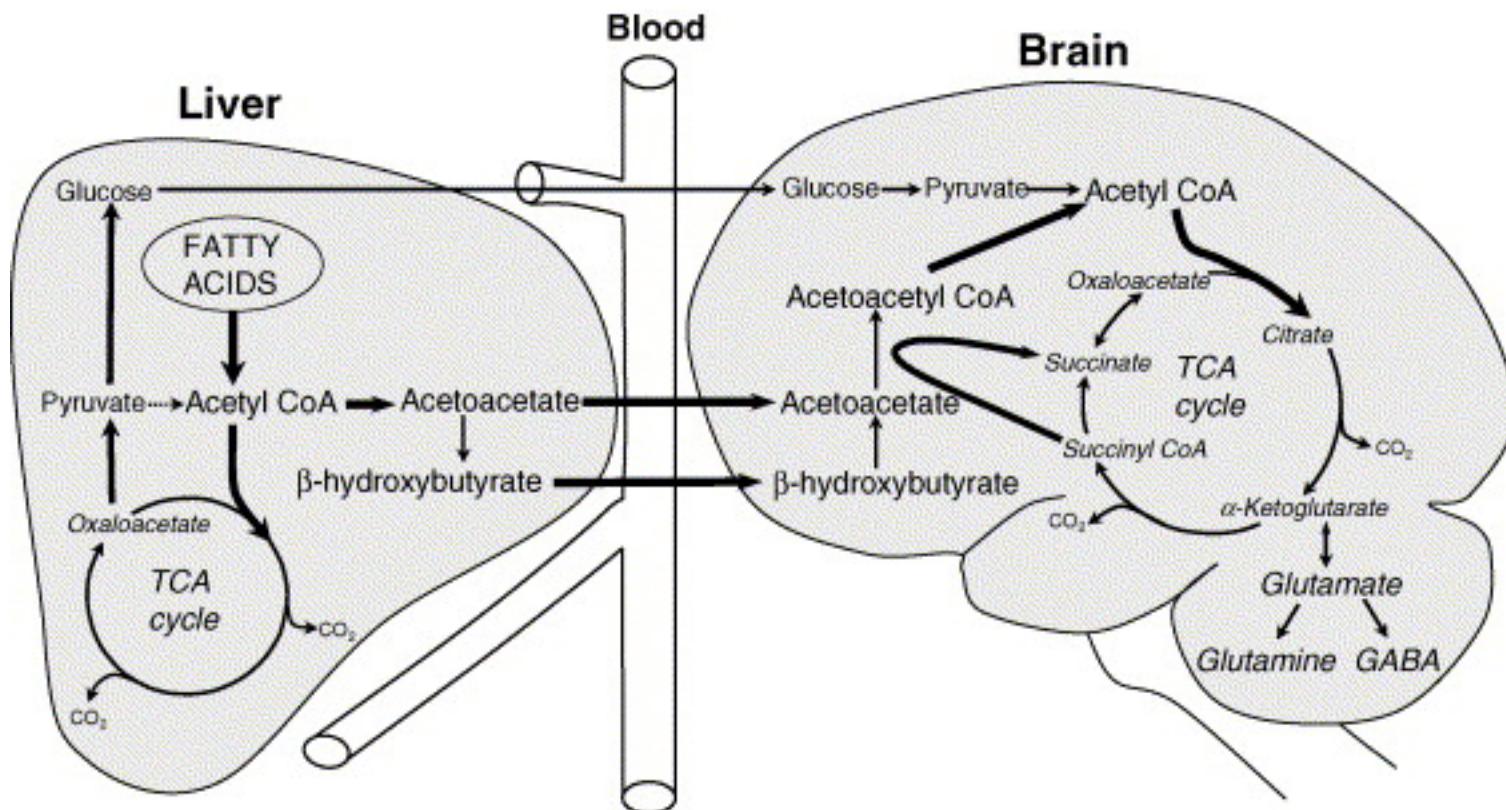


Scheer F AJL, Hilton MF, Mantzoros CS, Shea S A (2009) Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 106: 4453–4458. doi: 10.1073/pnas.0808180106.

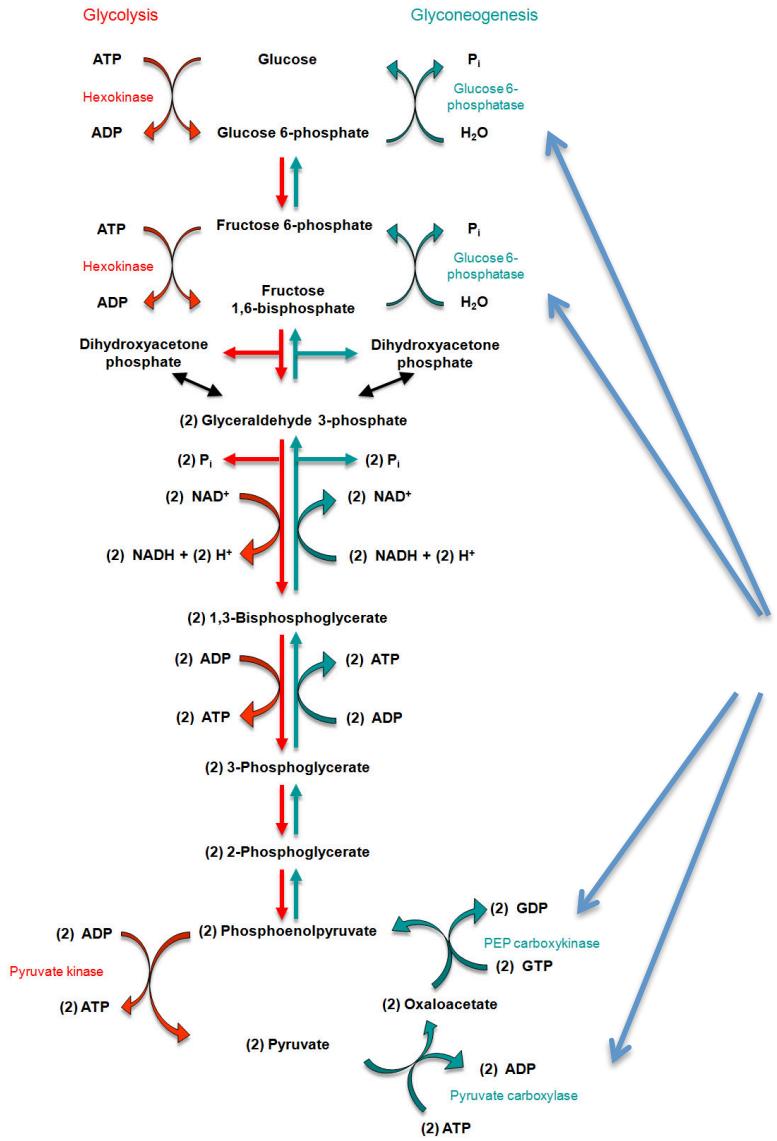
# Major Chronic Responses to Stress

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

# Brain Requires Glucose Supply

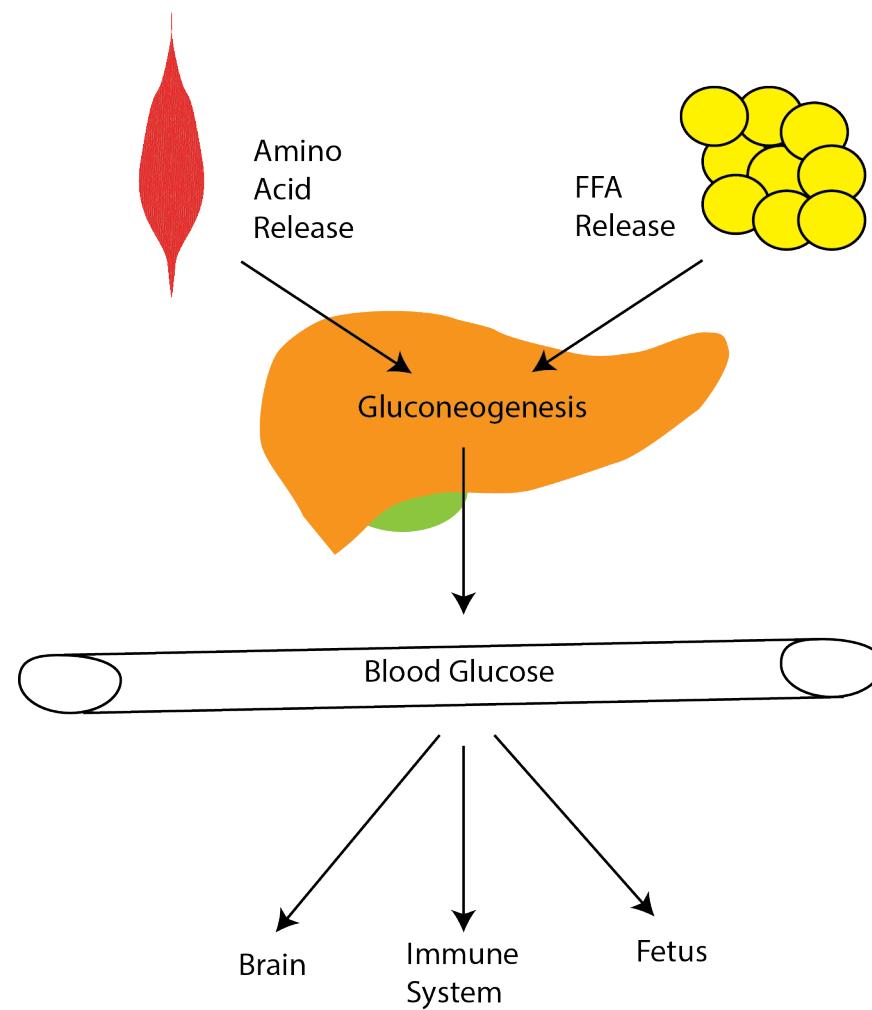


# Regulation of Gluconeogenesis



Activation of mRNA transcription  
by glucocorticoids in the liver

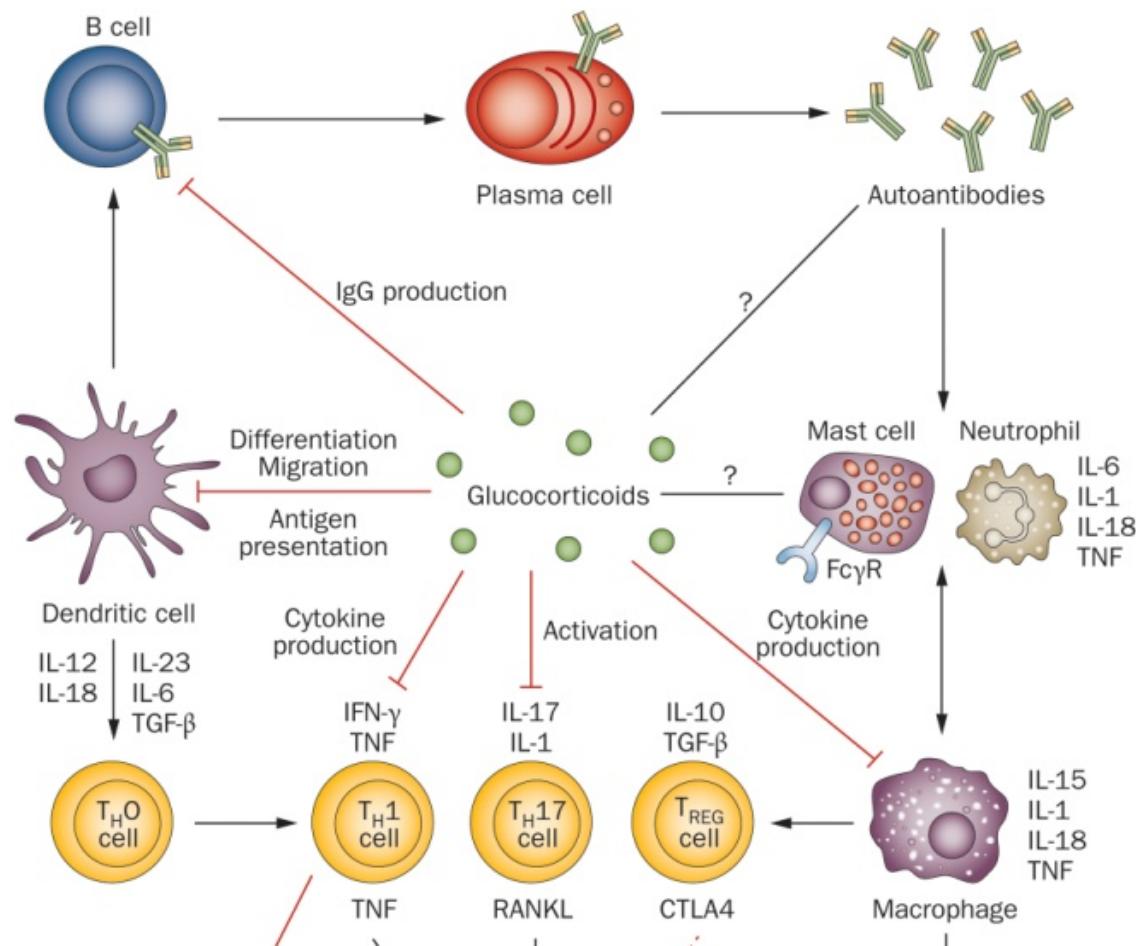
# Cortisol Maintains Blood Glucose Levels



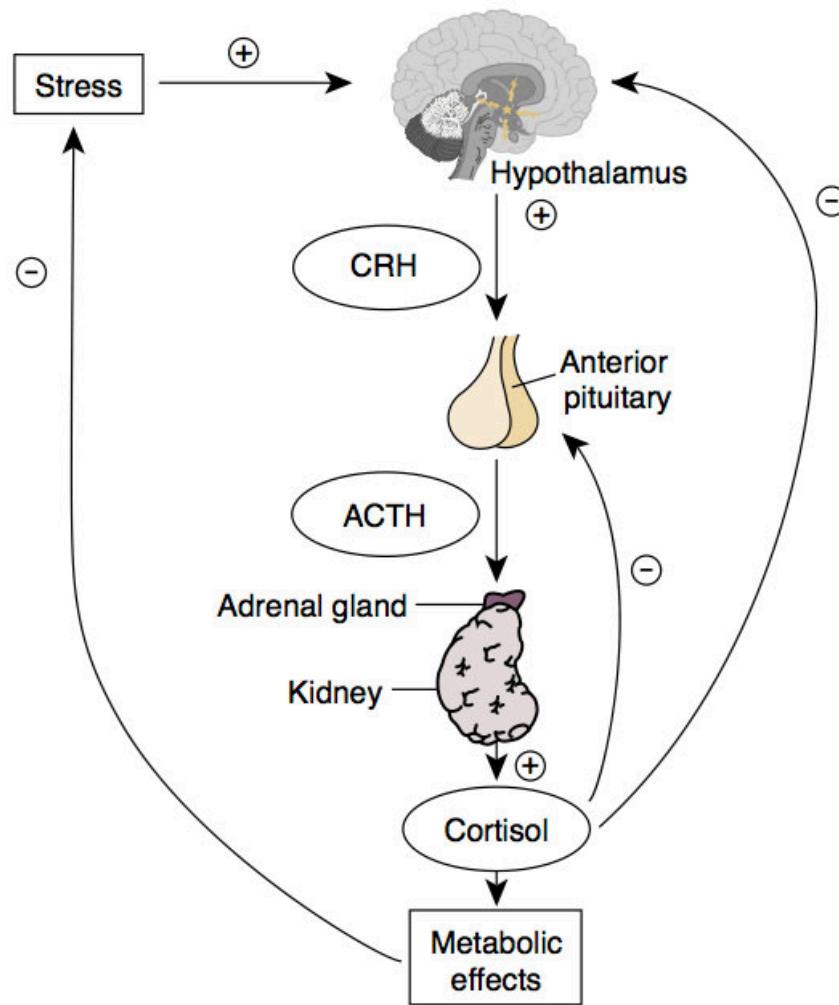
# Three Mechanisms to Maintain Blood Glucose Levels

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

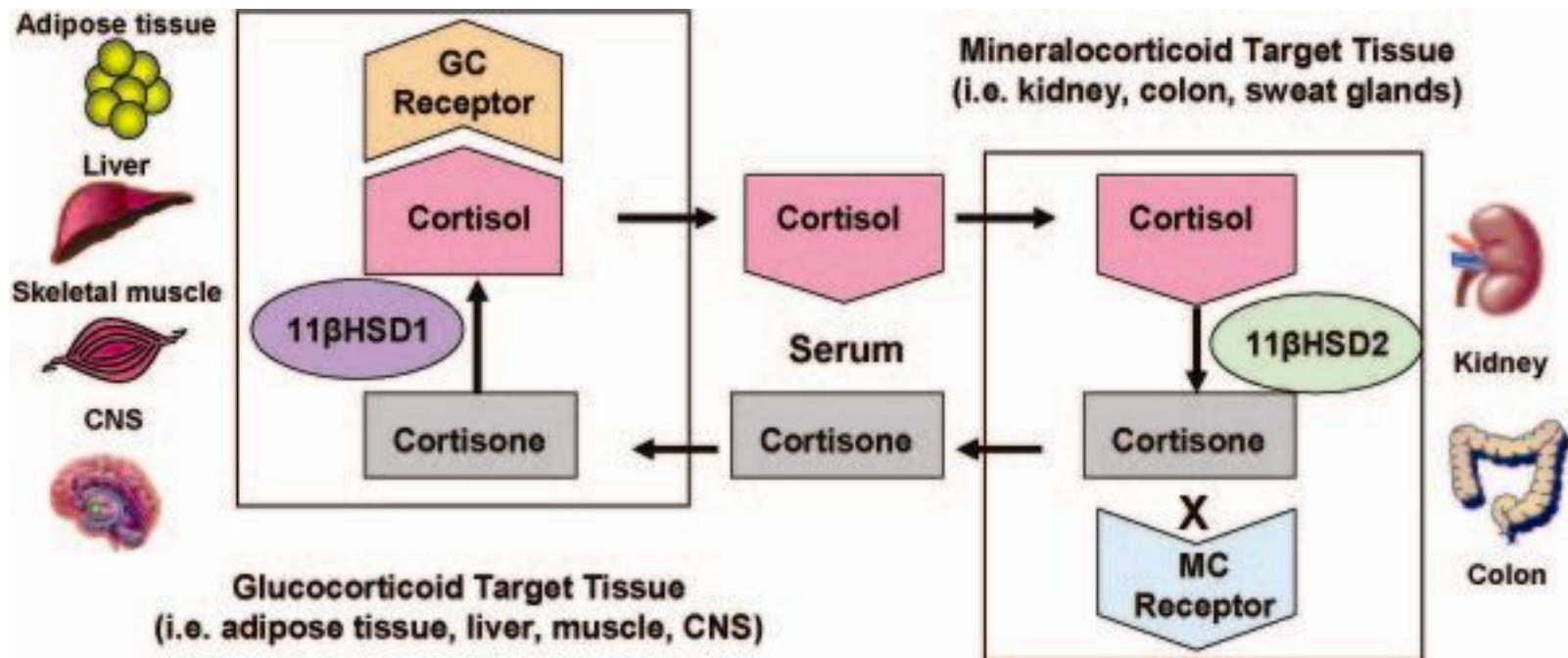
# Effects of Cortisol on Immune Function



# HPA Axis



# $11\beta$ -HSD and Local Concentrations of Glucocorticoids



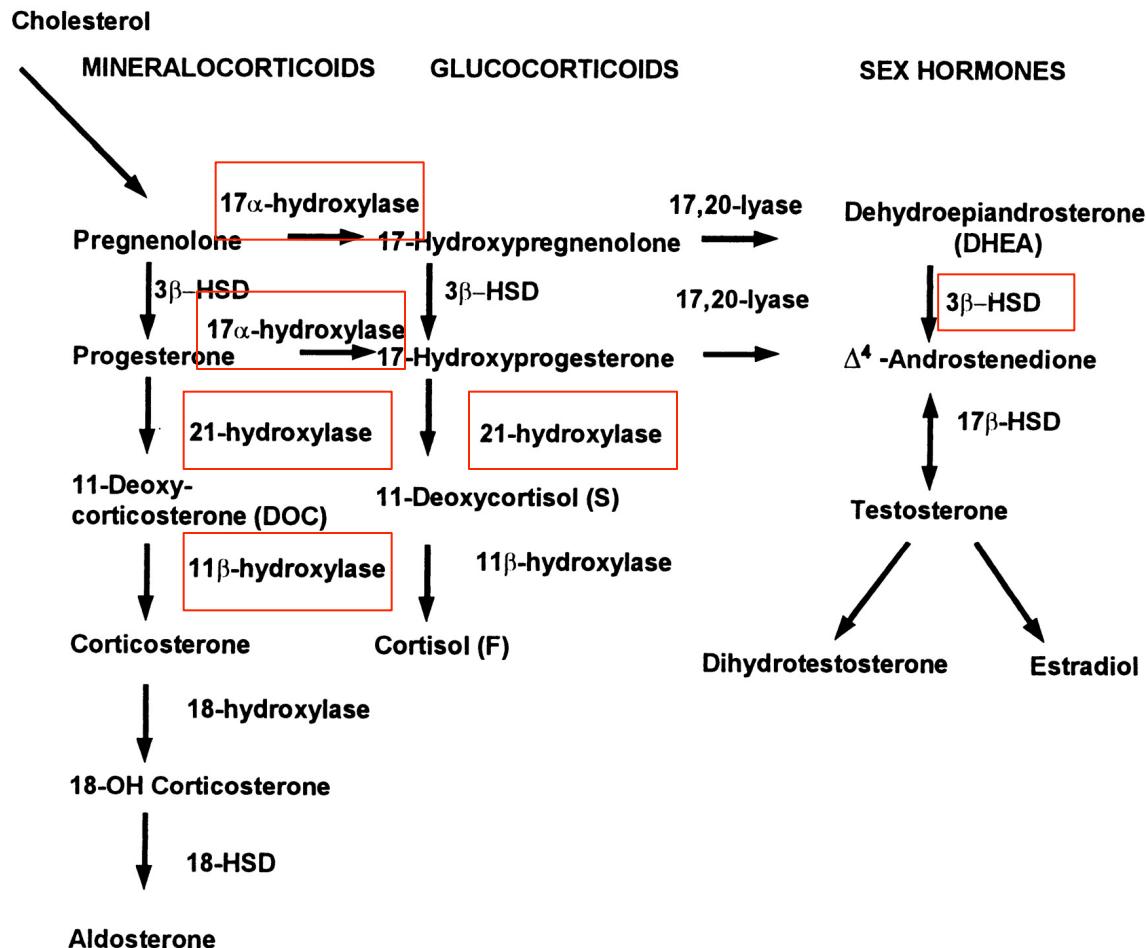
In off target tissues,  
or to desensitize normal tissues

# **ADRENAL STEROID HORMONE DISFUNCTION**

# Main Types of Endocrine Dysfunction

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



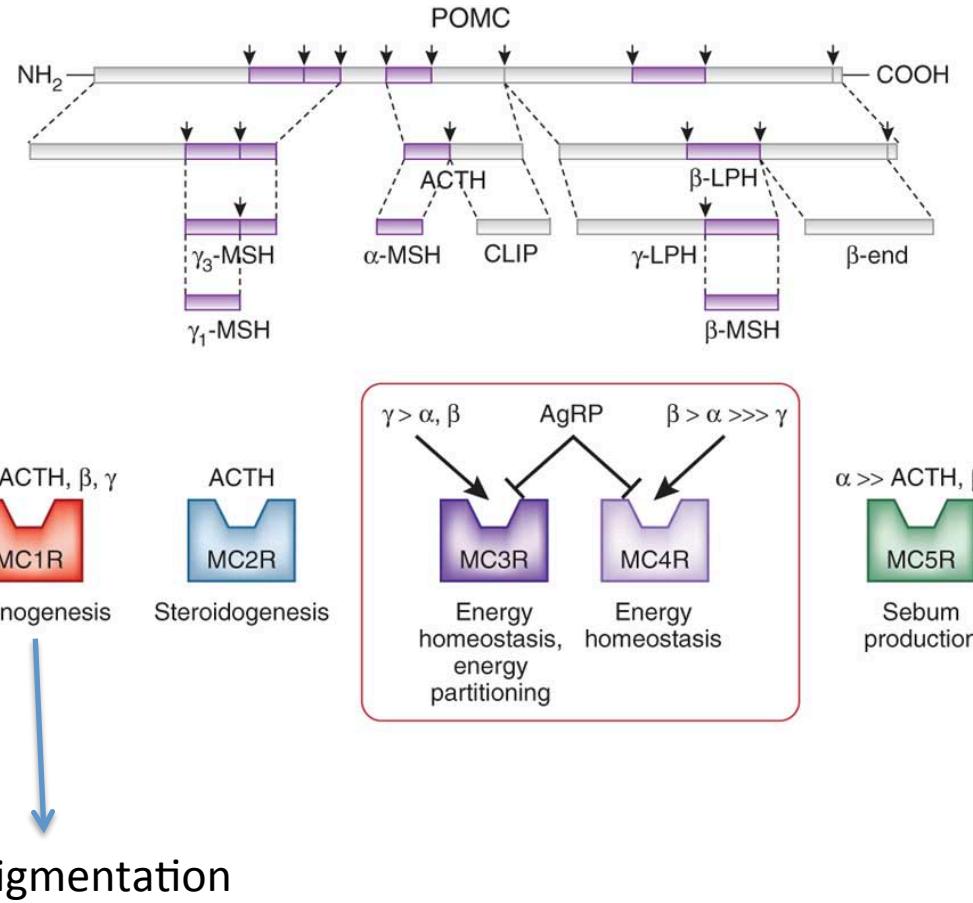
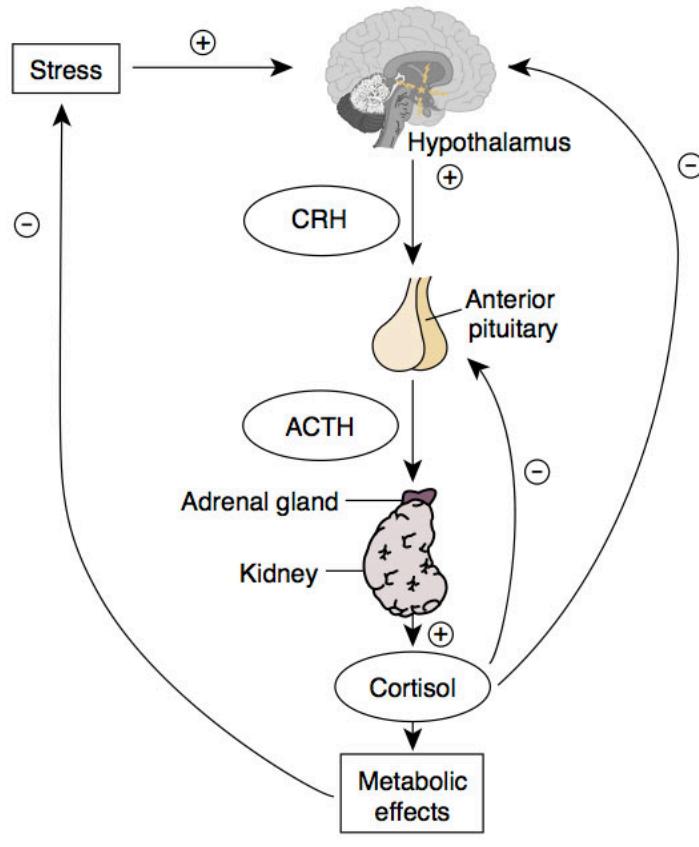
Maria I. New, and Robert C. Wilson PNAS  
1999;96:12790-12797

# 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



# Tumors Affecting Adrenal Function

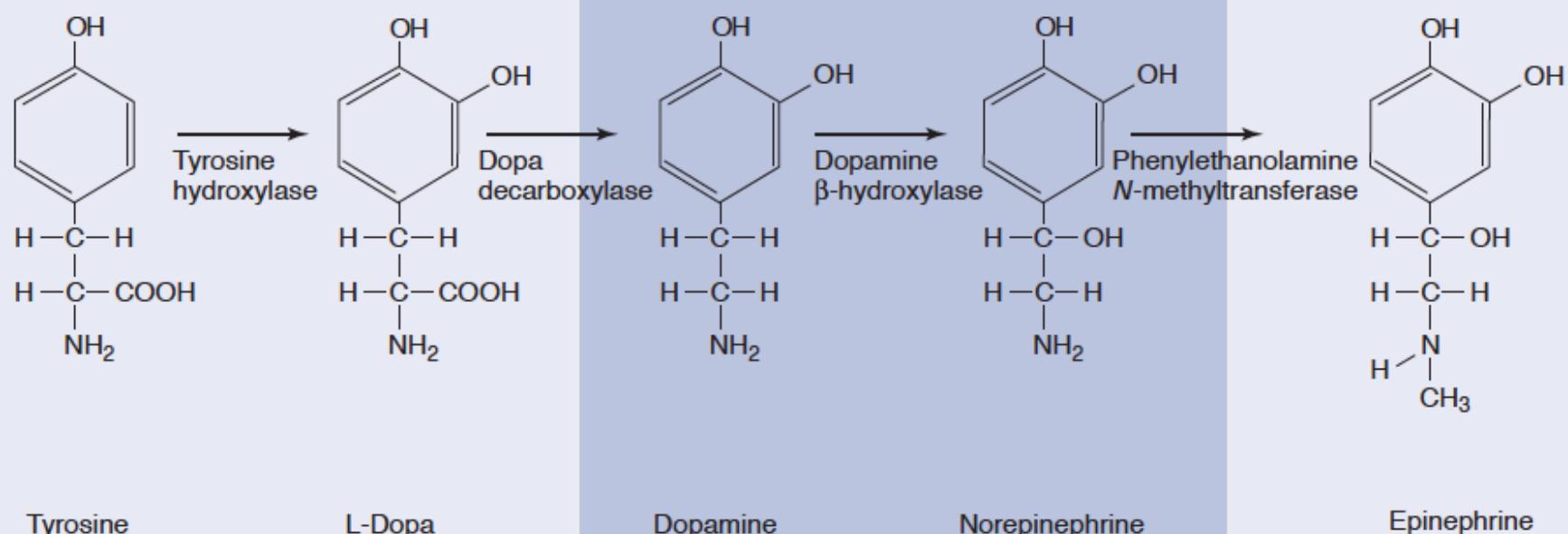
- Conn's syndrome (adenoma of zona glomerulosa)
- Cushing's syndrome
  - pituitary adenoma (ACTH releasing) or
  - adenoma of zona fasciculata

**ADRENALINE MEDIATES SHORT-  
TERM STRESS RESPONSES**

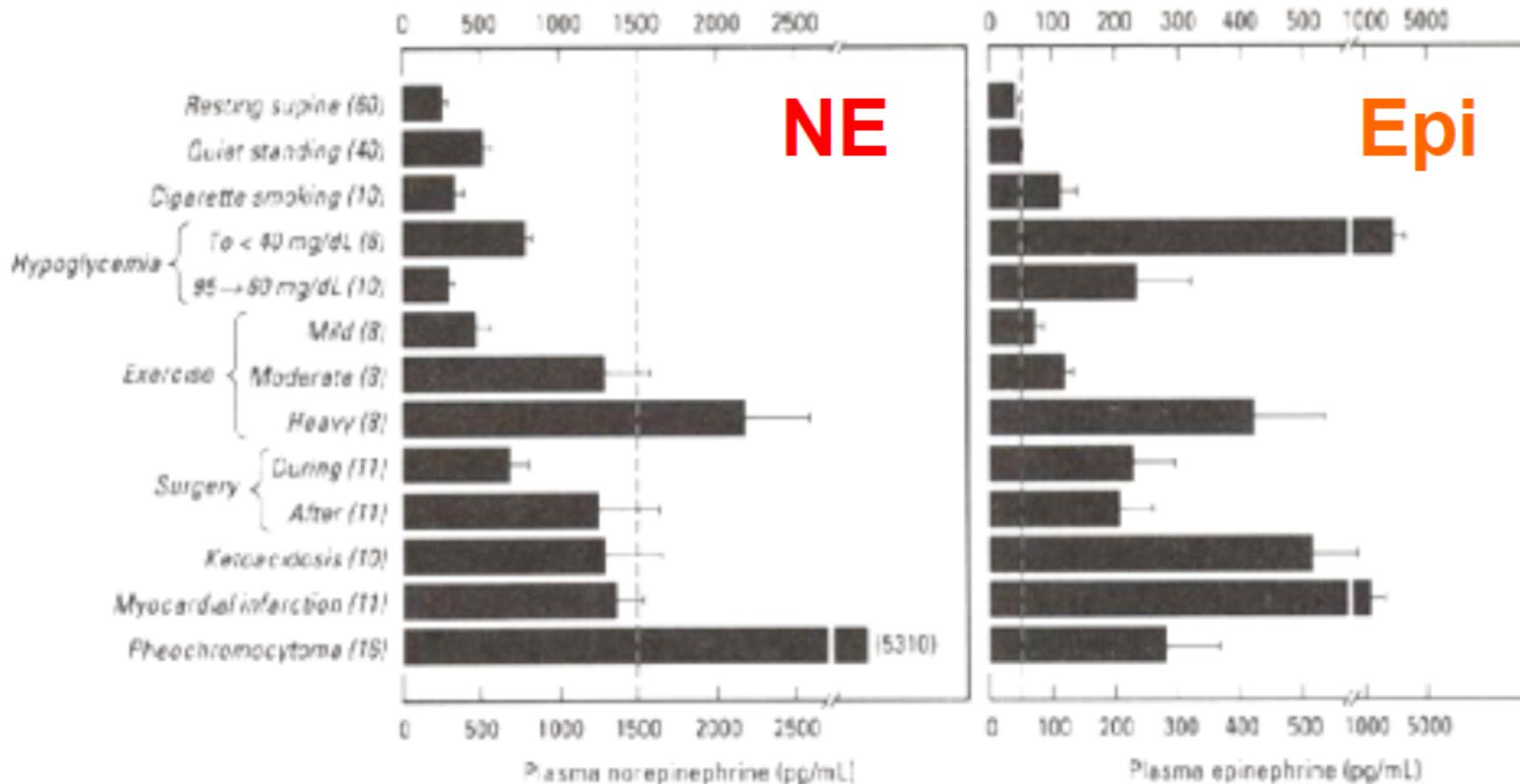
# Epinephrine Summary

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

# Epinephrine and Norepinephrine

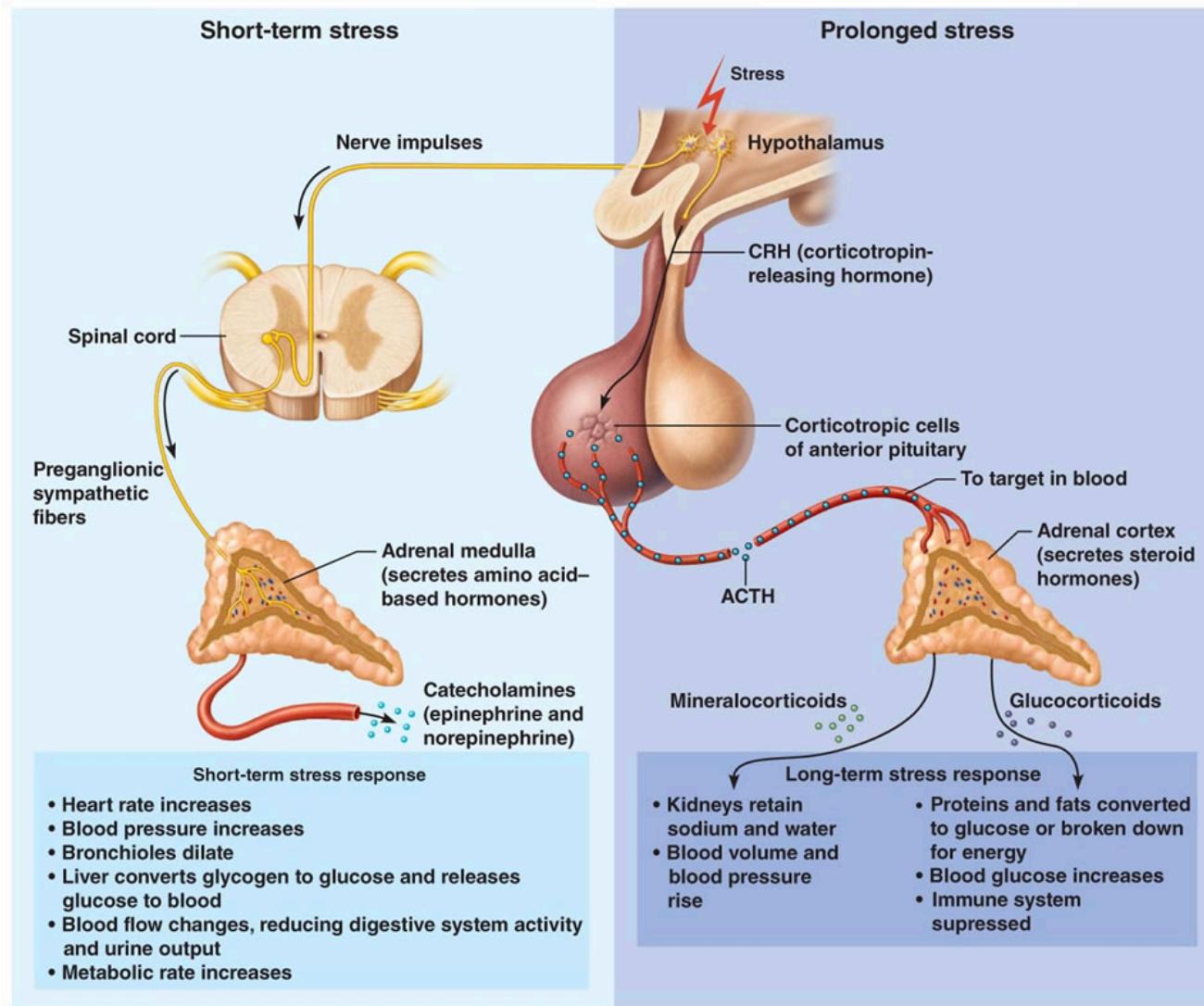


# Epinephrine vs Norepinephrine

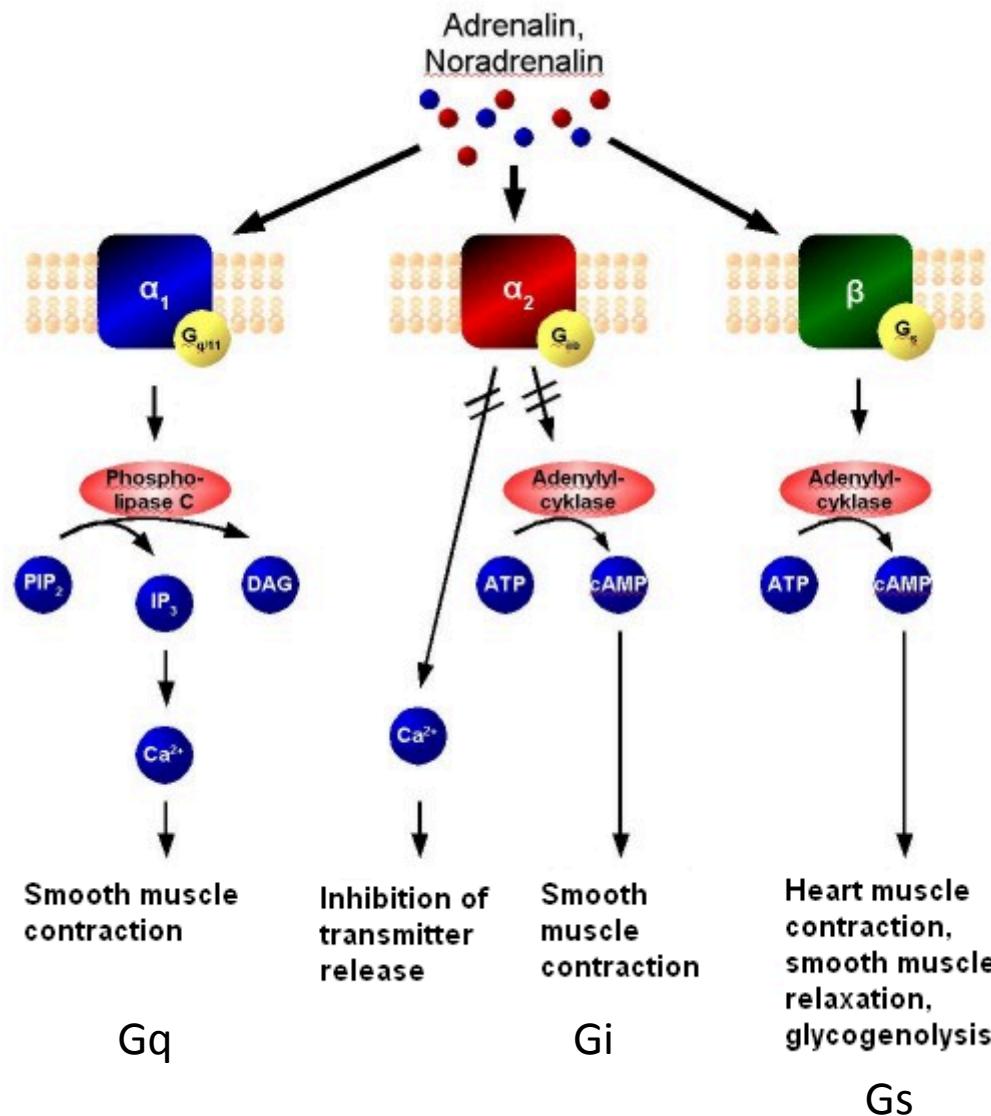


Dashed line is level in circulation needed to elicit a physiological response

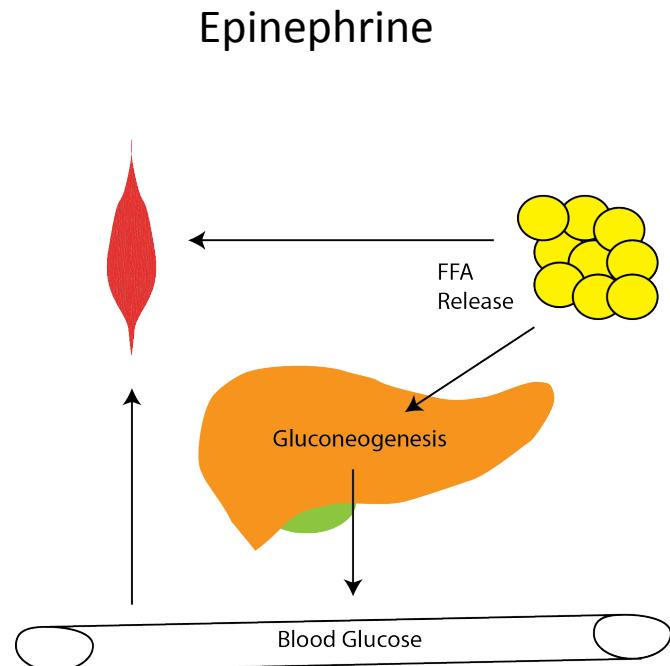
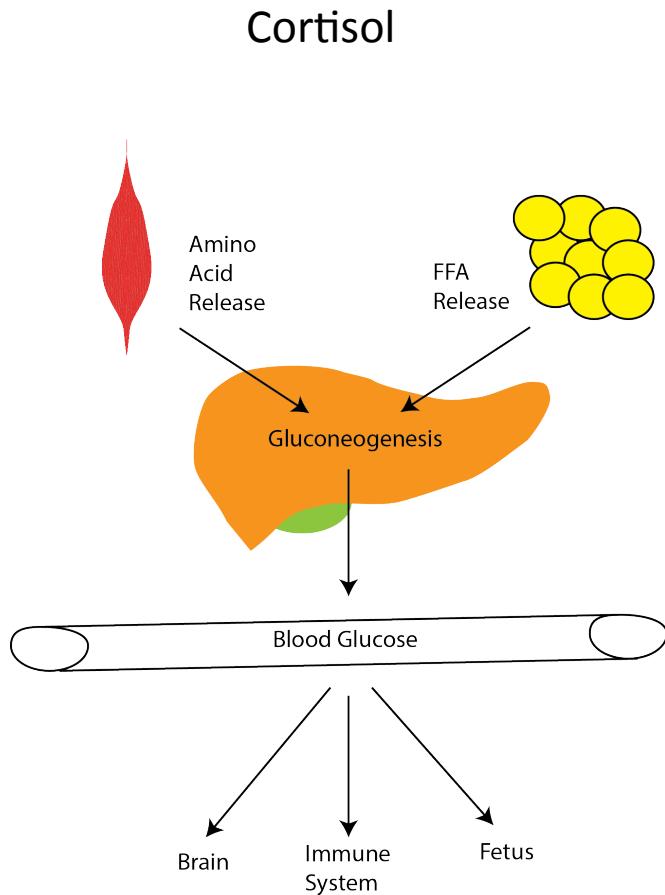
# Adrenaline vs Cortisol Release



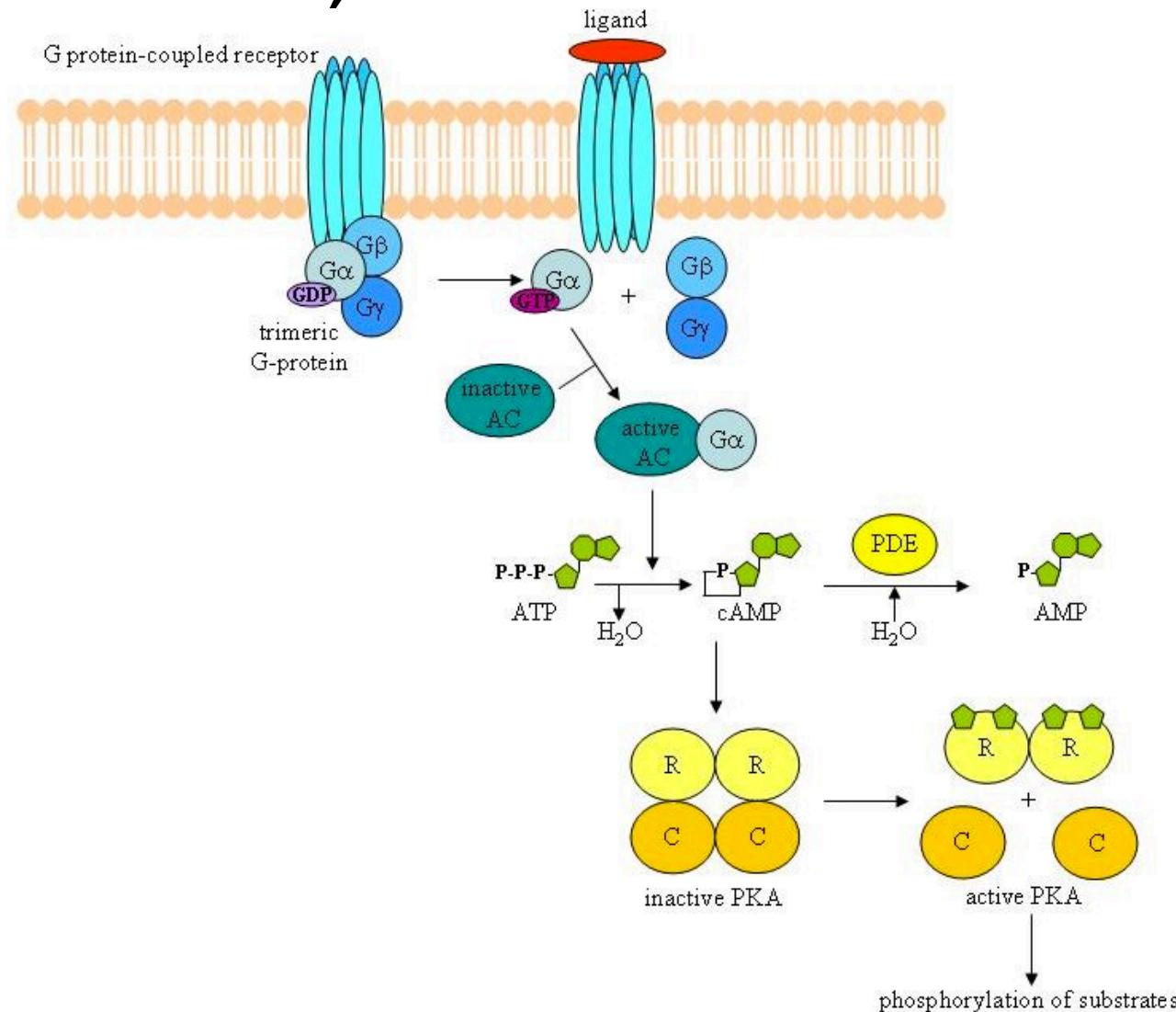
# Cardiovascular Roles of Epinephrine



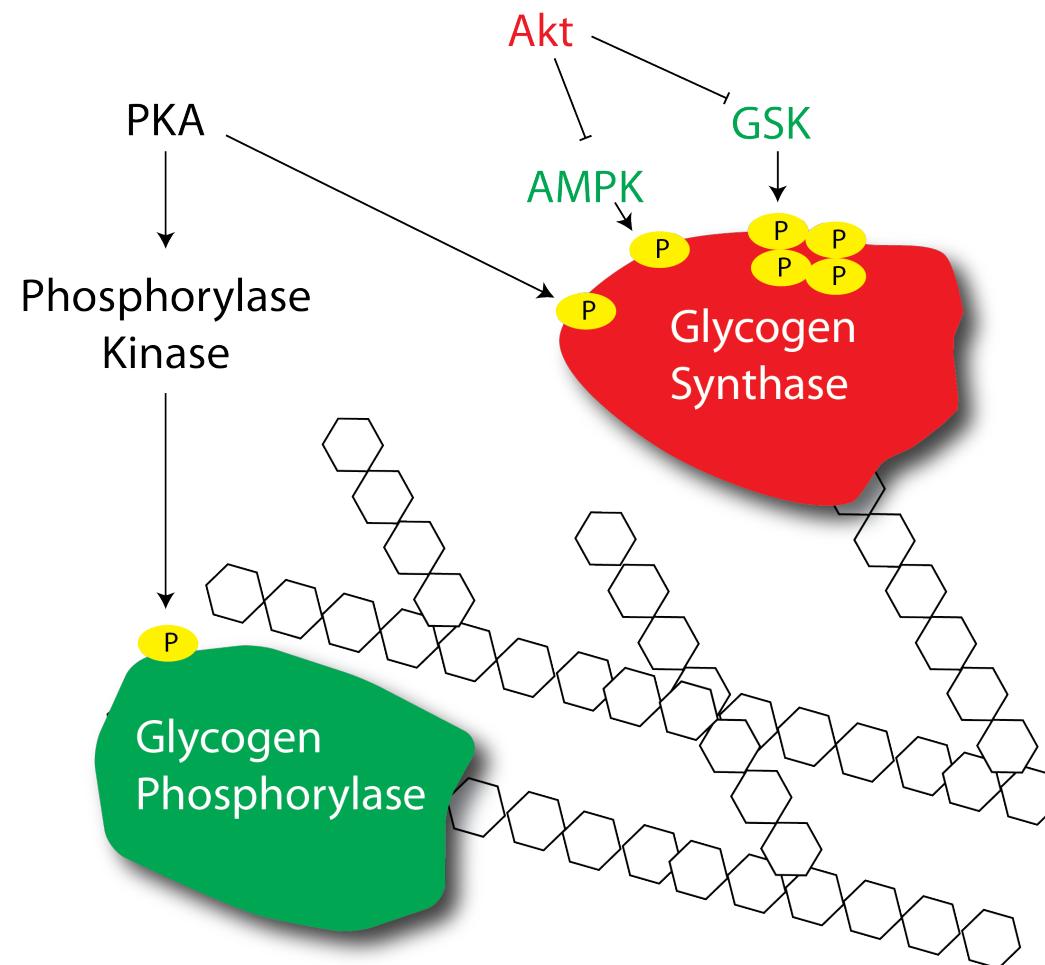
# Metabolic Roles of Epinephrine



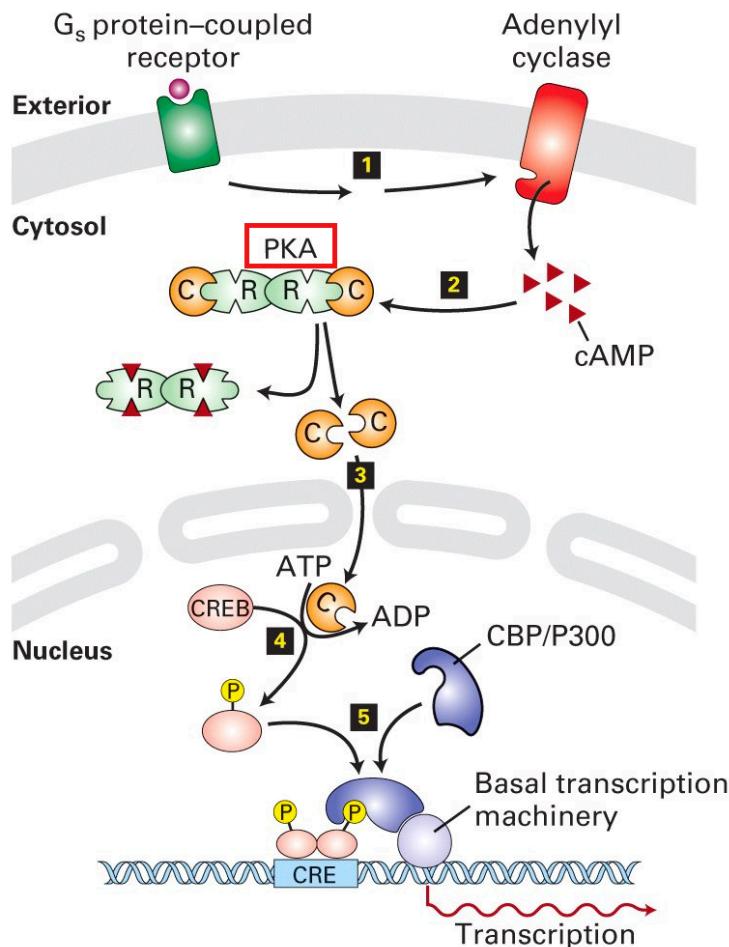
# Epinephrine Binds B-AR/Gs in Skeletal Muscle, Liver and Fat Tissue



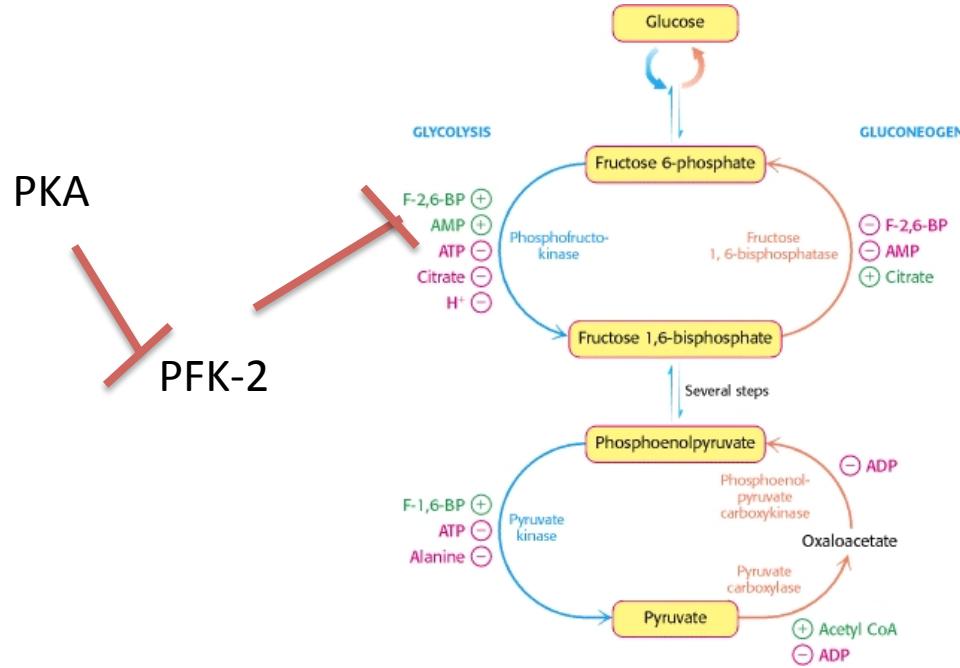
# Epinephrine Mediated Activation of Glycogenolysis



# Dual Effects of Epinephrine on Glucconeogenesis in the Liver

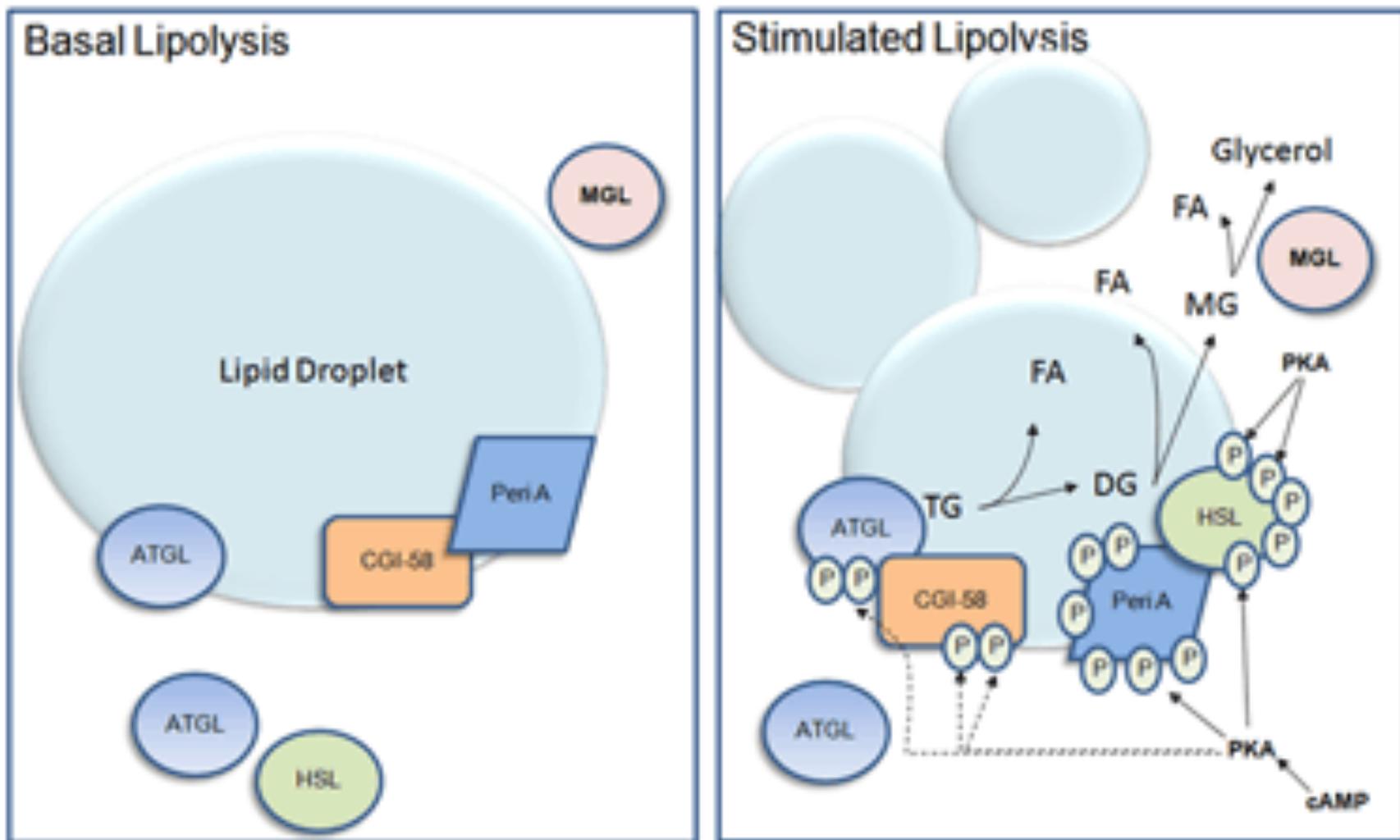


Gluconeogenic Gene Transcription

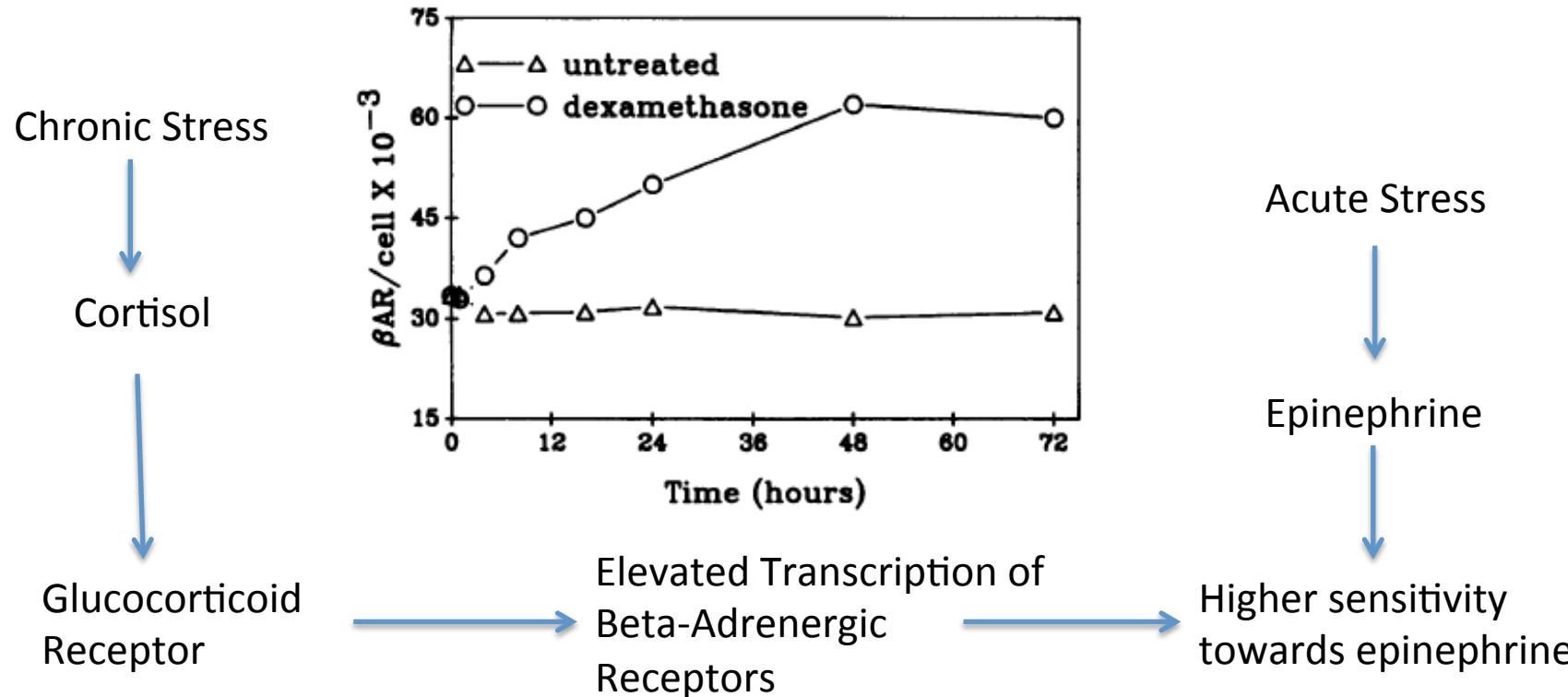


Post-Translational  
Induction of  
Gluconeogenesis

# Effects of Epinephrine on Lipid Breakdown



# Short Term and Long Term Stress



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

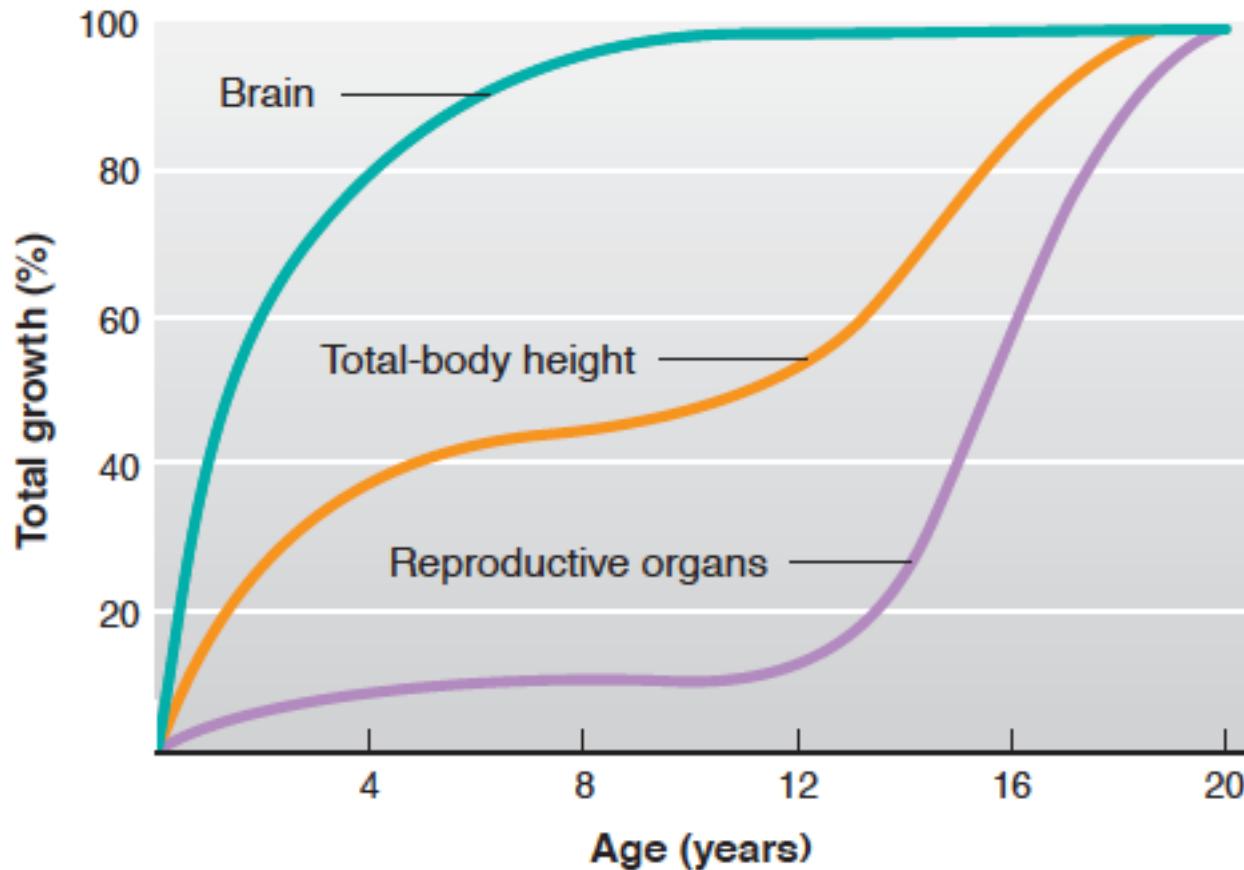
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- List the major metabolic actions of catecholamines.
- Contrast the thresholds for actions vs. plasma levels of epi and NE under common conditions, like exercise, and in the disease pheochromocytoma

# 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



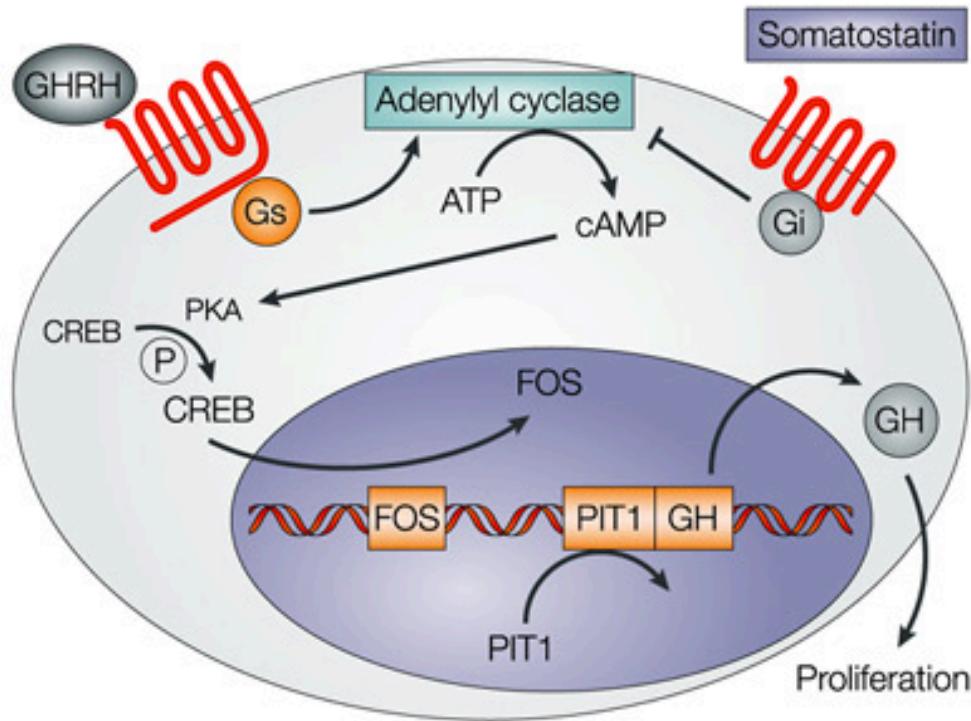
# Hormones During Growth

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

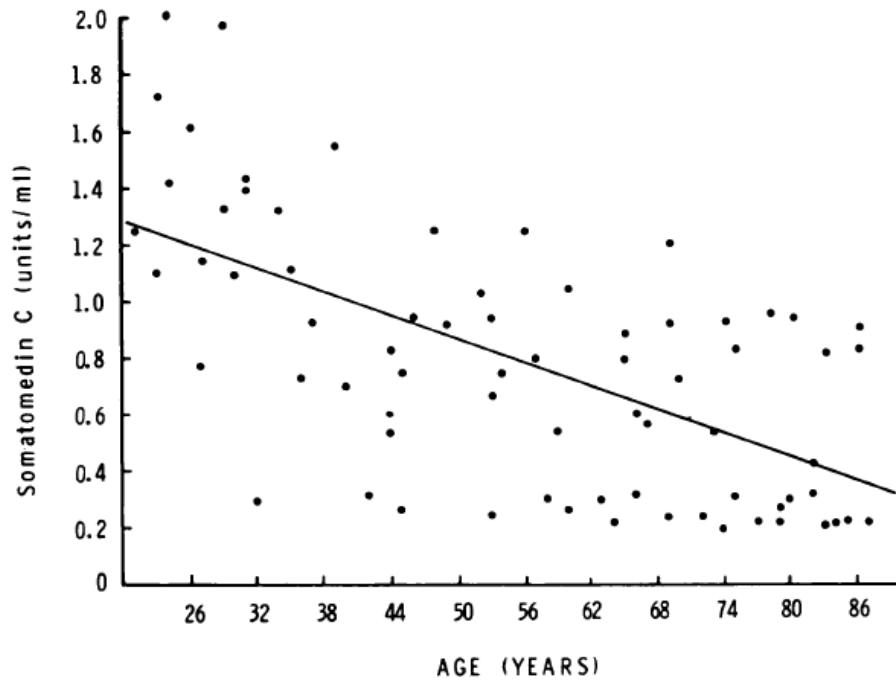
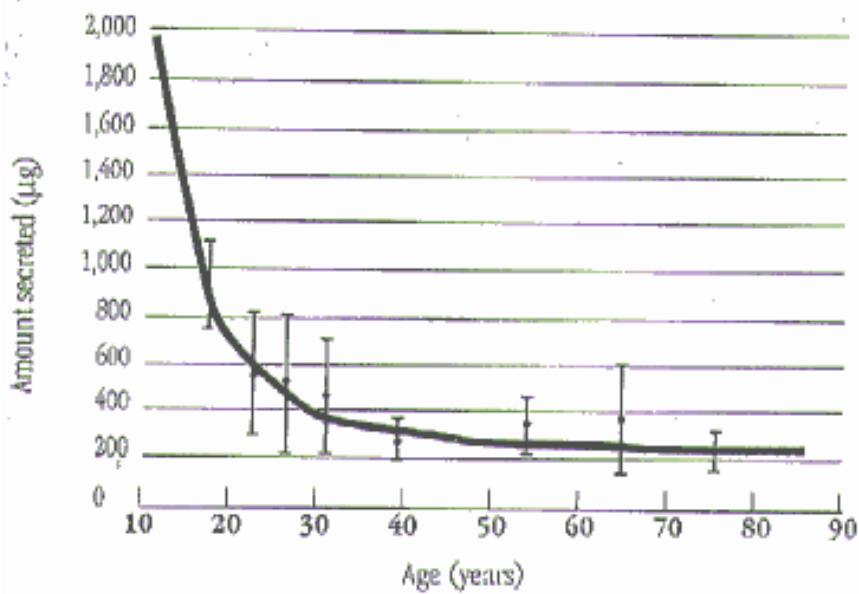
<b>What chemical type is it?</b>	Protein	
<b>Where is it made?</b>	Somatotropes of Anterior Pituitary	
<b>What causes its release?</b>	GHRH release (also regulated by somatostatin)	
<b>What is its receptor?</b>	Growth Hormone Receptor	JAK/STAT
<b>What tissues does it affect?</b>	Liver	IGF-1 Release
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

# Regulation of GH Release



# GH and Aging

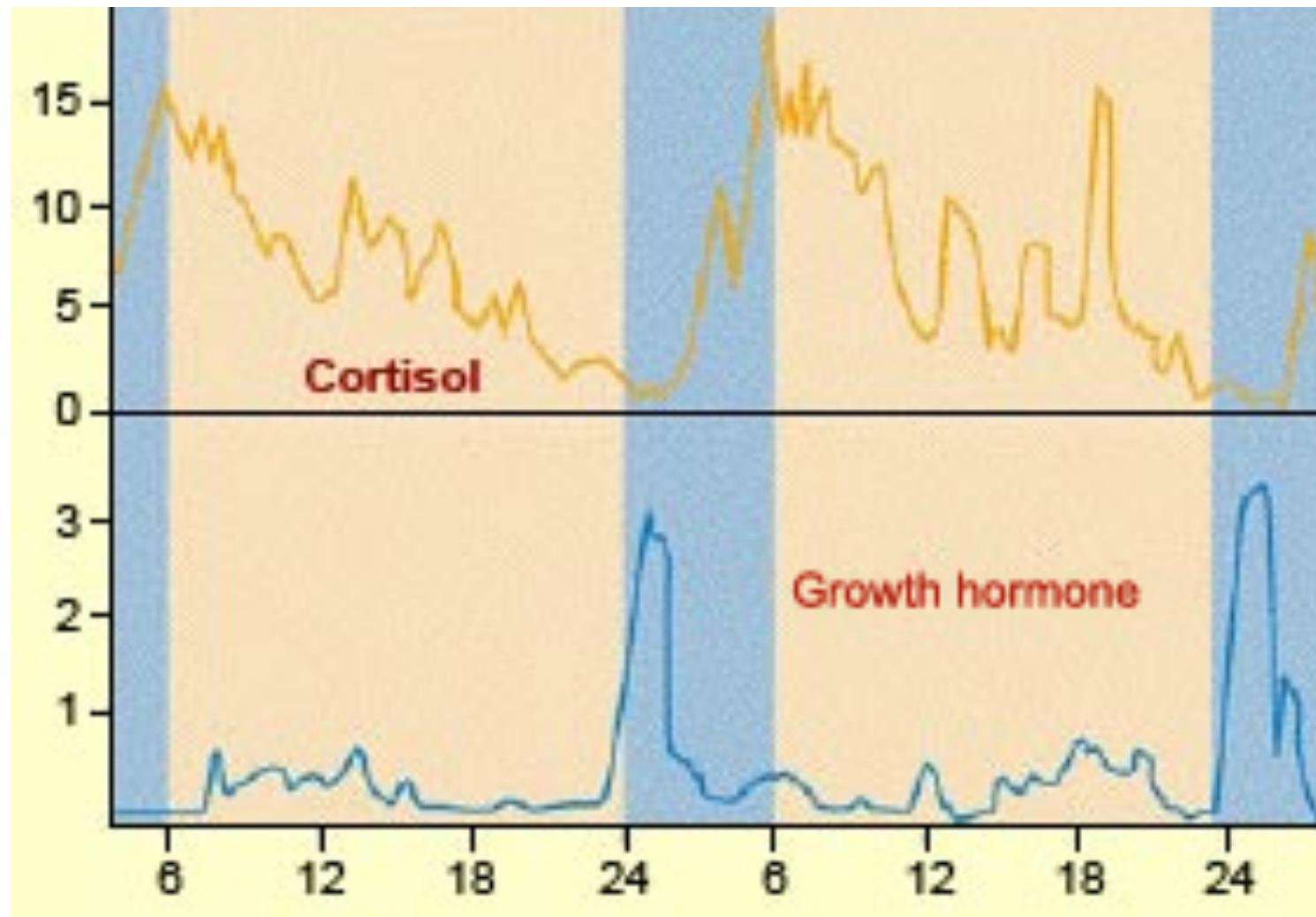
Growth Hormone Decline



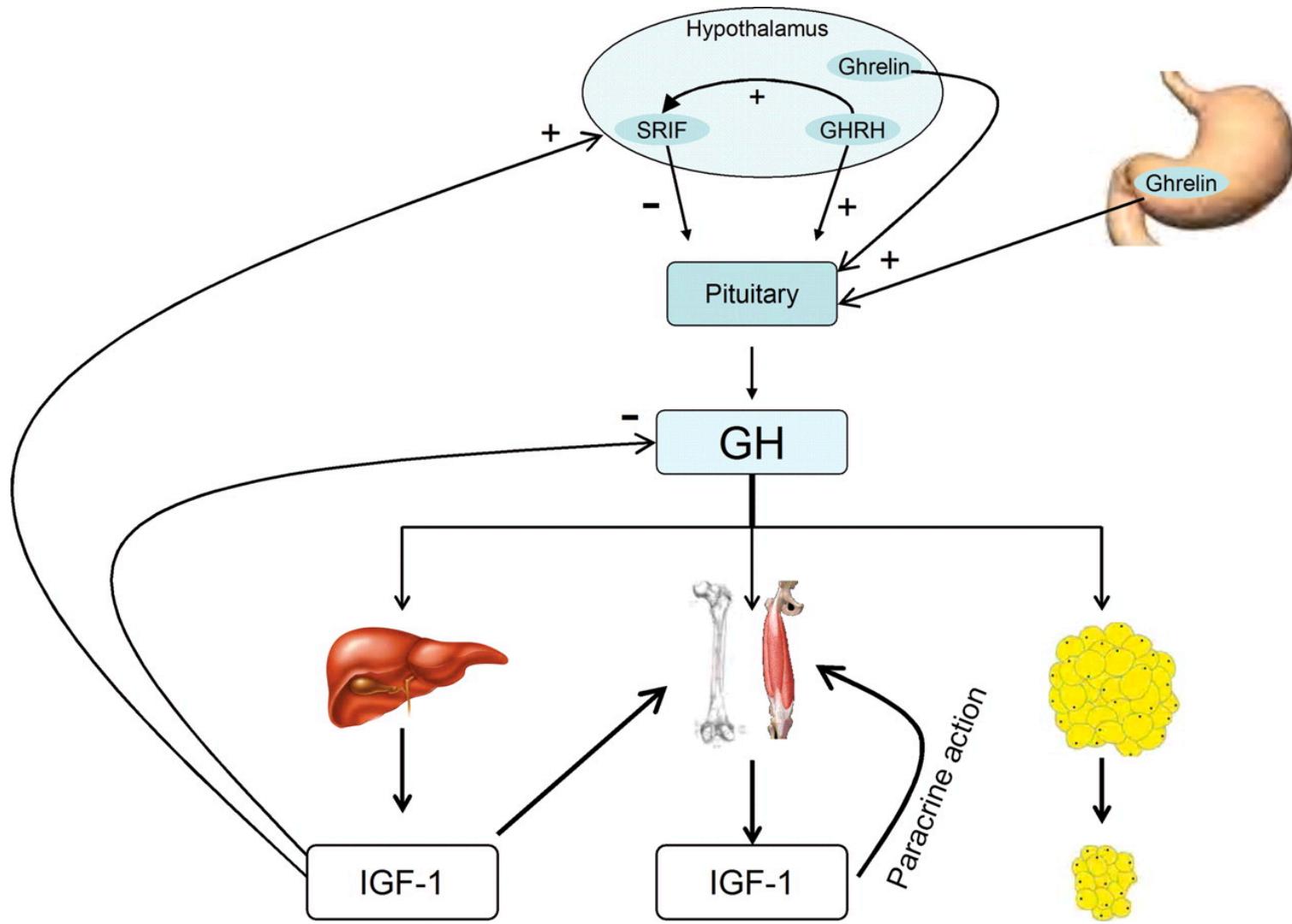
GHRH Levels

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.

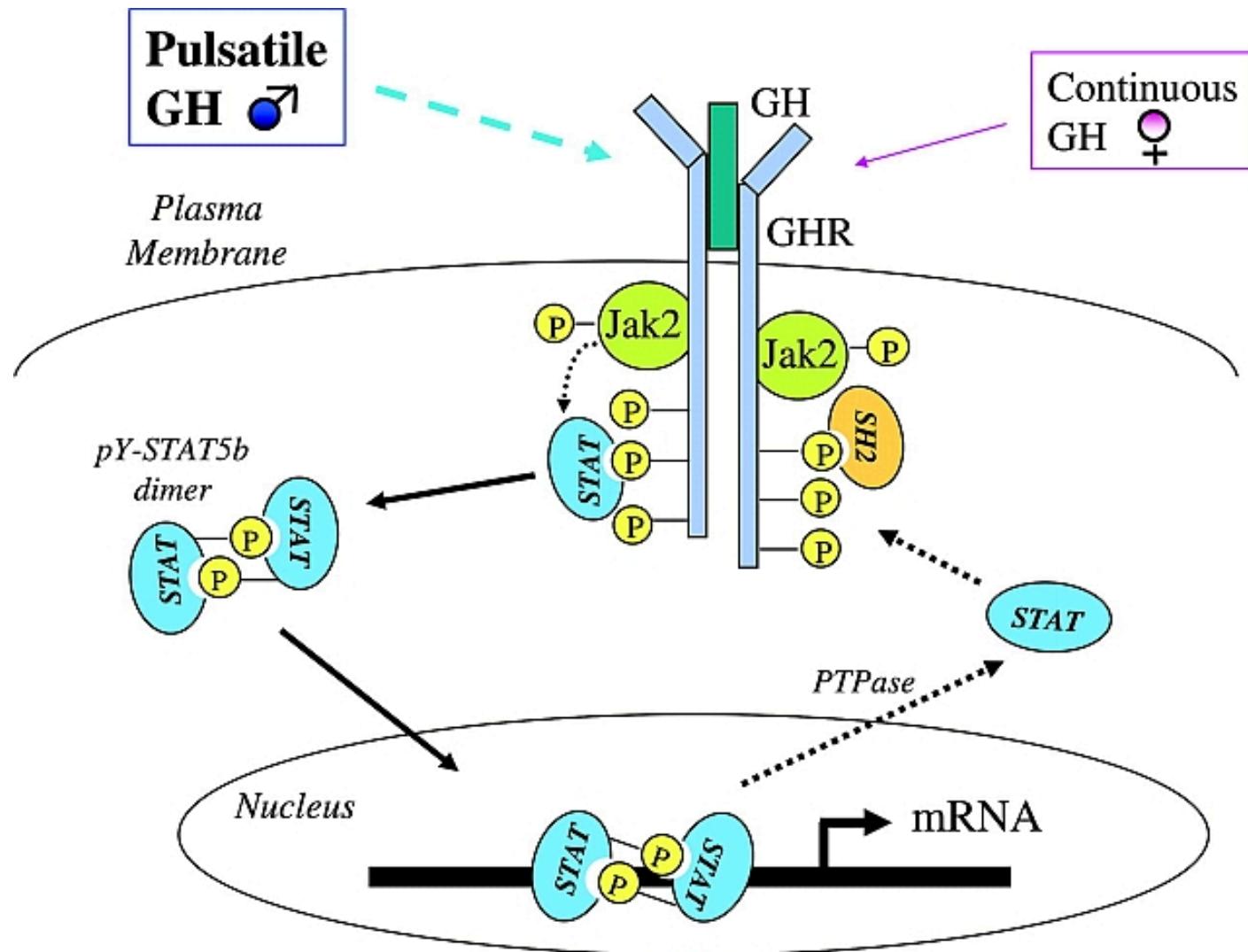
# Diurnal Rhythms of GH Release



# Growth Hormone Causes IGF-1 Release



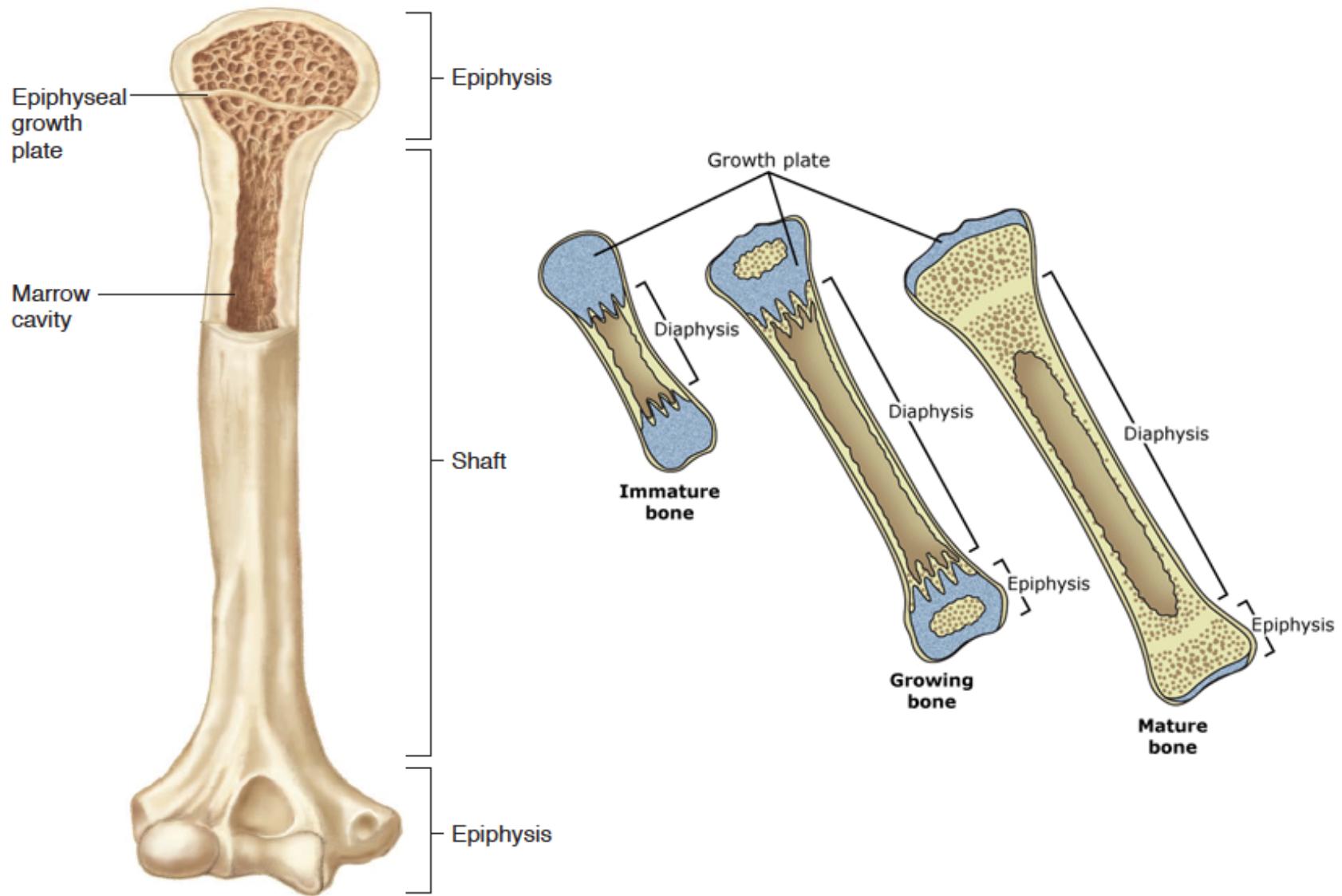
# Growth Hormone Receptor



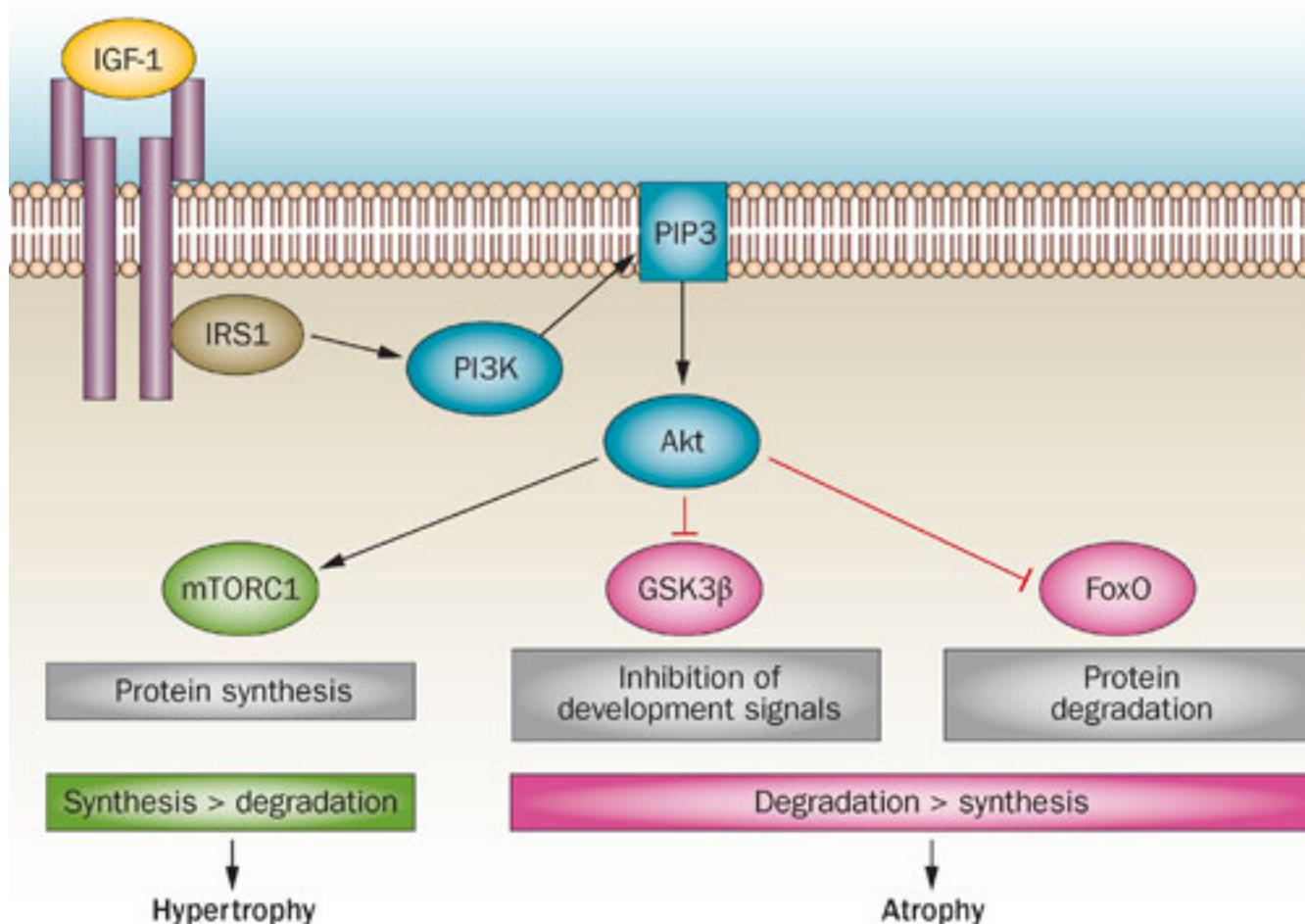
# IGF-1 Summary

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

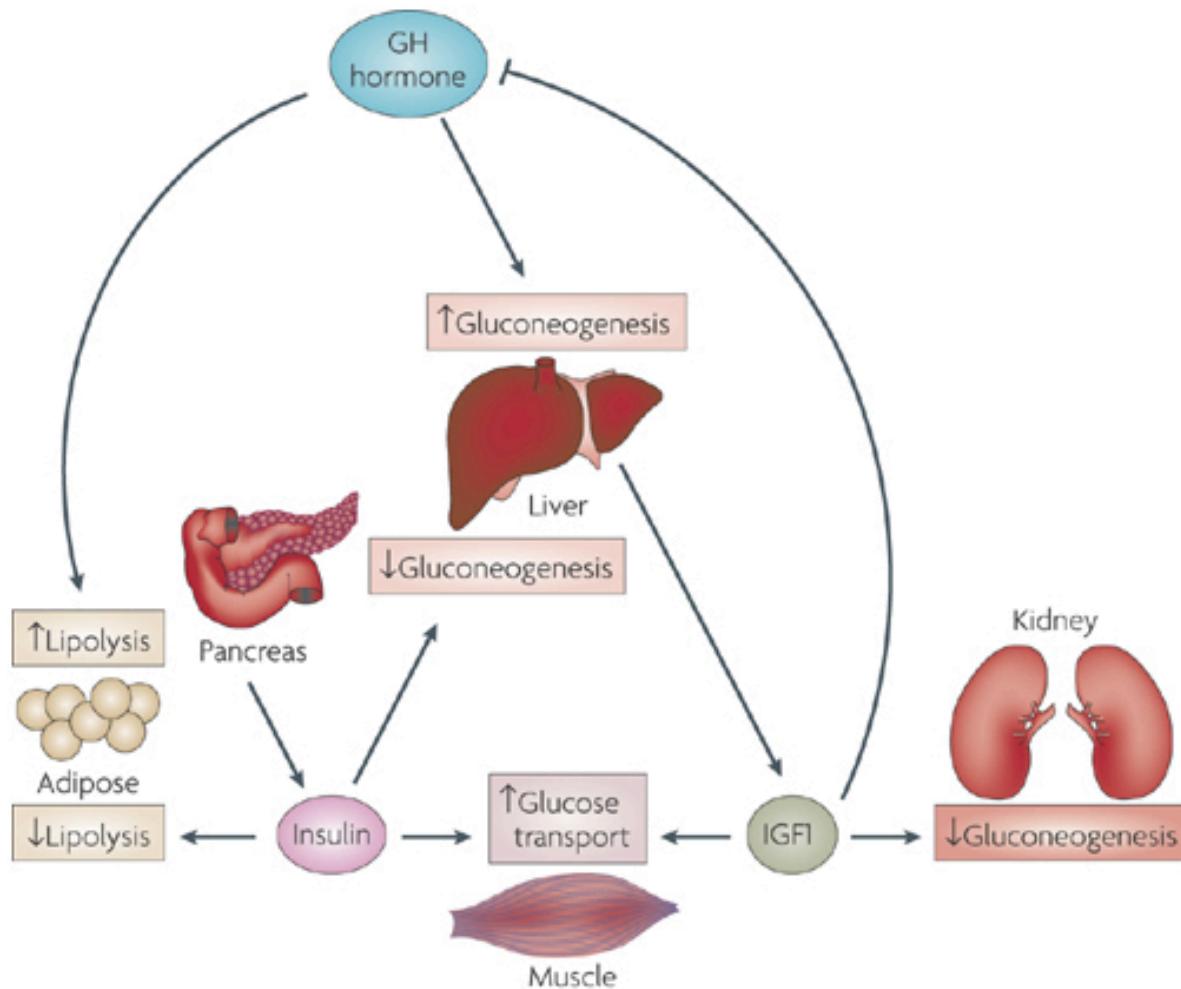
# Regulation of Bone Growth



# Regulation of Muscle Growth

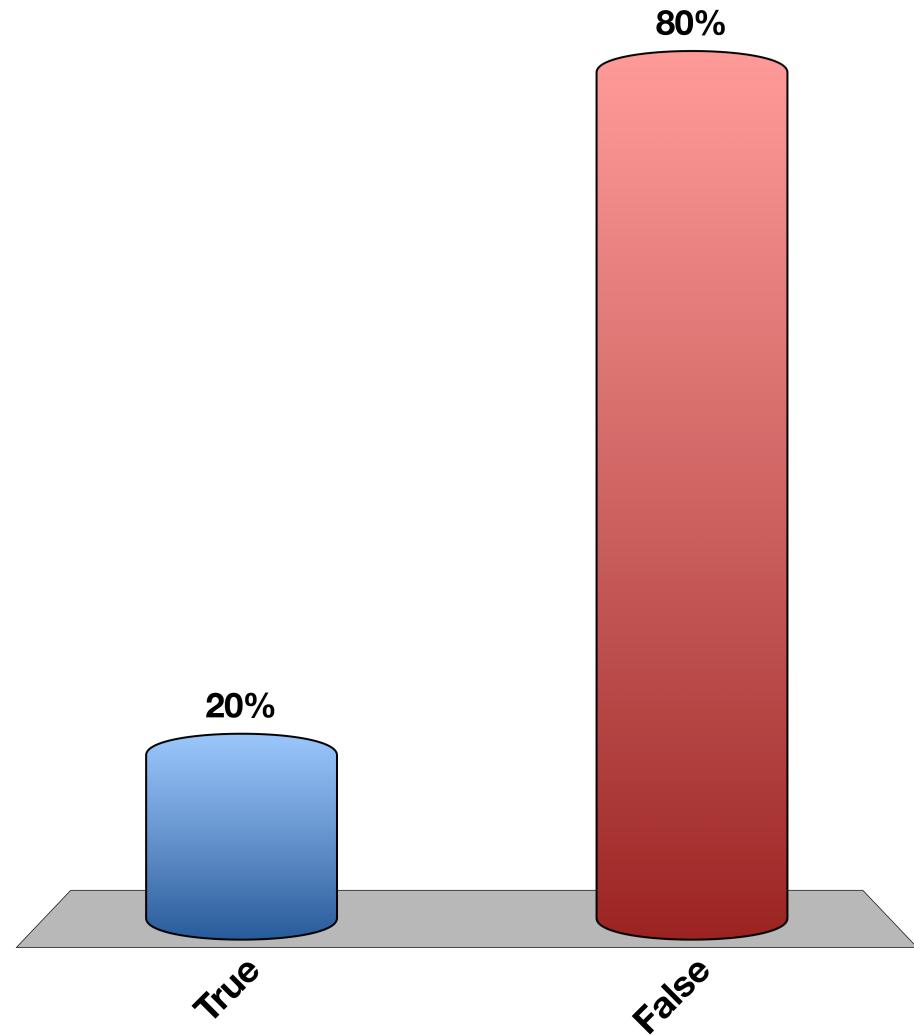


# Effects of GH/IGF1 on Metabolism

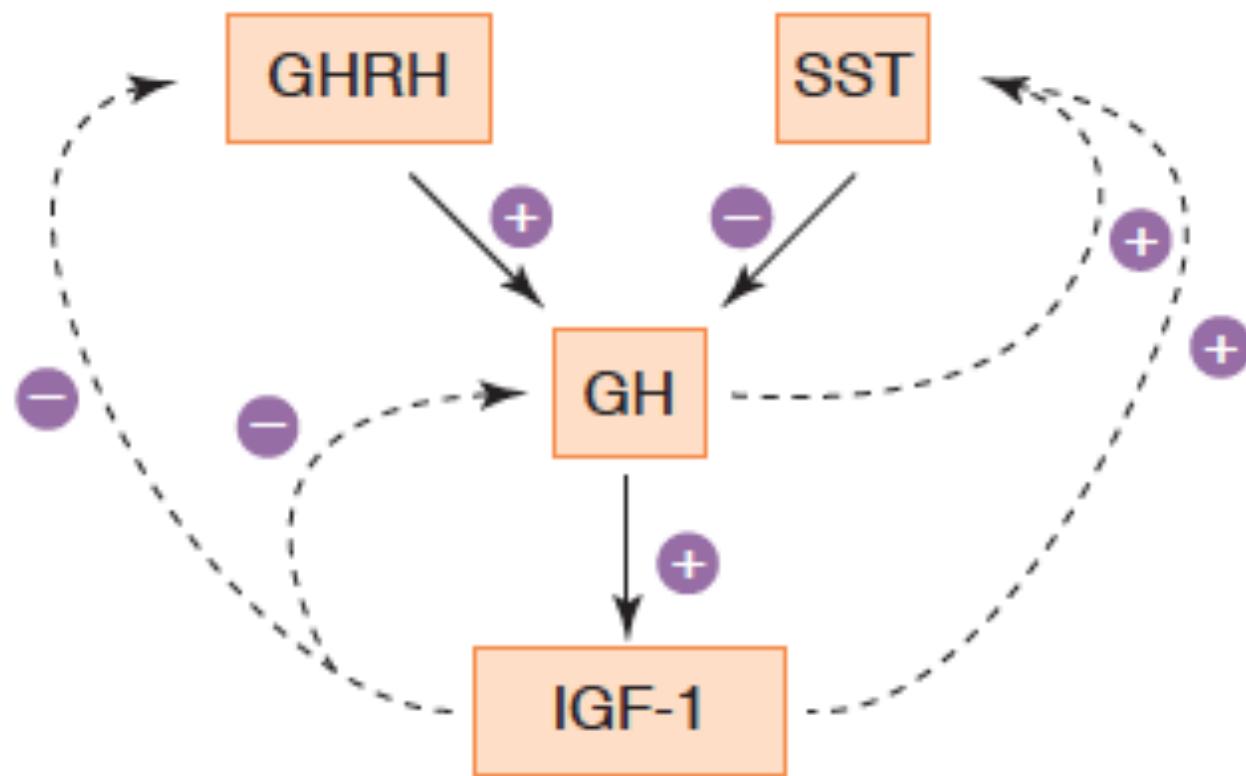


# Can you recapitulate all the effects of GH by Providing IGF-1?

- A. True
- B. False



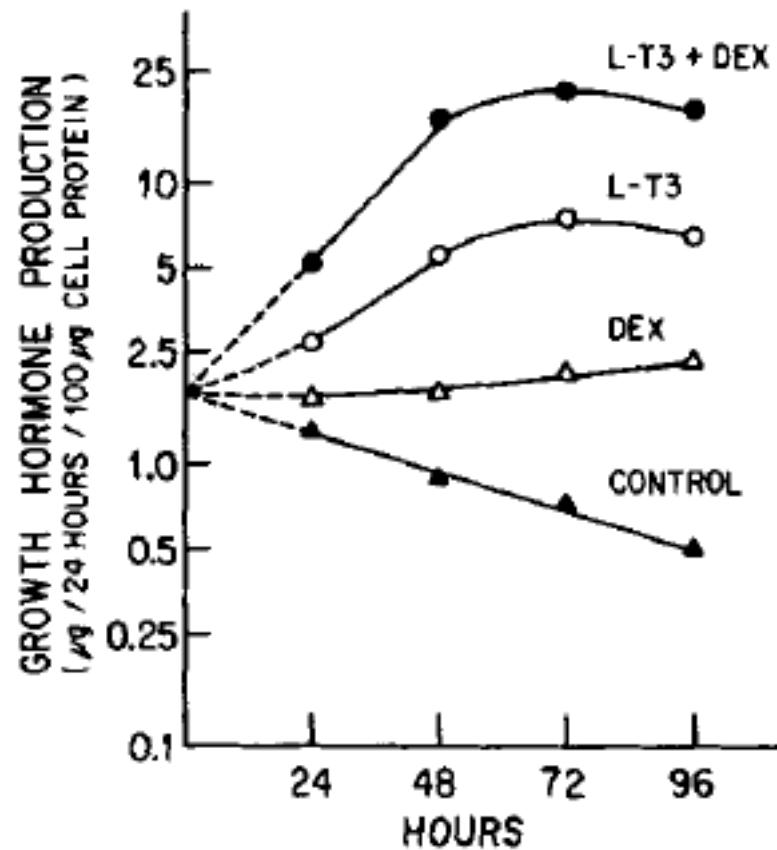
# Negative Feedback of GH



# Other Hormones Influencing Growth

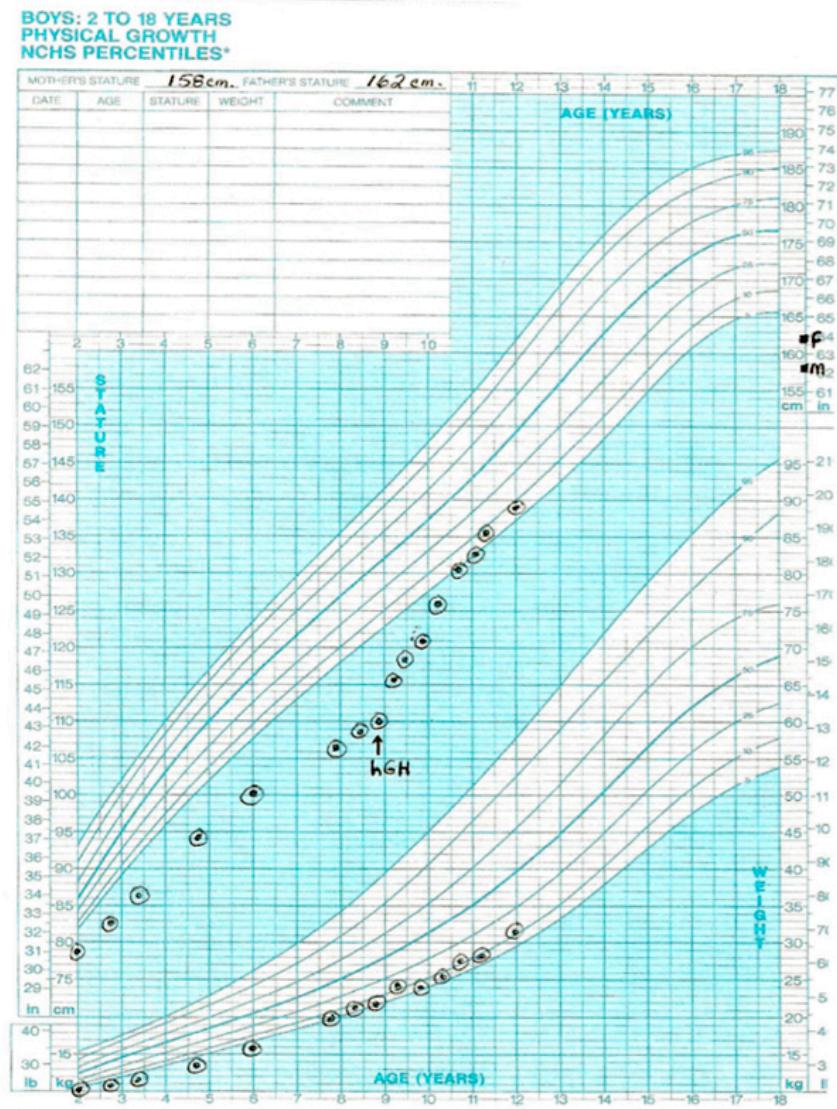
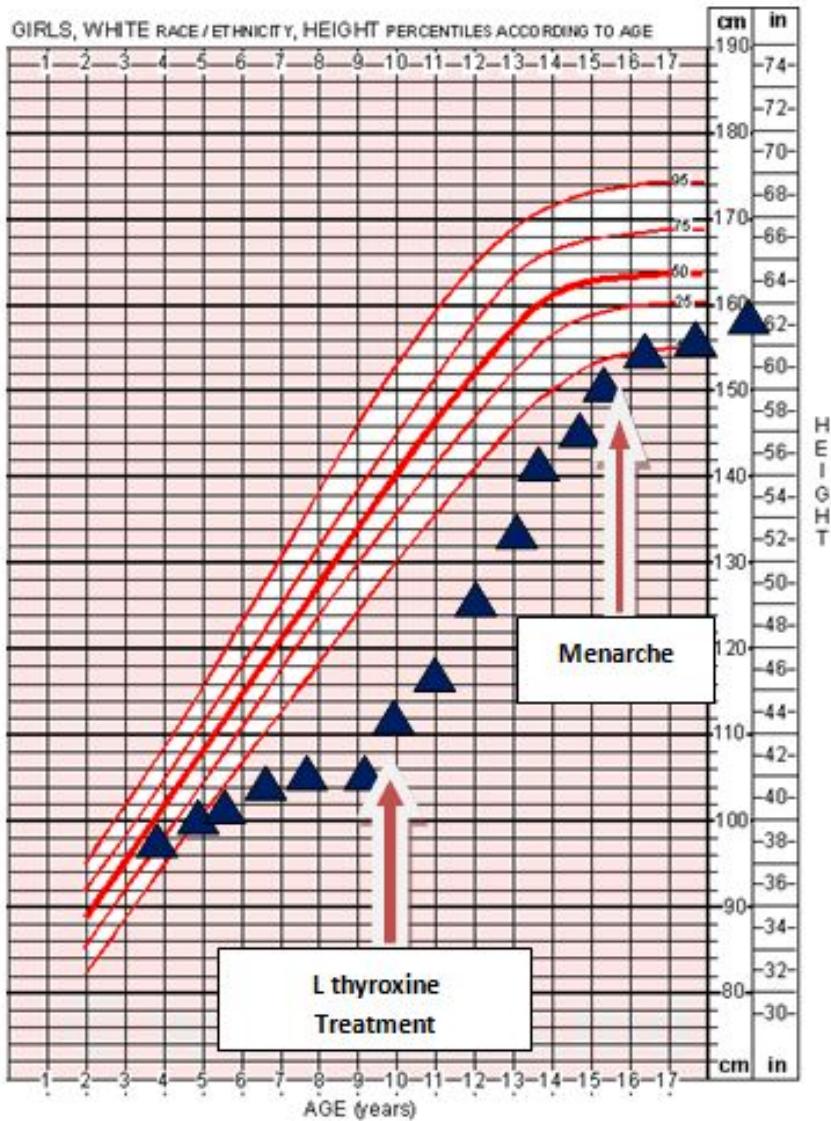
Insulin	Stimulates fetal growth Stimulates postnatal growth by stimulating secretion of IGF-1 Stimulates protein synthesis
Thyroid hormone	Permissive for growth hormone's secretion and actions Permissive for development of the central nervous system
Testosterone	Stimulates growth at puberty, in large 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.