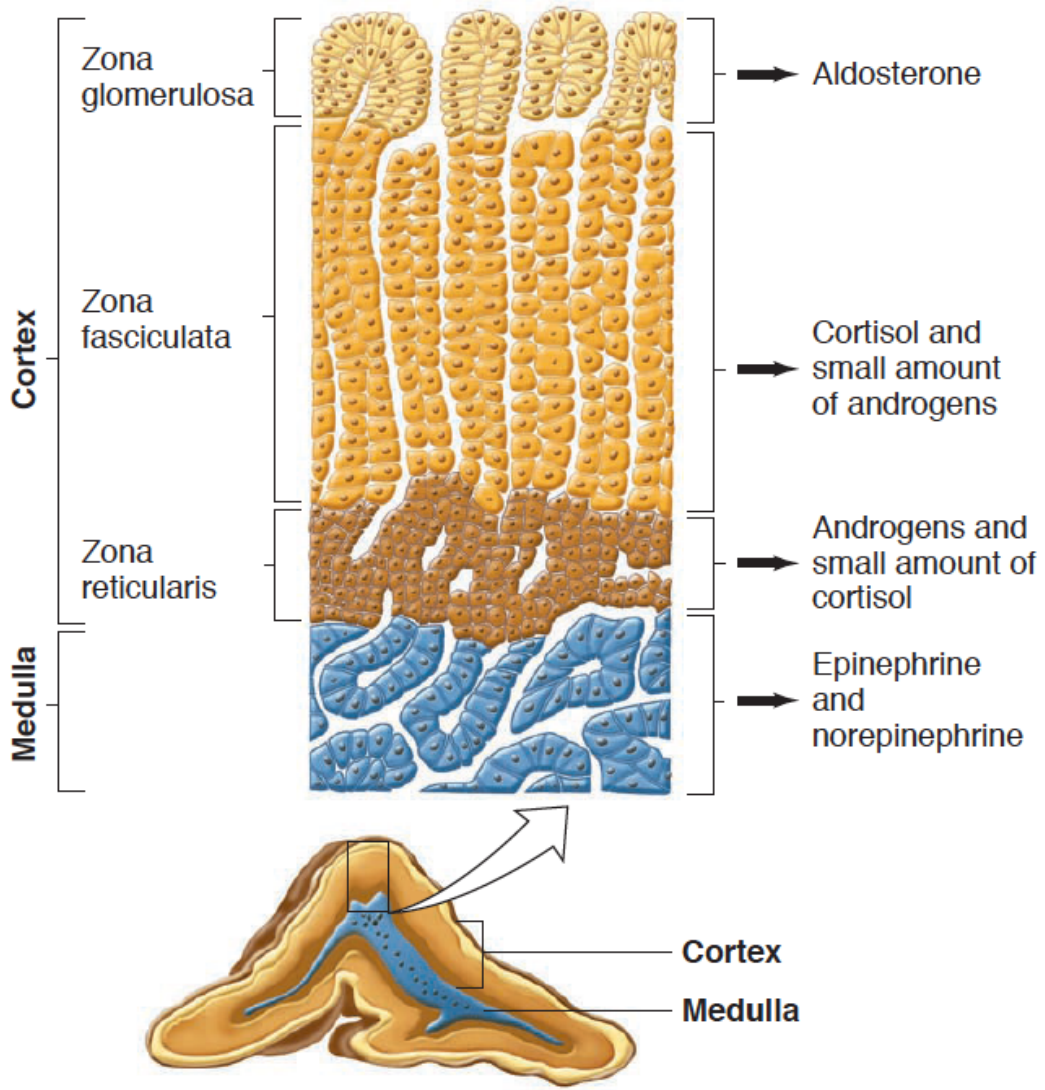
Adrenal Gland and Stress Hormones

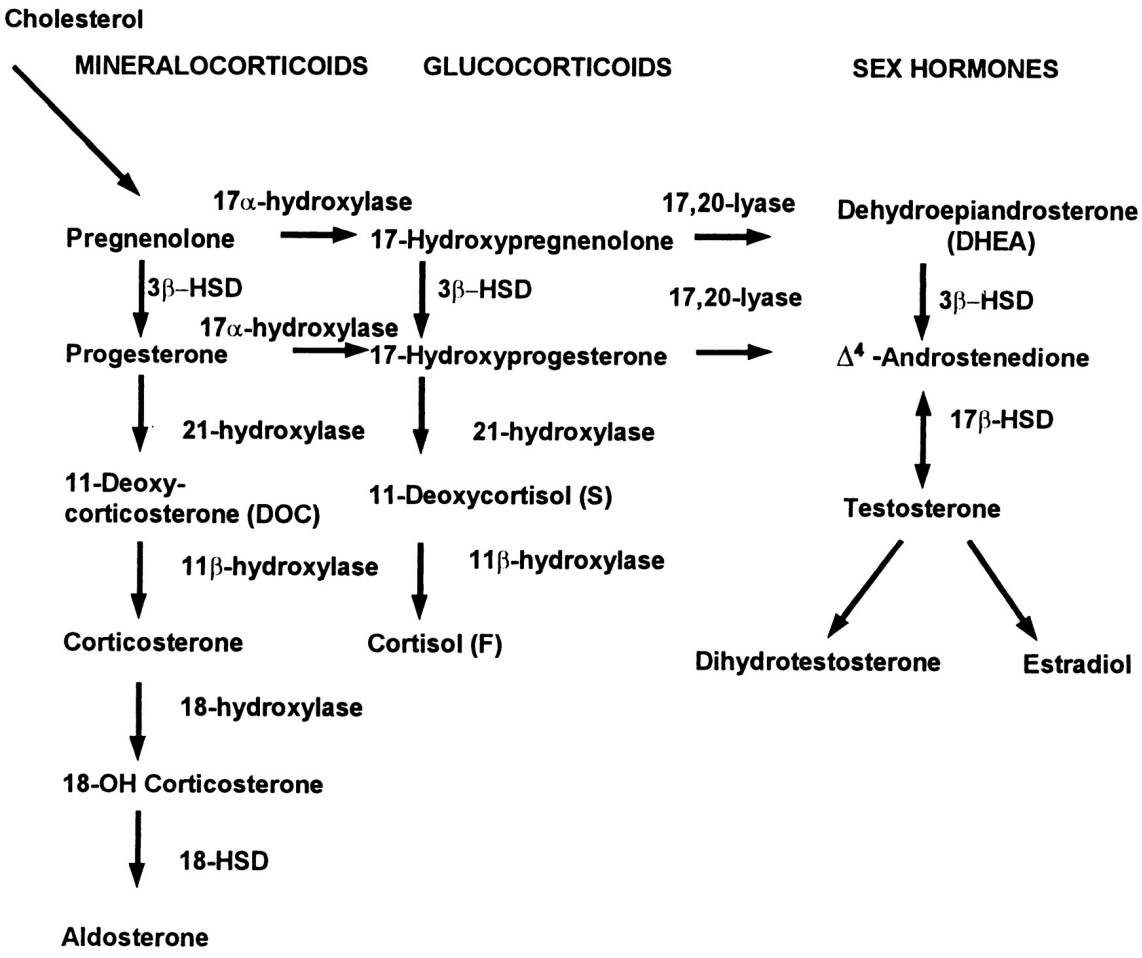
Learning Objectives

- Name three zones in the adrenal cortex and major regulator(s) of each zone.
- Name three steroidogenesis pathways and their major products.
- 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.
- 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

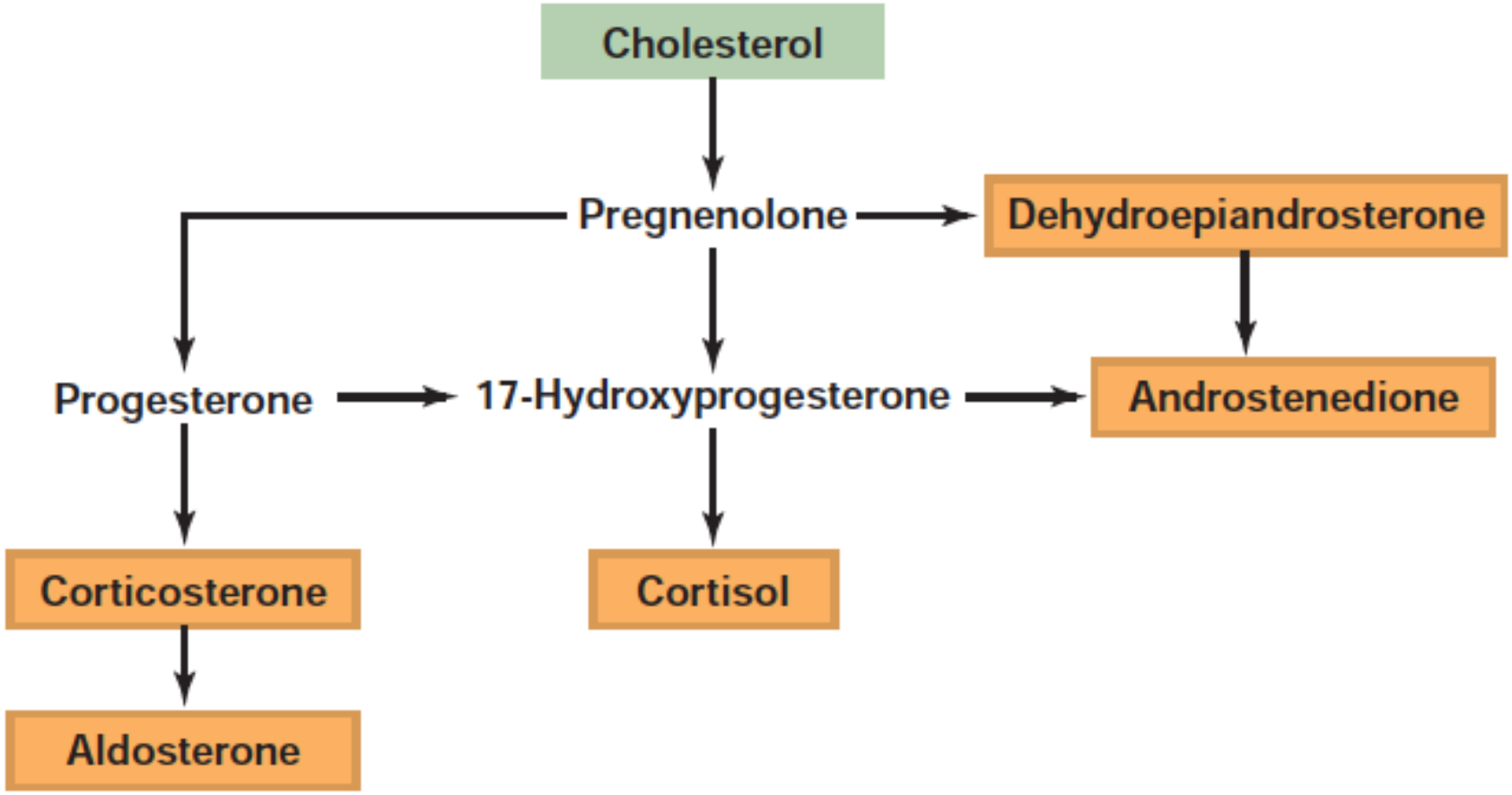


Steroid Hormone Biosynthesis

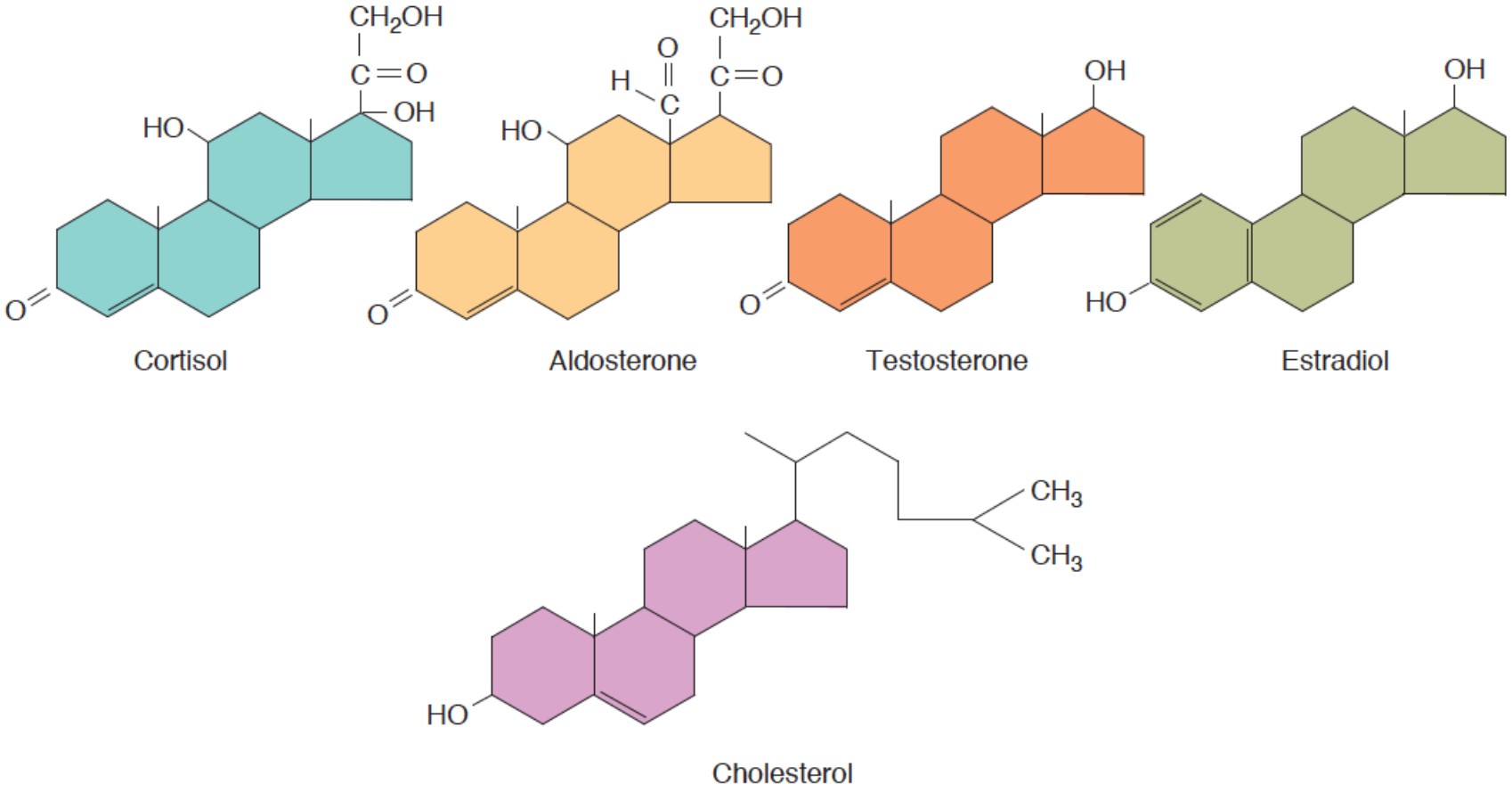


Maria I. New, and Robert C. Wilson PNAS 1999;96:12790-12797

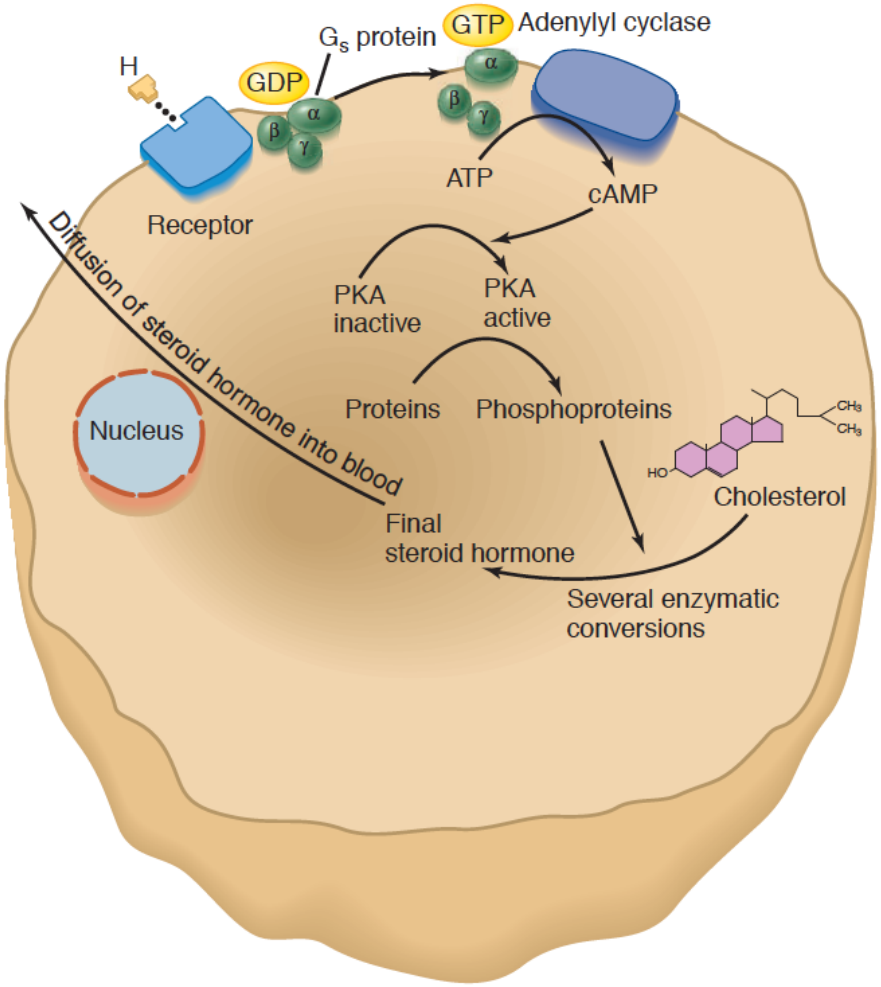
Steroid Hormone Synthesis



Steroid Hormones Released From Adrenal Medulla

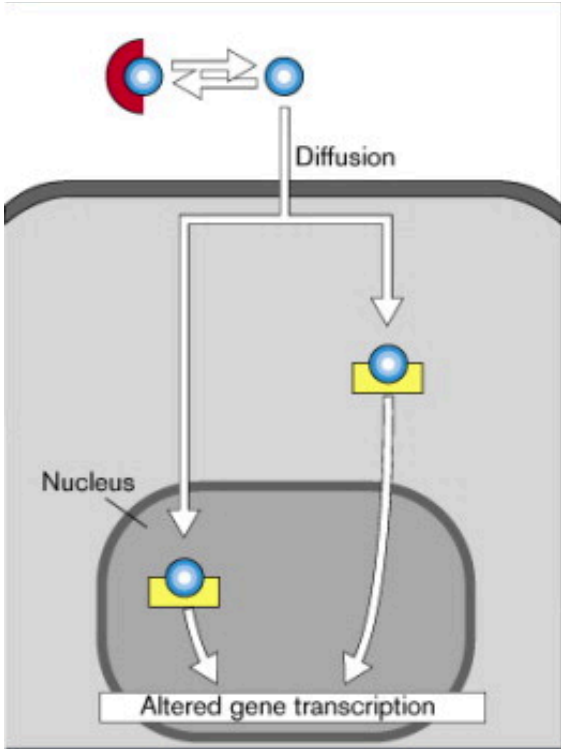


Adrenal Steroid Hormone Synthesis Mechanisms



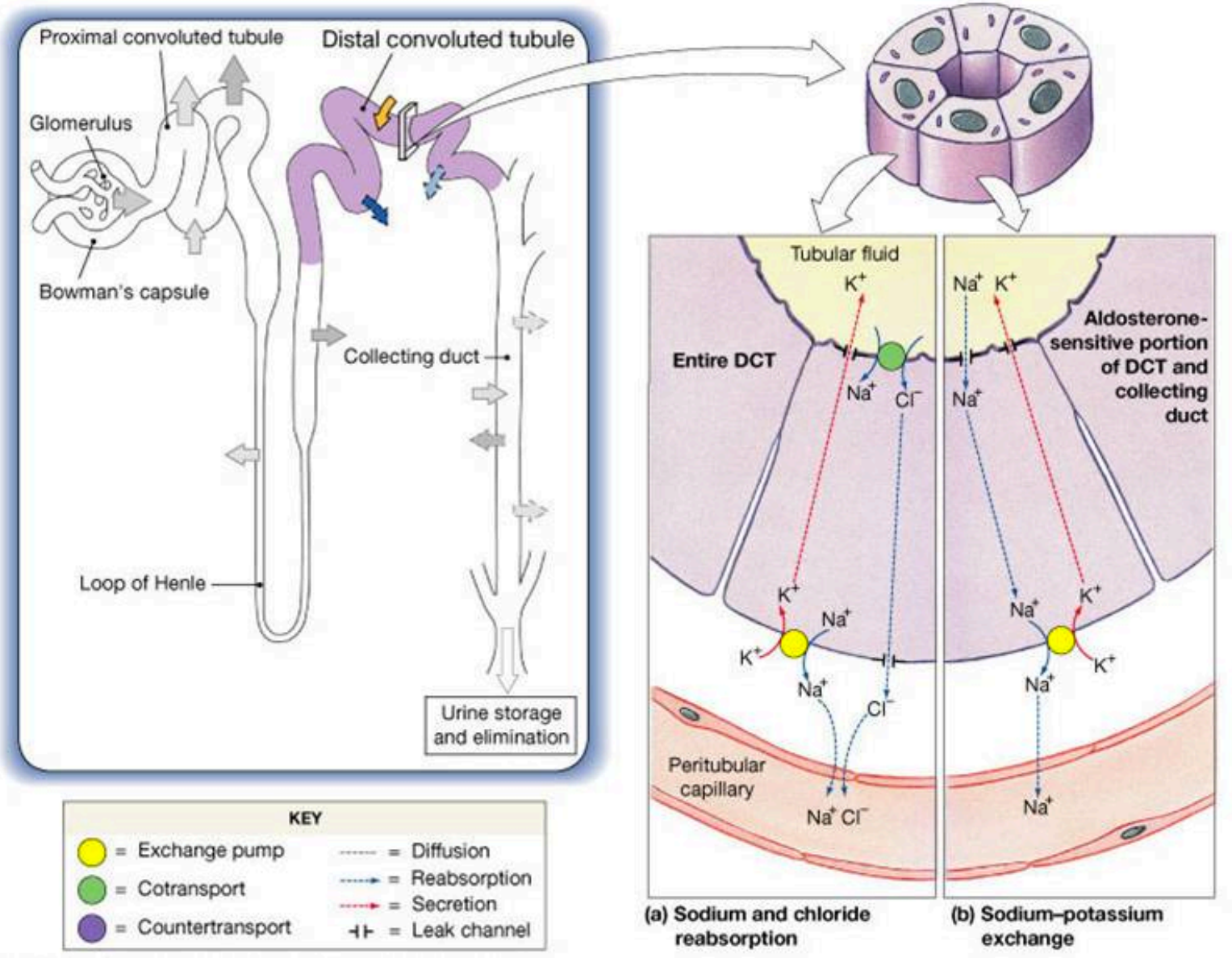
Signal	Receptor	Hormone
ACTH	MC2R (GPCR - Gs)	Cortisol
Angiotensin II	AGTR1 (GPCR – Gq)	Aldosterone

Both Aldosterone and Cortisol Function Through Nuclear Hormone Signaling



ALDOSTERONE REGULATES MINERAL BALANCE

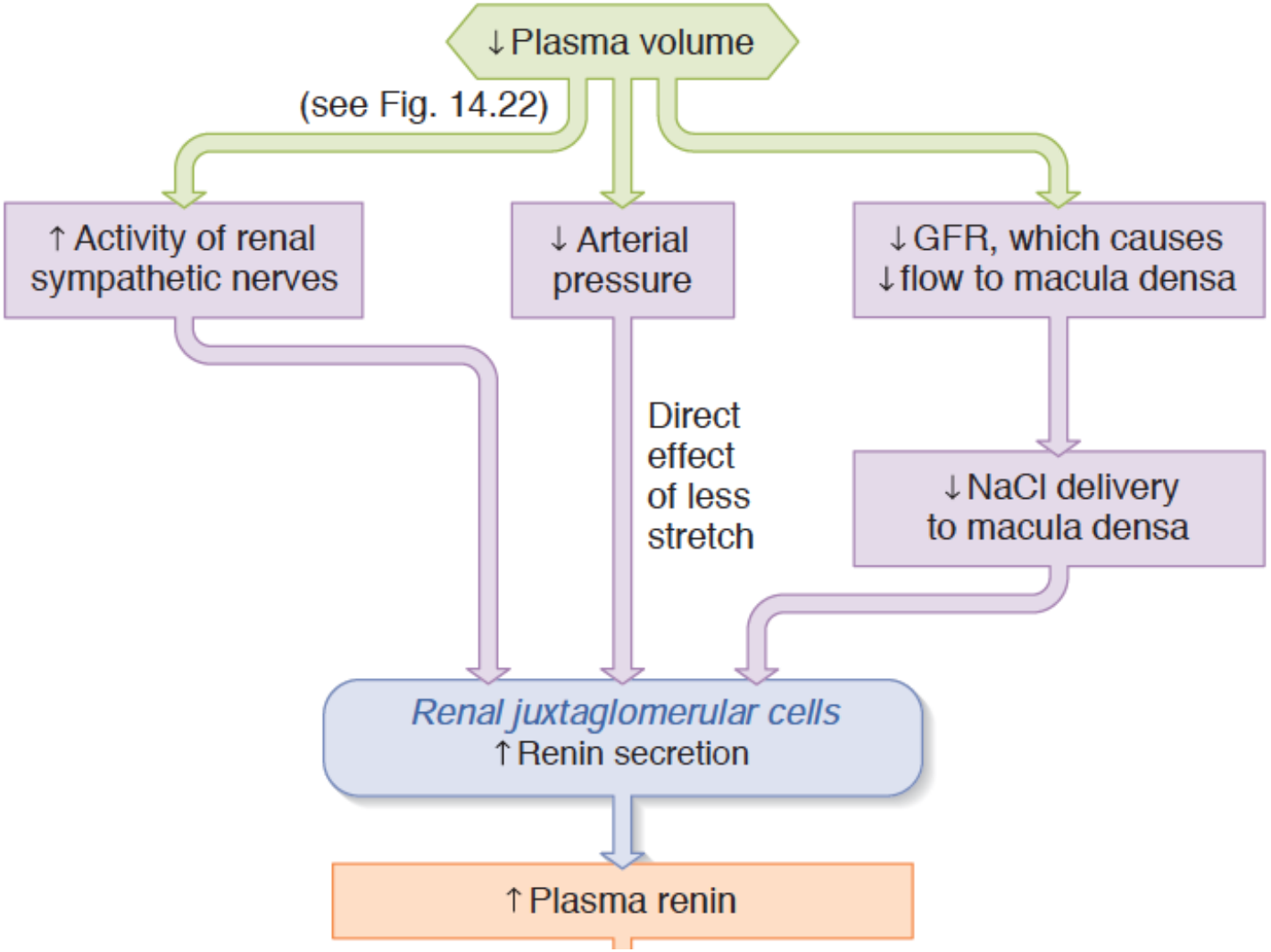
Key Aldosterone Effectors



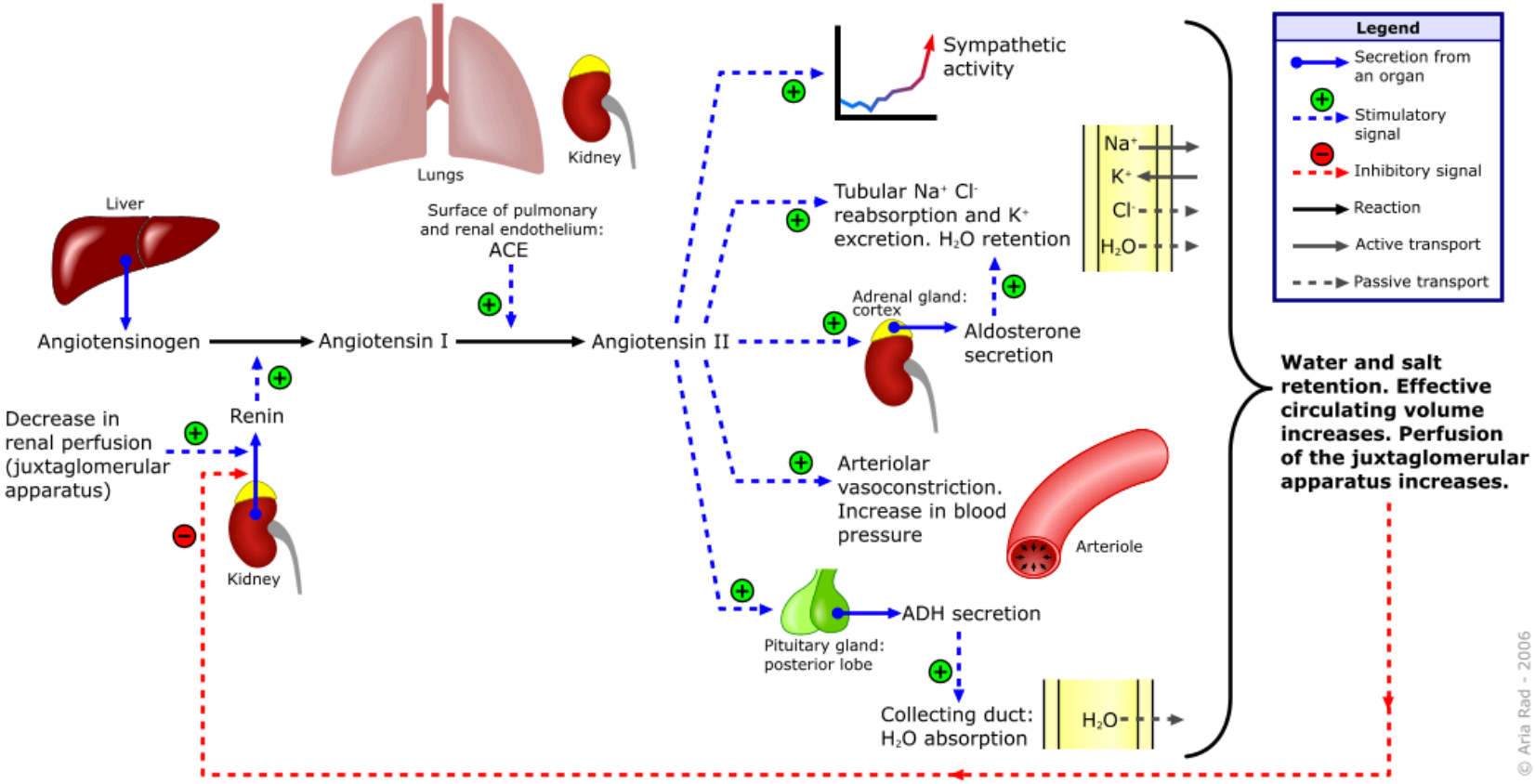
ENac

Na/K

Renin as a Volume/Pressure Sensor



The Renin/Angiotensin System

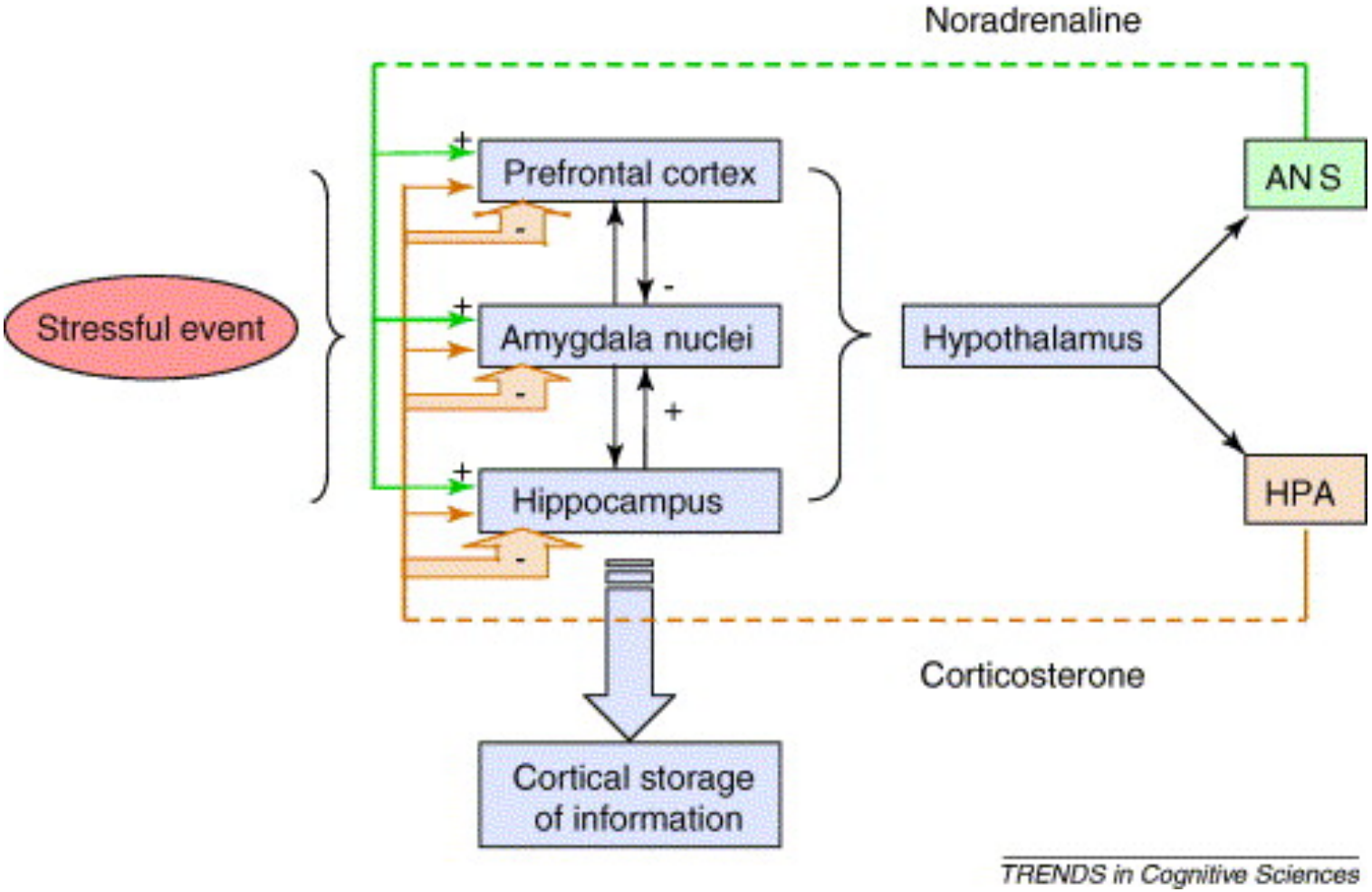


STRESS RESPONSIVE HORMONES

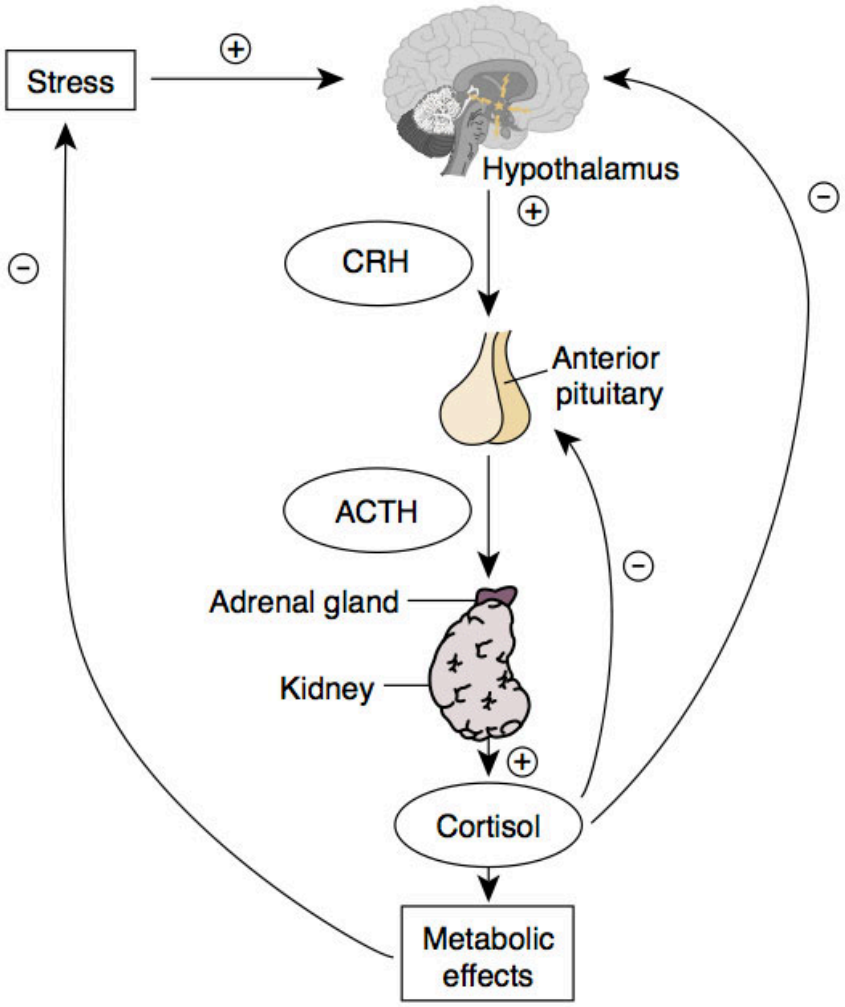
Two Types of Stress Response

- Adrenaline
- Cortisol

CRH Release

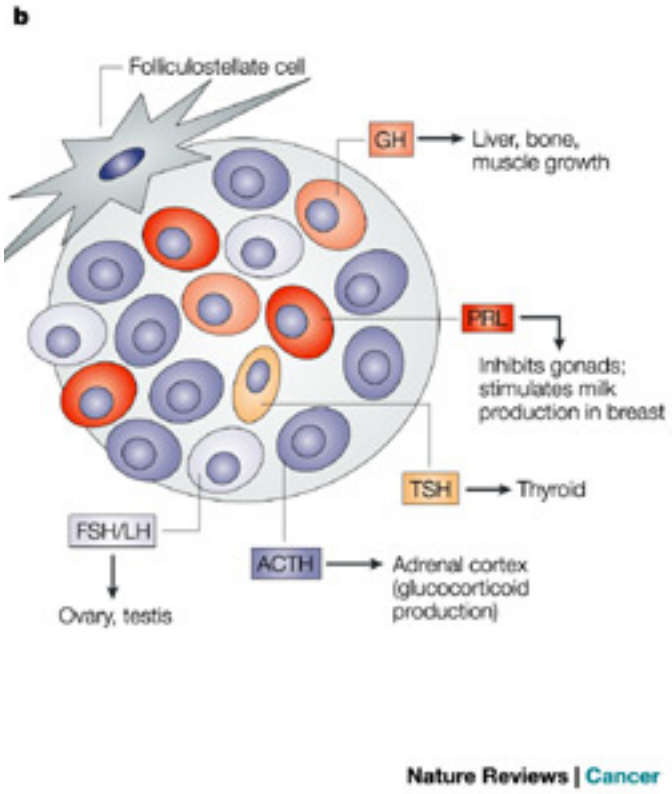

Noradrenaline
Prefrontal cortex
Amygdala nuclei
Hippocampus
Stressful event
Hypothalamus
ANS
HPA
Corticosterone
Cortical storage of information
TRENDS in Cognitive Sciences

HPA Axis


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

Anterior Pituitary

Hypothalamic	Anterior Pituitary	Cells
CRH	ACTH	Corticotropes
TRH	TSH/Prolactin	Thyrotropes/ Lactotropes
GnRH	LH/FSH	Gonadotropes
GHRH	GH (increase)	Somatotropes
Somatostatin	GH (decrease)	Somatotropes



Asa SL, Ezzat S (2009) The pathogenesis of pituitary tumors. Annu Rev Pathol 4: 97–126. doi:10.1146/annurev.pathol.4.110807.092259.

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

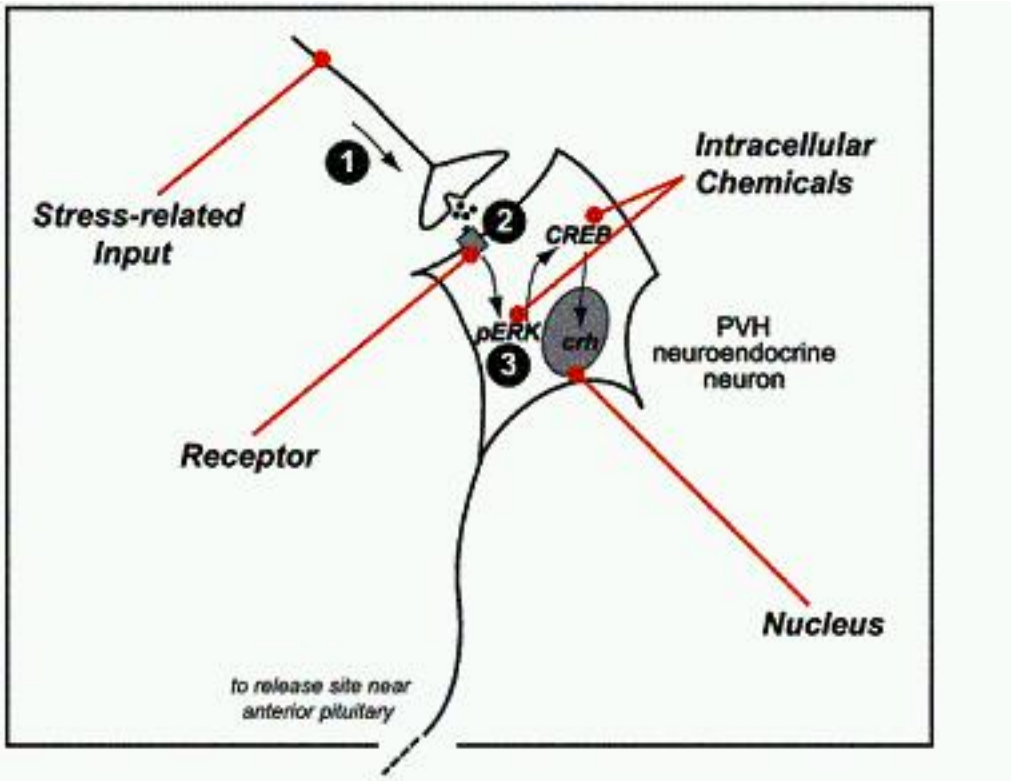
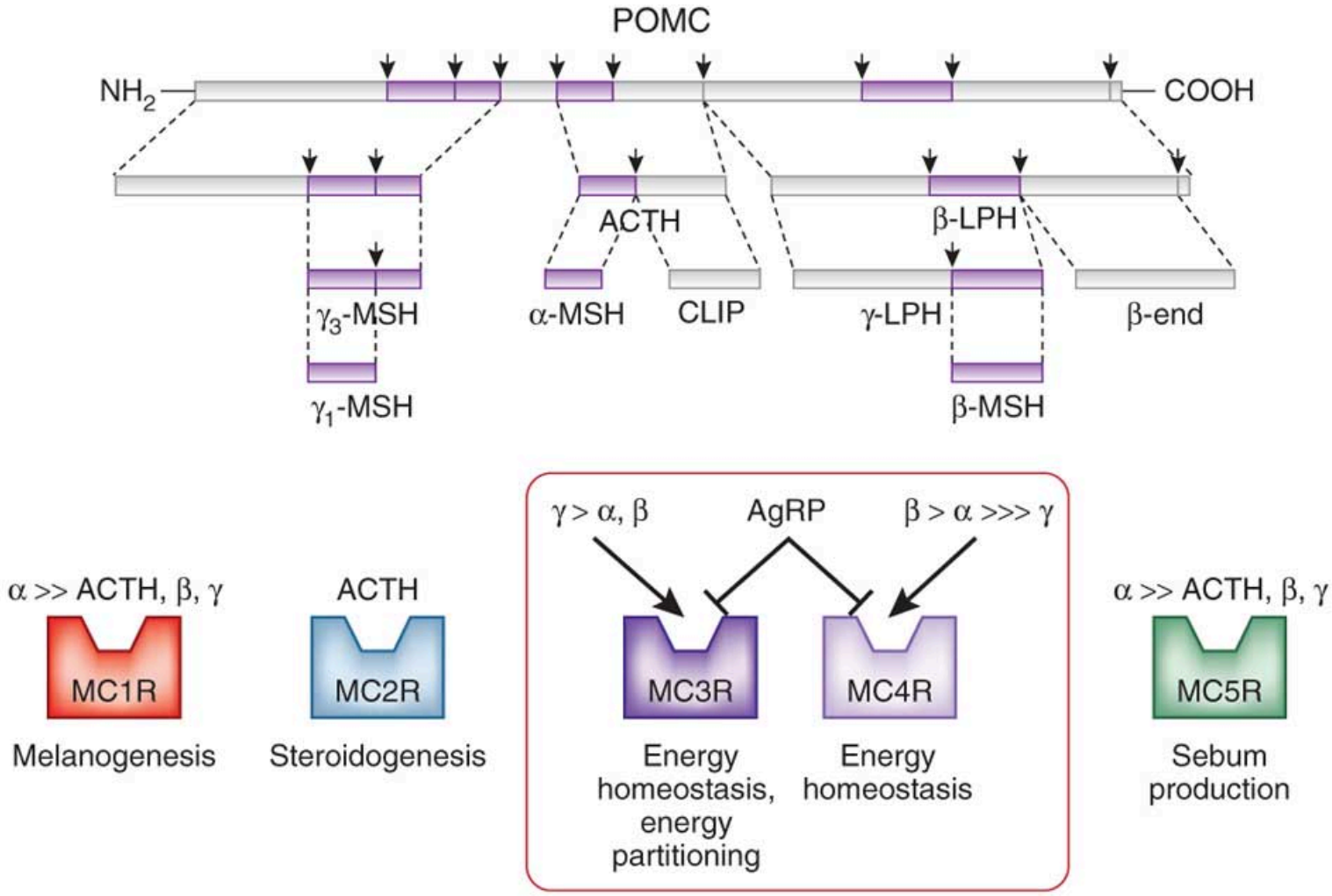
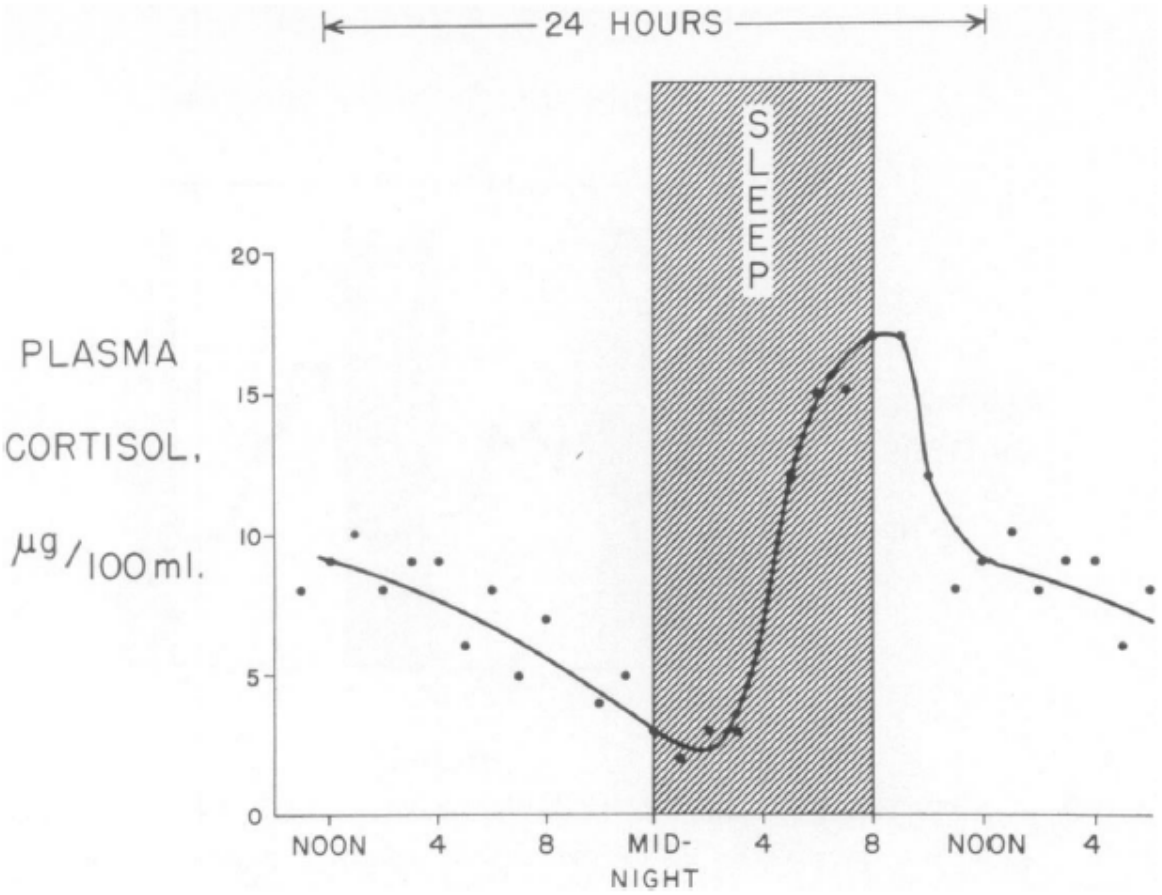


Figure 1. Activation of the CRH gene in the nucleus of a CRH neuroendocrine neuron in response to stress.

ACTH and other Hormones are Generated from POMC Transcripts

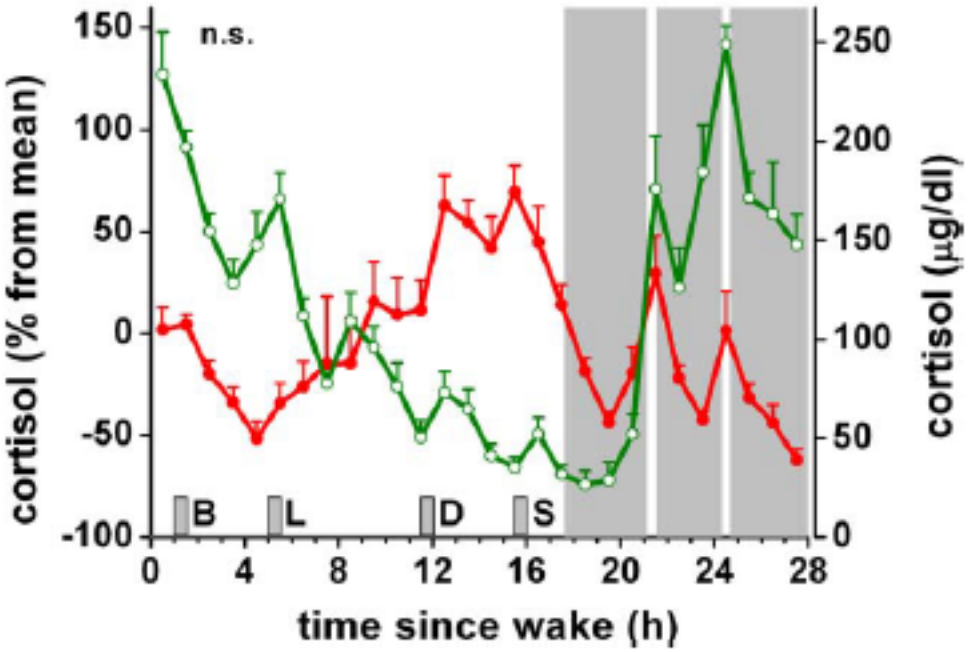


Daily Rhythms of Cortisol Release



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

Night Time Workers



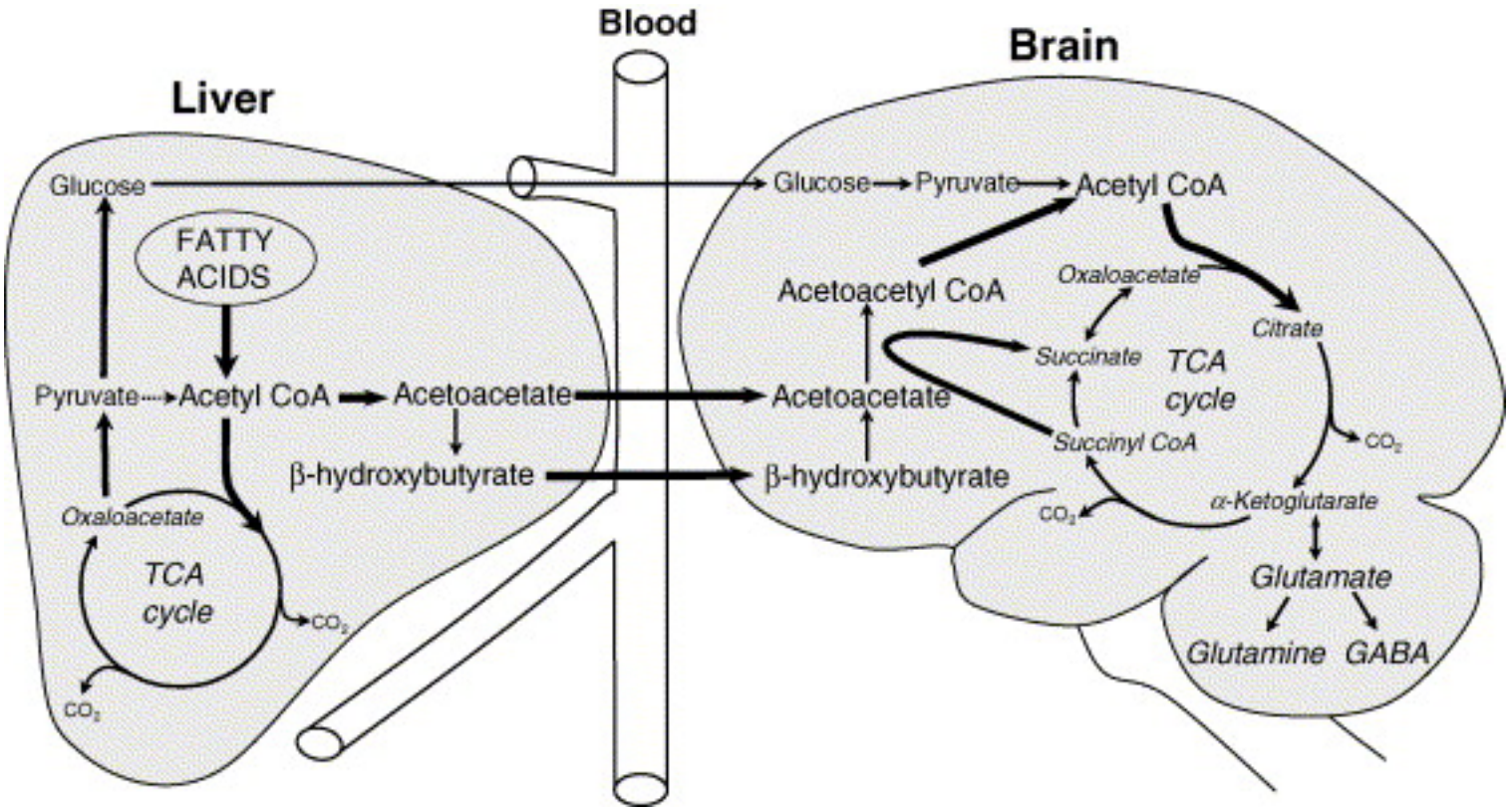
Normal
Sleep disrupted

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.

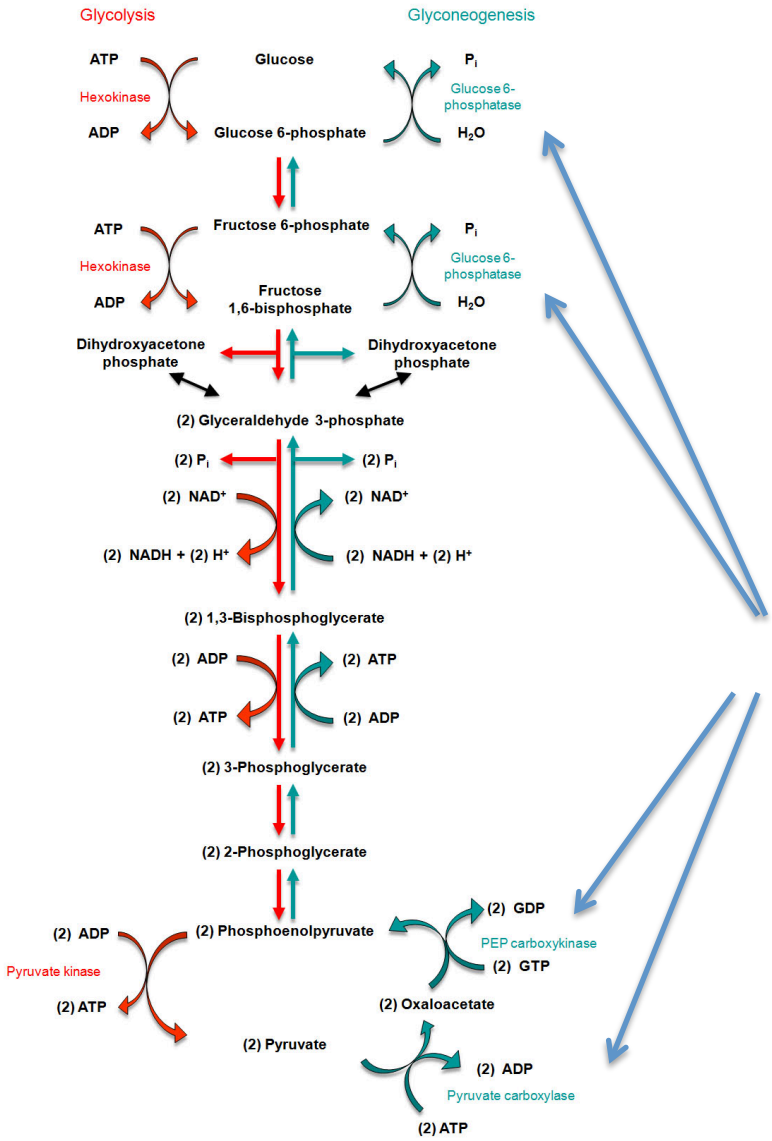
Major Chronic Responses to Stress

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

Brain Requires Glucose Supply

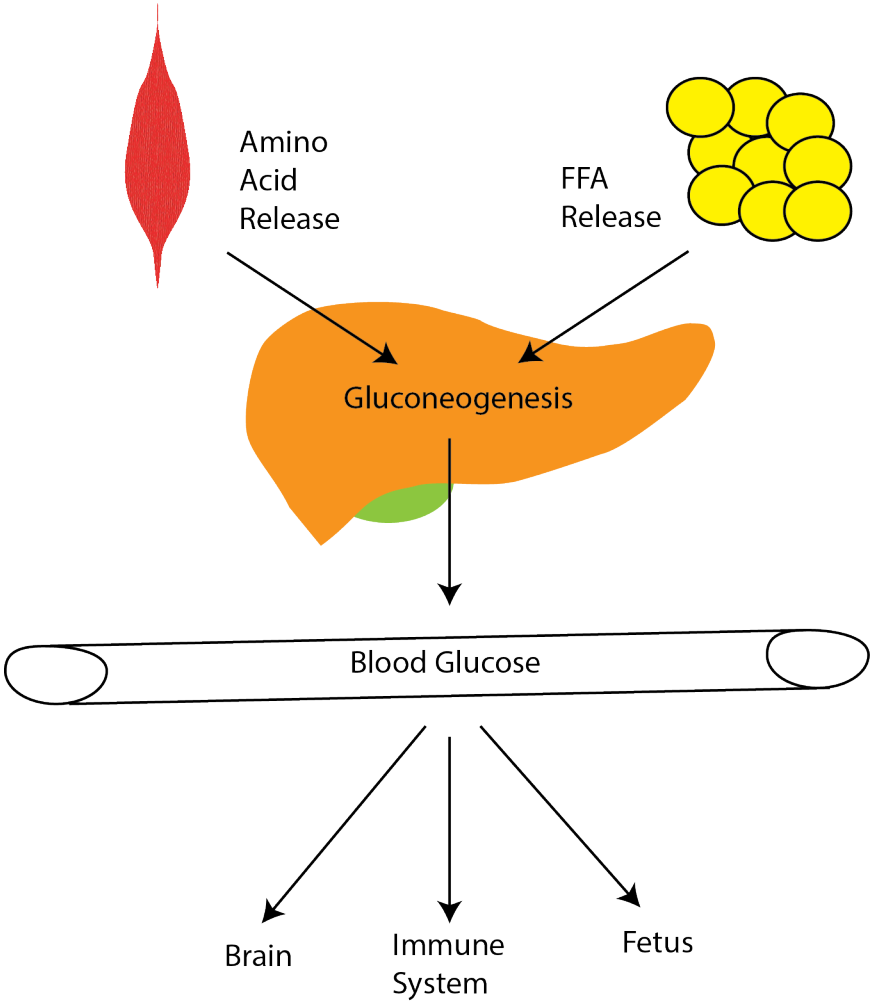


Regulation of Gluconeogenesis



Activation of mRNA transcription by glucocorticoids in the liver

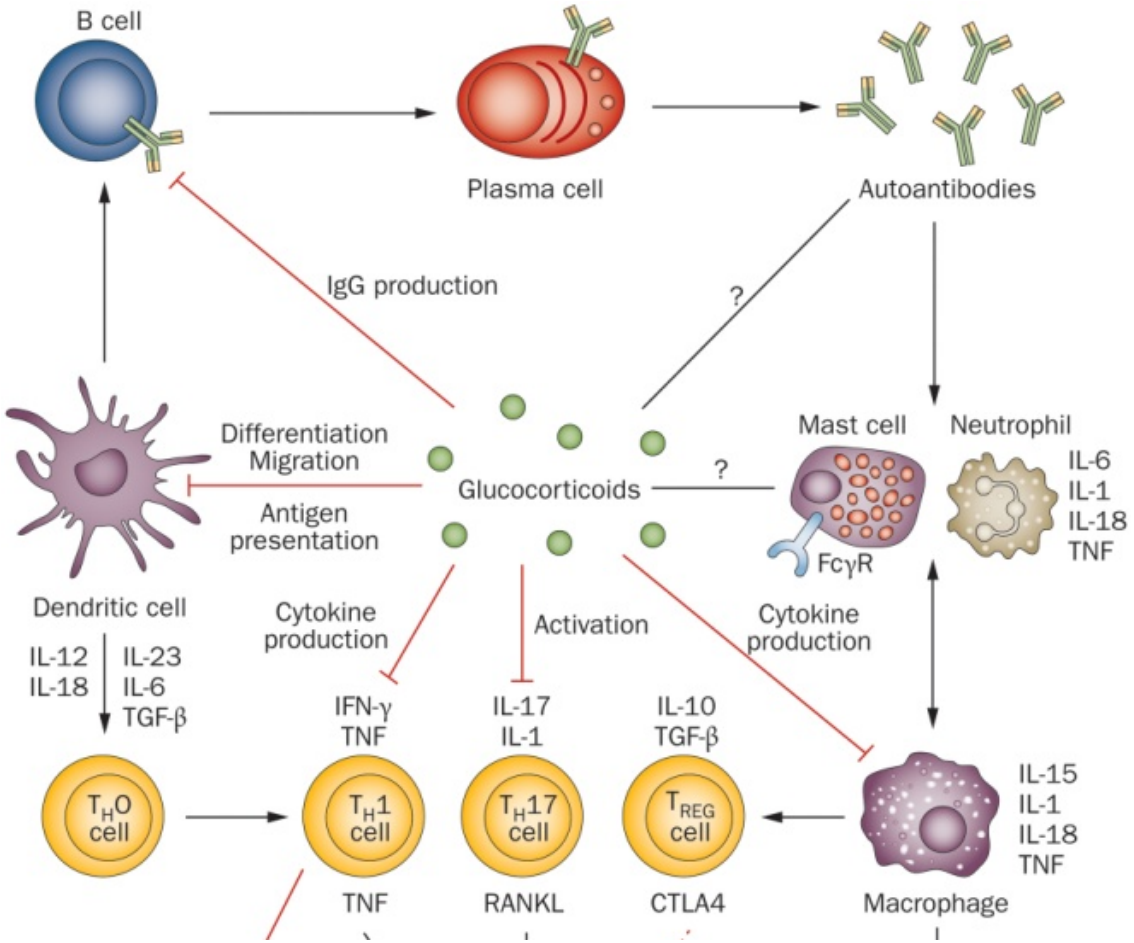
Cortisol Maintains Blood Glucose Levels



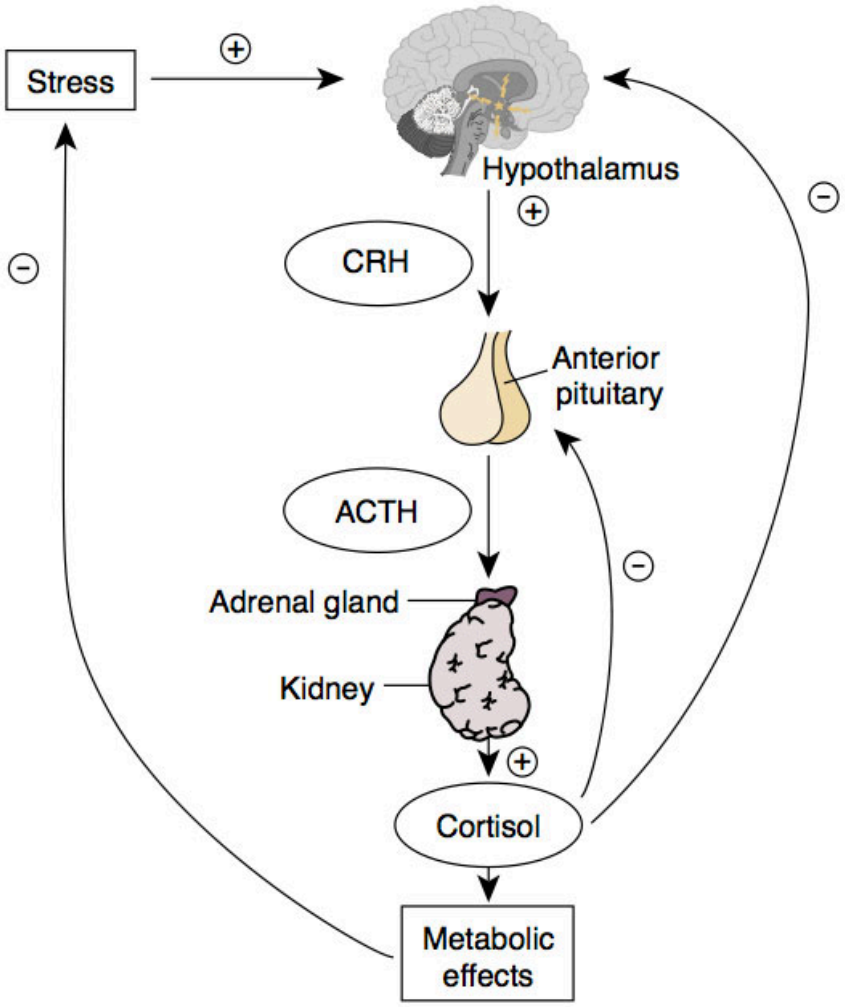
Three Mechanisms to Maintain Blood Glucose Levels

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

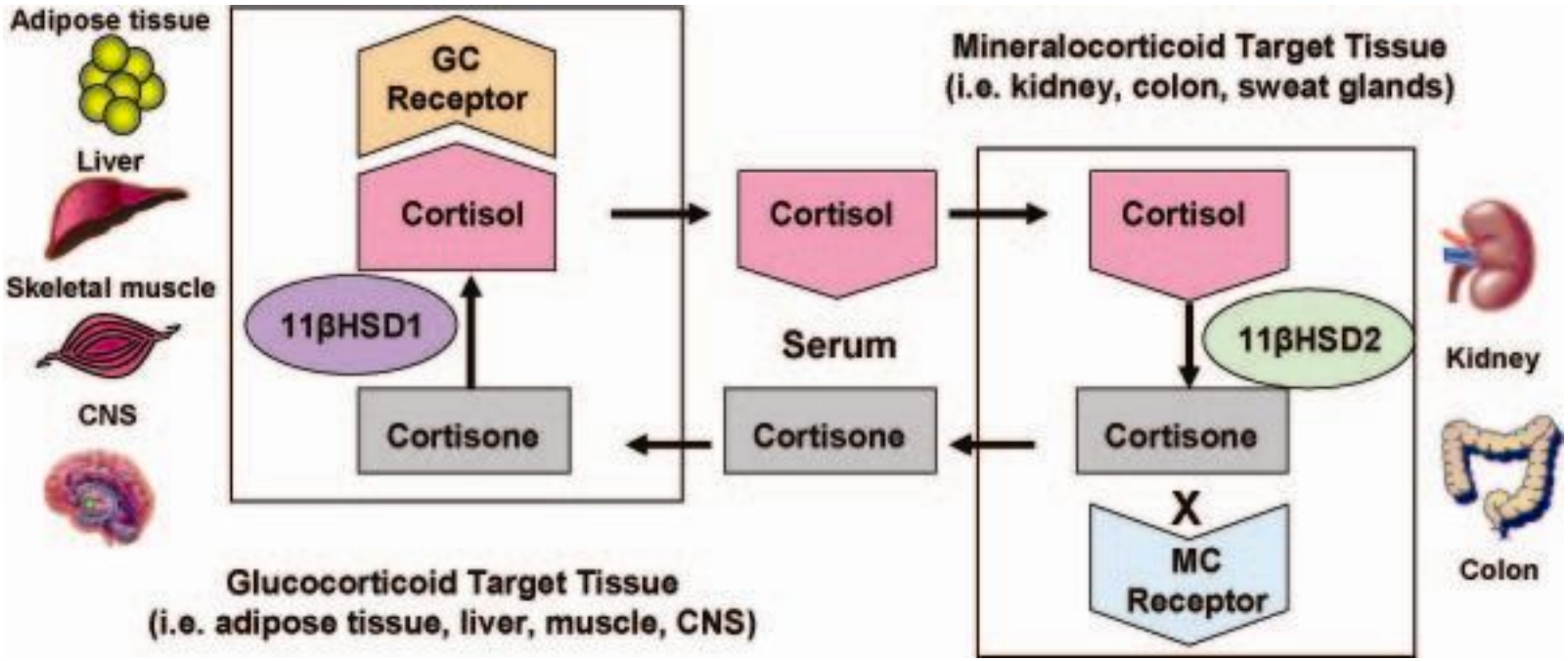
Effects of Cortisol on Immune Function



HPA Axis


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

11β-HSD 2 and Local Concentrations of Glucocorticoids



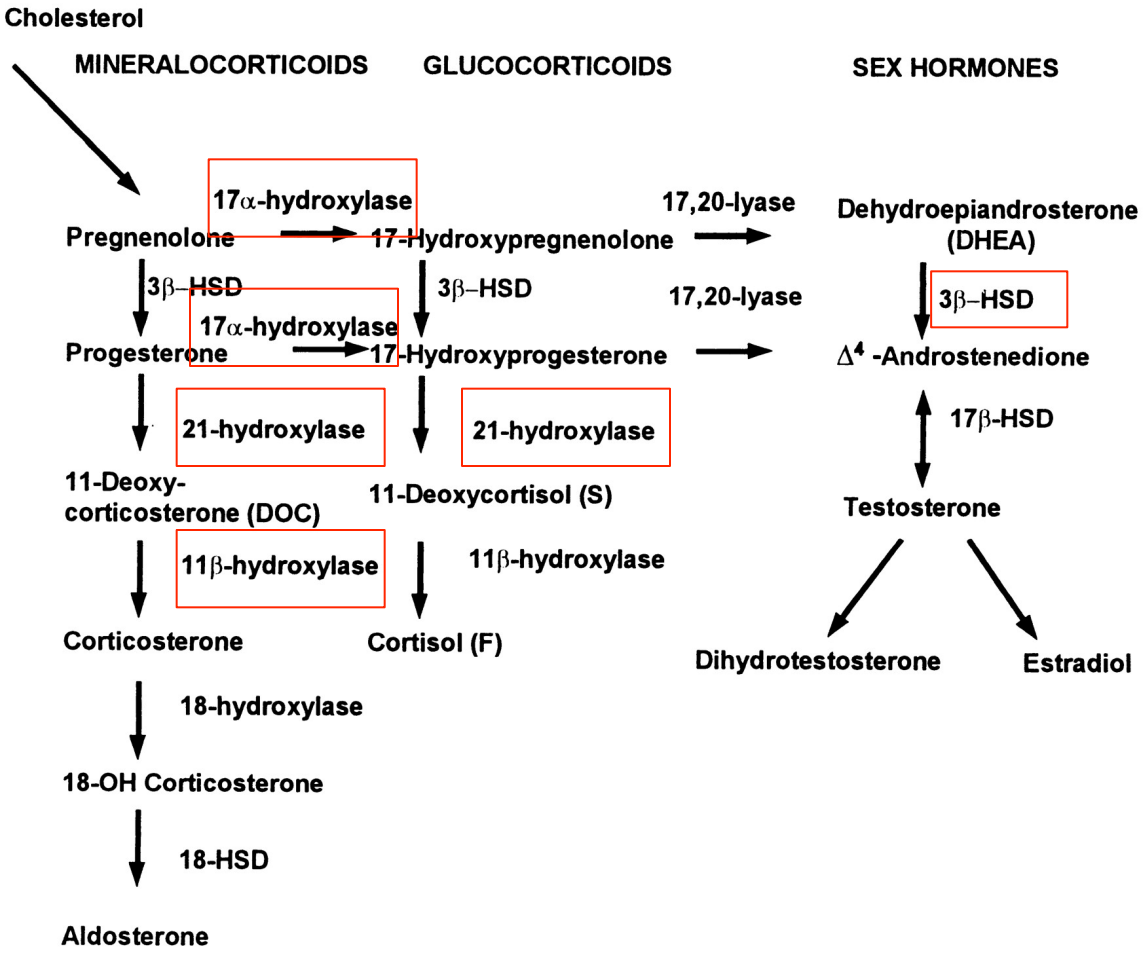
In off target tissues,
or to desensitize normal tissues

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

Cushing's Syndrome (ACTH overproducing tumors) have

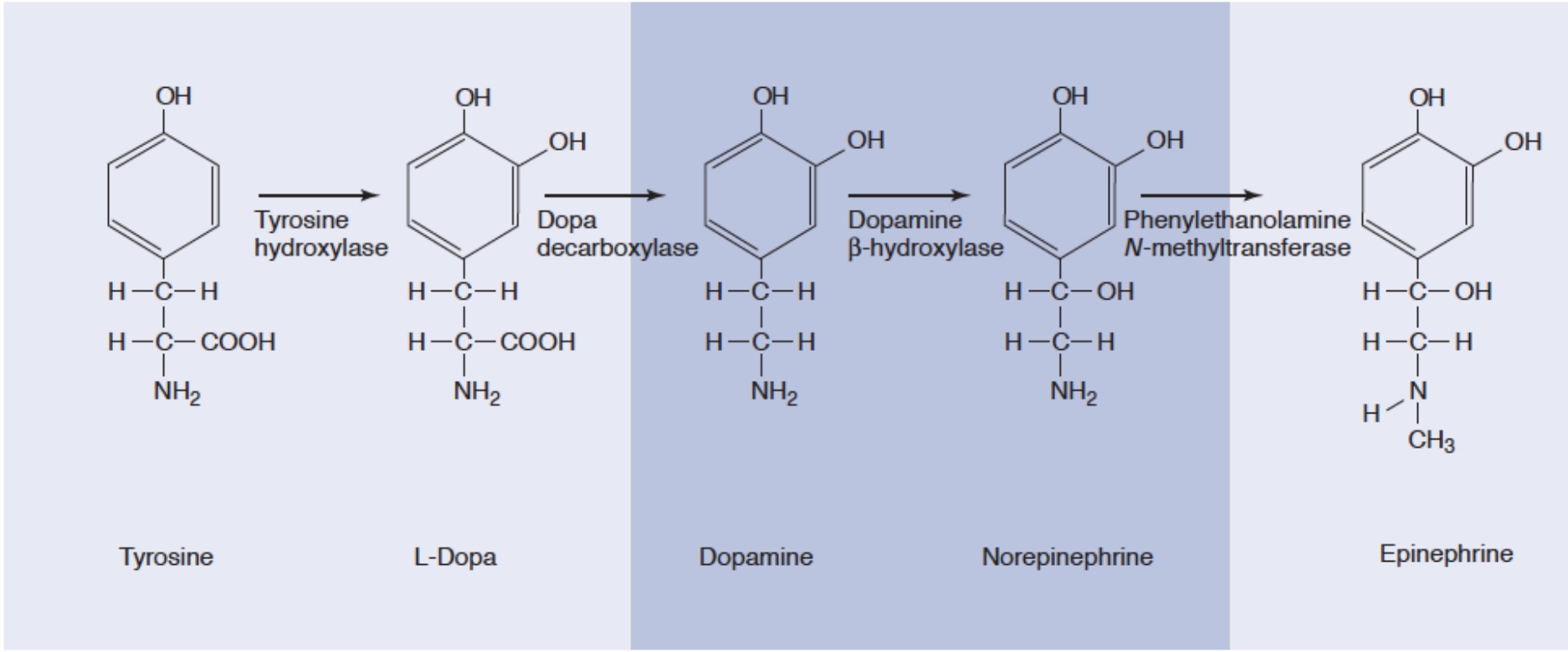
A. Elevated CRH
B. Lowered CRH
C. Lowered Cortisol
D. Lowered Aldosterone

ADRENALINE MEDIATES SHORT-TERM STRESS RESPONSES

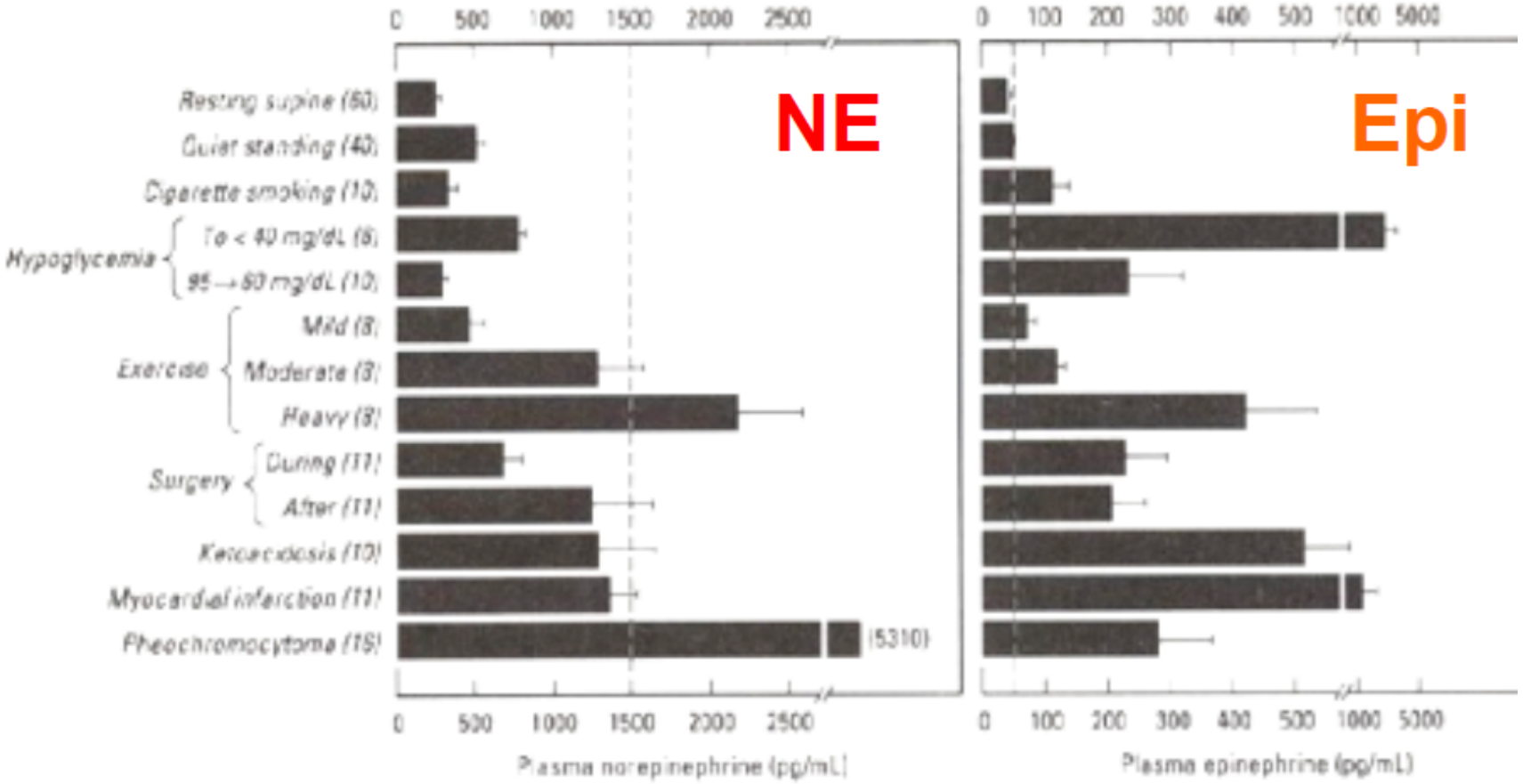
Epinephrine Summary

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

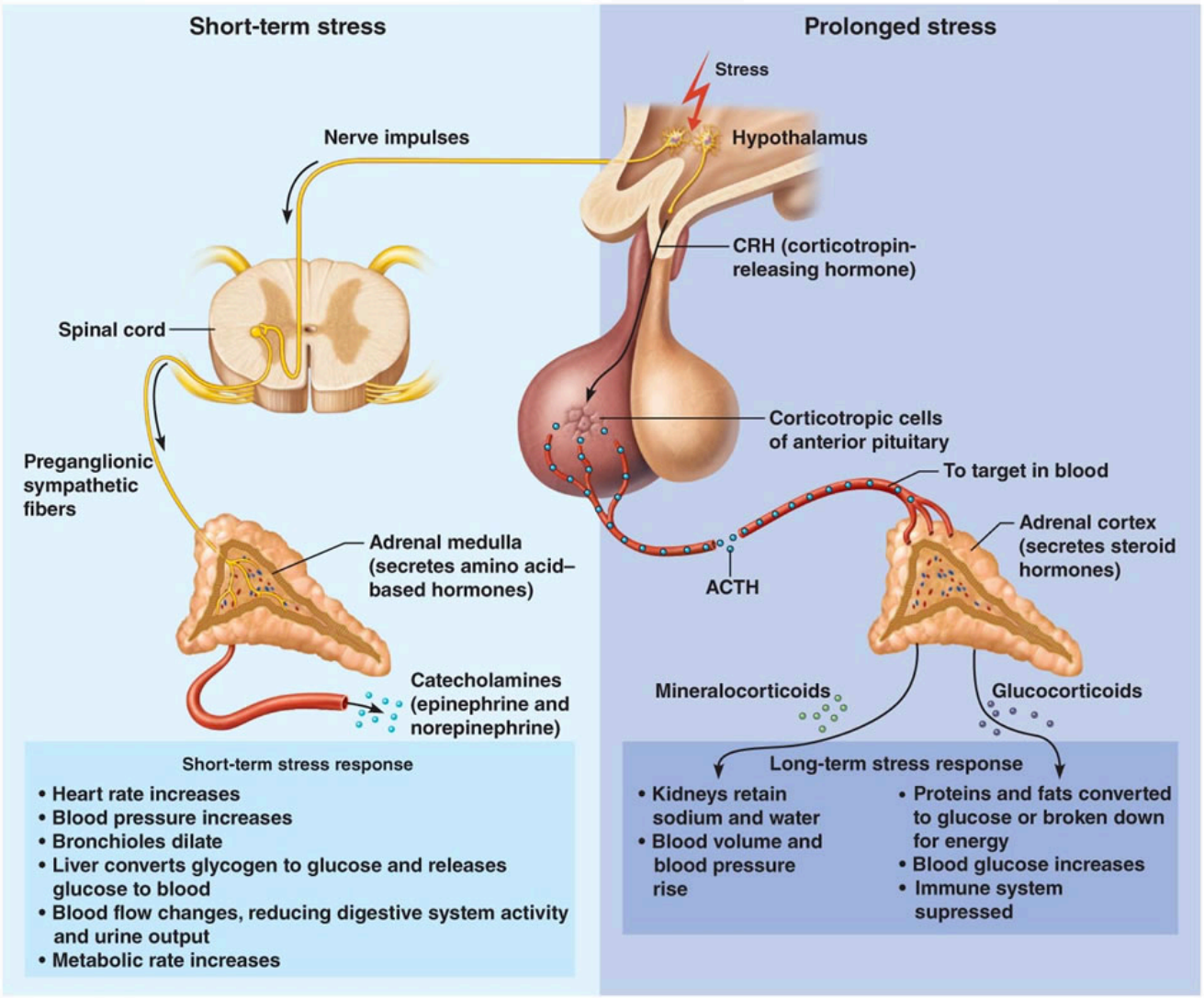


Epinephrine vs Norepinephrine

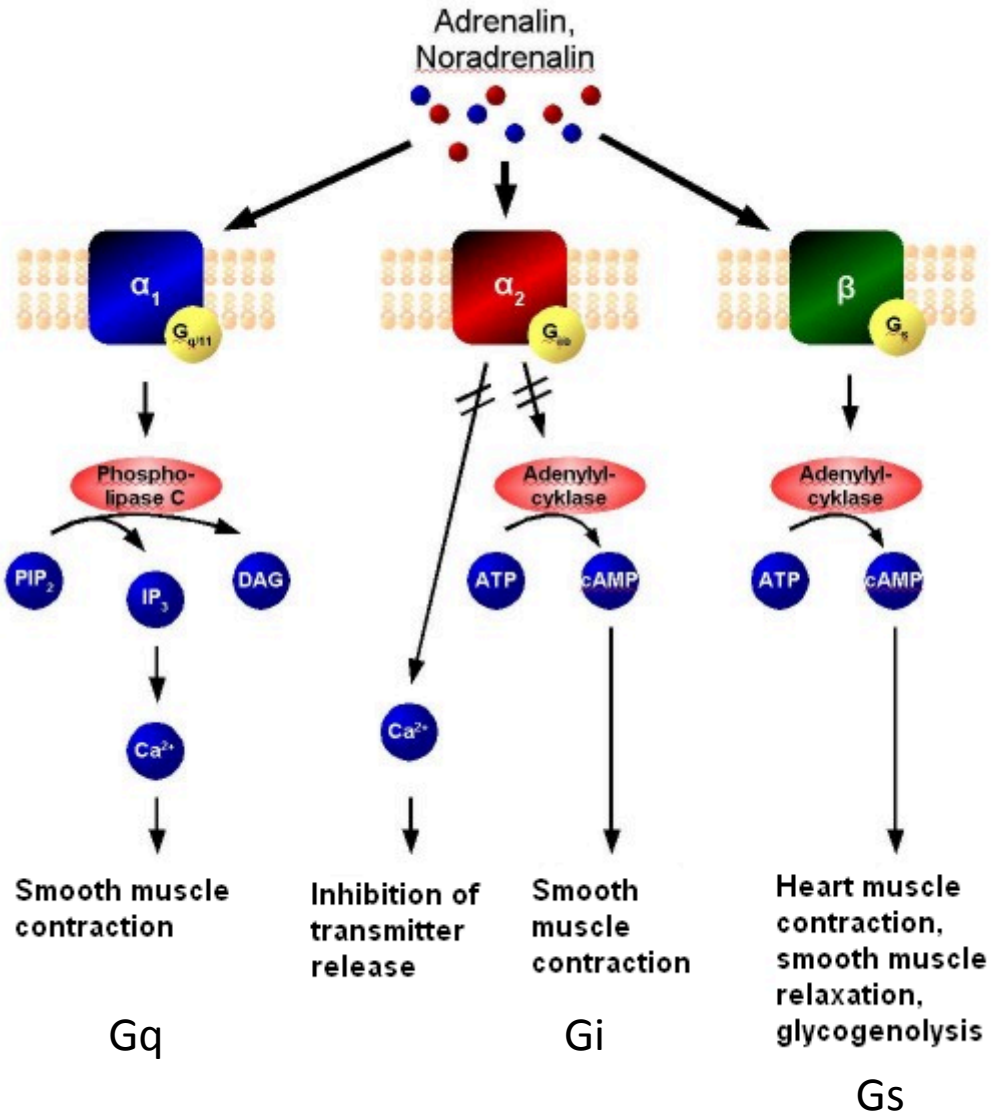


Dashed line is level in circulation needed to elicit a physiological response

Adrenaline vs Cortisol Release



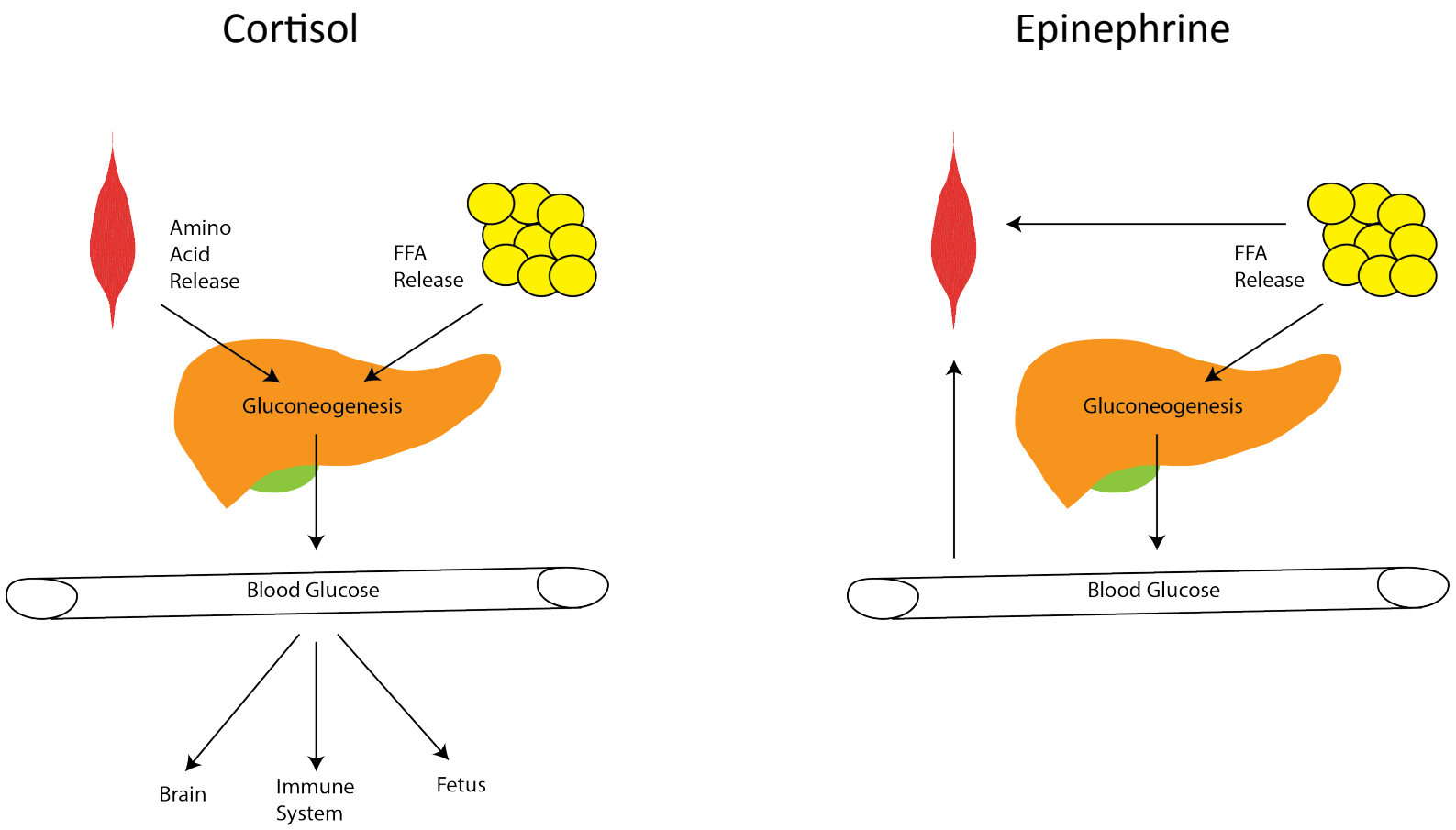
Cardiovascular Roles of Epinephrine



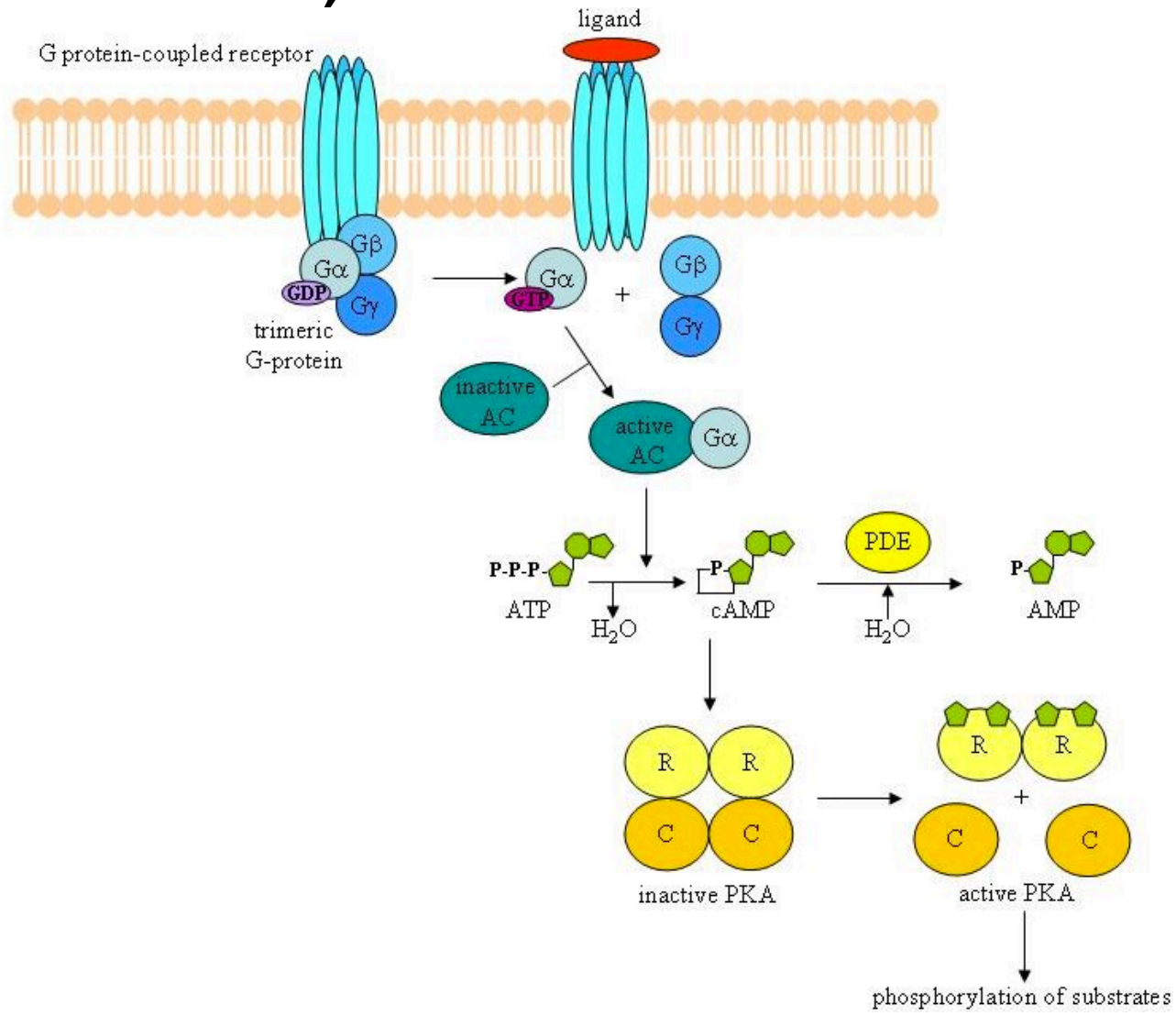
What would a beta blocker prevent?

A. Cortisol induction of gluconeogenesis
B. Stress-induced reduction of heart rate
C. Vasodilation of GI smooth muscle
D. Stress-induced blood flow to muscle

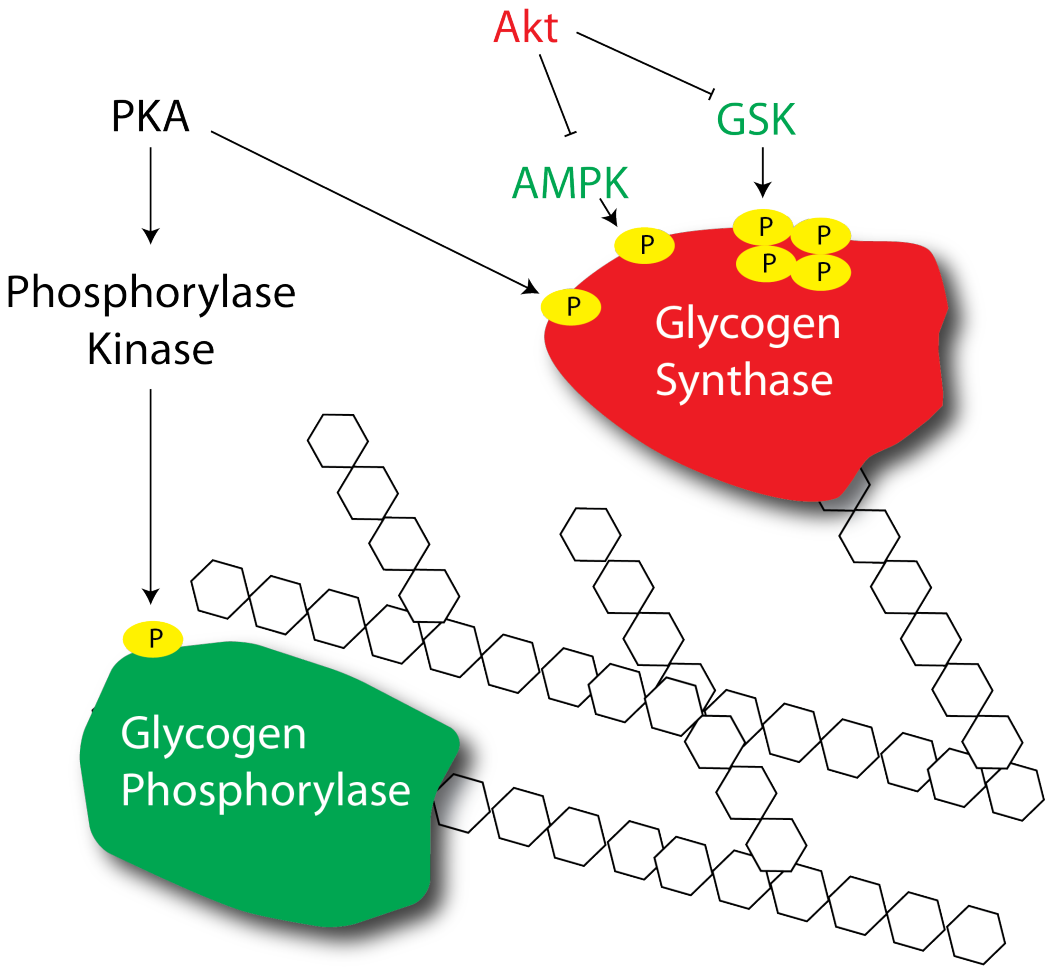
Metabolic Roles of Epinephrine



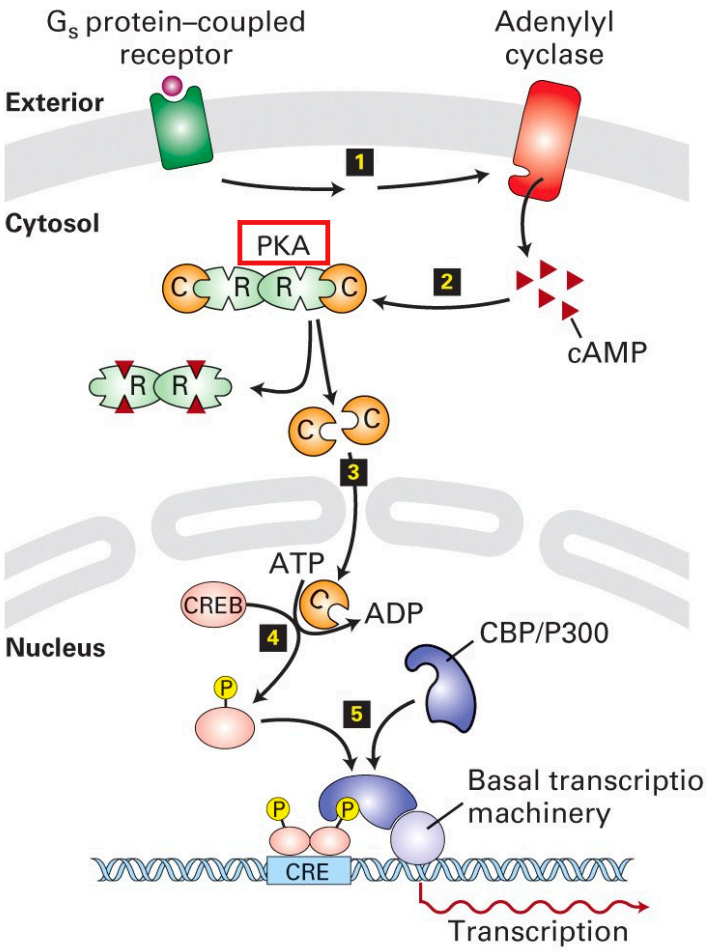
Epinephrine Binds B-AR/Gs in Skeletal Muscle, Liver and Fat Tissue



Epinephrine Mediated Activation of Glycogenolysis



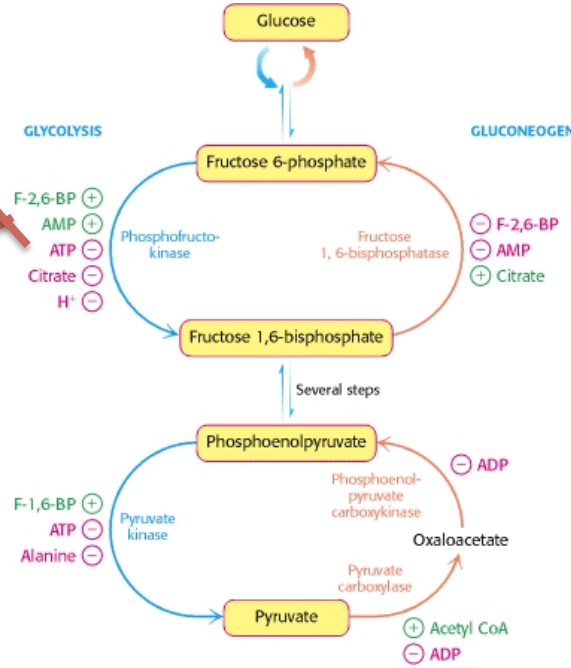
Dual Effects of Epinephrine on Gluconeogenesis in the Liver



Gluconeogenic Gene Transcription

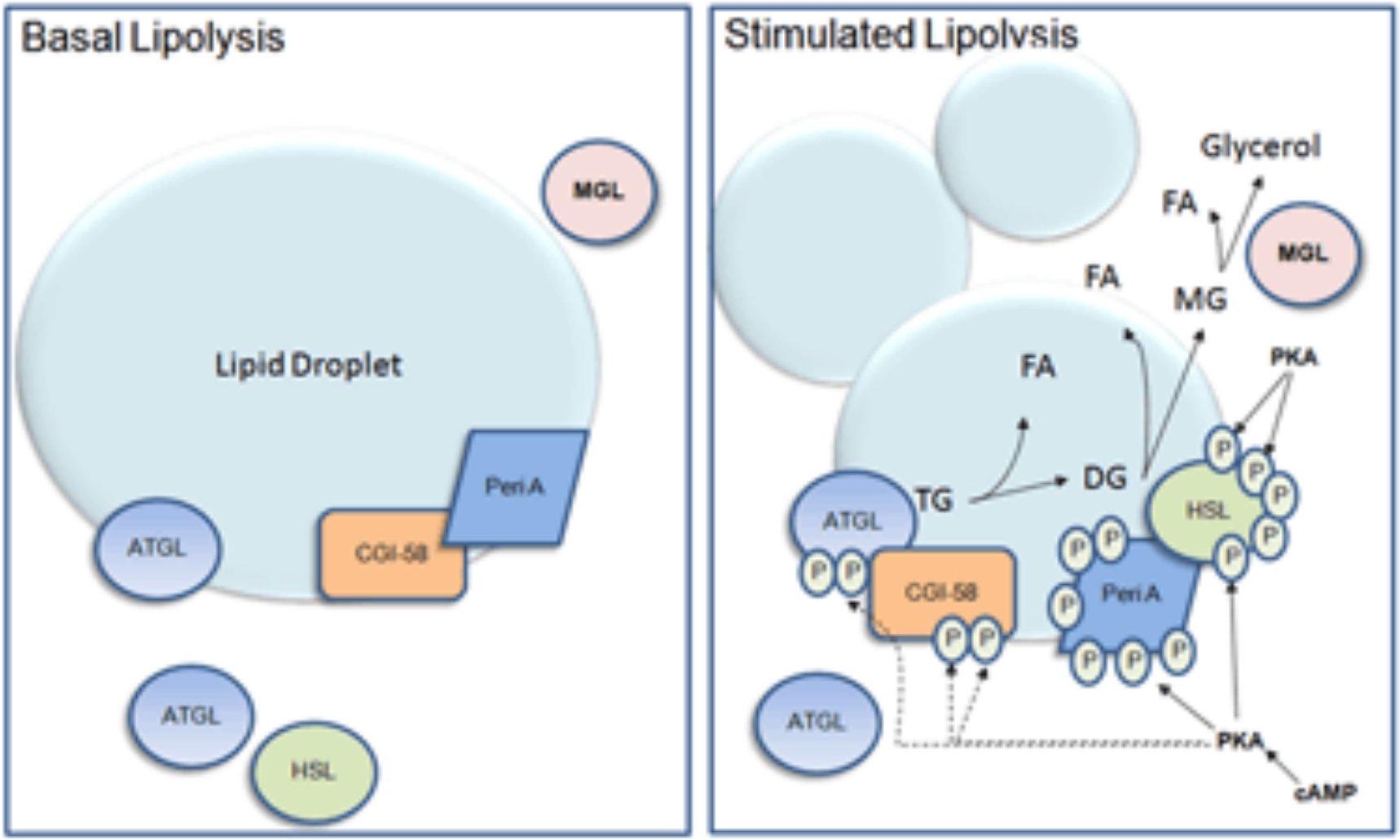
PKA

PFK-2



Post-Translational Induction of Gluconeogenesis

Effects of Epinephrine on Lipid Breakdown

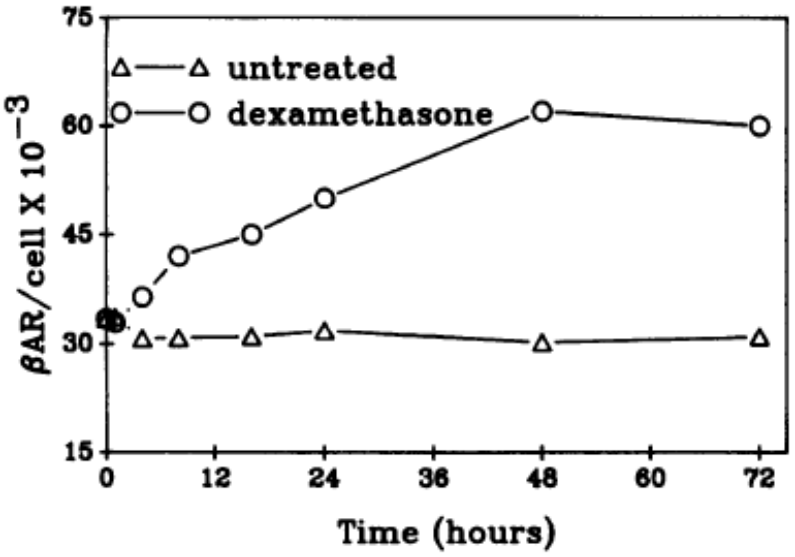


Short Term and Long Term Stress

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?