Endocrine Control Systems

Why should a dentist (or a doctoral student) care about endocrinology

- Clinical manifestations of endocrine pathophysiology
  - Diabetes (Insulin Insufficiency/Resistance)
    - Periodontitis
    - Mucusal disease
    - Altered taste
    - Parotid gland enlargent
    - Potential hypo/hyperglycemia
  - Hypoparathyroidism (Not Enough PTH)
    - Low calcium density, hypoplasia of enamel and dentin
    - Candidiasis
    - Delayed eruption, shortened roots
  - Hyperthyroidism (T3/T4 Overproduction)
    - Malocclusion
    - Demineralization
    - Anxiety/restlessness
  - Acromegaly (GH Overproduction)
    - Accelerated tooth eruption
    - Enlarged jaw, abberant tooth spacing
  - Cushing's (Cortisol Overproduction)
    - Periodontis, swelling of gums
    - Easy bruising
  - Addison's Disease (Cortisol Insufficiency)
    - Blotchy melanin patches in oral mucosa

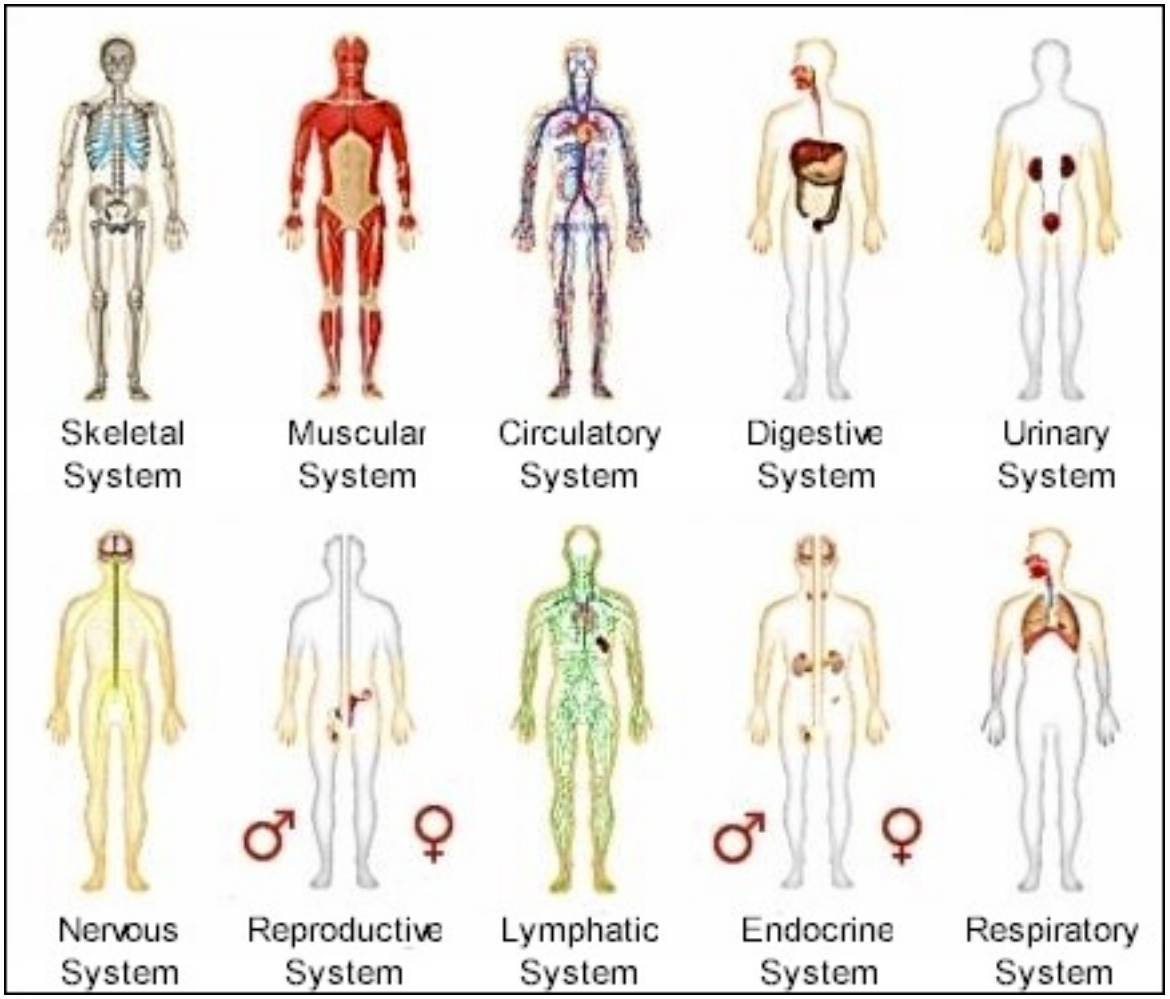
Learning Objectives

- Define endocrine, paracrine, autocrine, and exocrine systems, define neuro-secretory cells by giving a few examples.
- List major chemical categories of hormones and give several examples that belong to each class.
- List important factors that determine hormone levels in circulation.
- Explain cellular actions of hormones via membrane and nuclear receptors, including an understanding of the rates by which these processes can affect cells.
- Define basal secretion and stimulated secretion of endocrine glands.
- Describe negative and positive feedback system using an example.
- Explain with examples neuroendocrine integration.

Things you (should) already know

- Regulation of renal function (Tigyi)
  - Renin/Angiotensin/Aldosterone/ANF/Vasopressin
- Regulation of GI function (Johnson)
  - Gastrin/CCK/GIP/Secretin/VIP/Motilin
- Blood Pressure Regulation (O'Connell)
  - Angiotensin/Vasporessin/Adrenaline/Noradrenaline/ Dopamine/Endothelin
- Cardiac Function (Mancarella)
  - ANP/Adrenaline/Noradrenaline/Acetylcholine
- Synaptic Transmission (Adebiyi)
  - Serotonin/Acetylcholine/GABA/Histamine/Aspartate/ Glutamate/NO

Organ Systems



Extracellular Sensing

https://www.youtube.com/watch?v=F6QMU3KD7zw

What are the important processes?

1. There has to be a signal
2. That signal has to be detected
3. The cell has to respond to that signal
4. After a while the signal has to be stopped

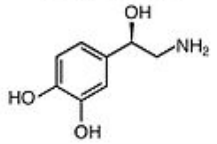
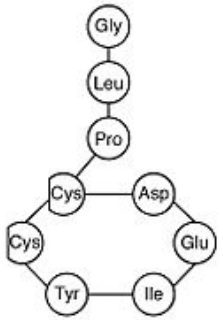
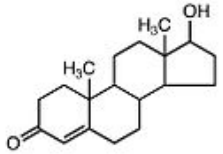
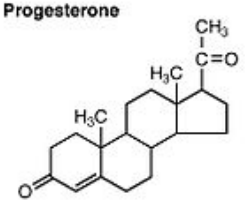
What do we need to know about a hormone?

- What kind of chemical is it?
- Where is it made?
- What causes its release?
- What are its receptors?
- What tissues does it effect?
- How does it get turned off

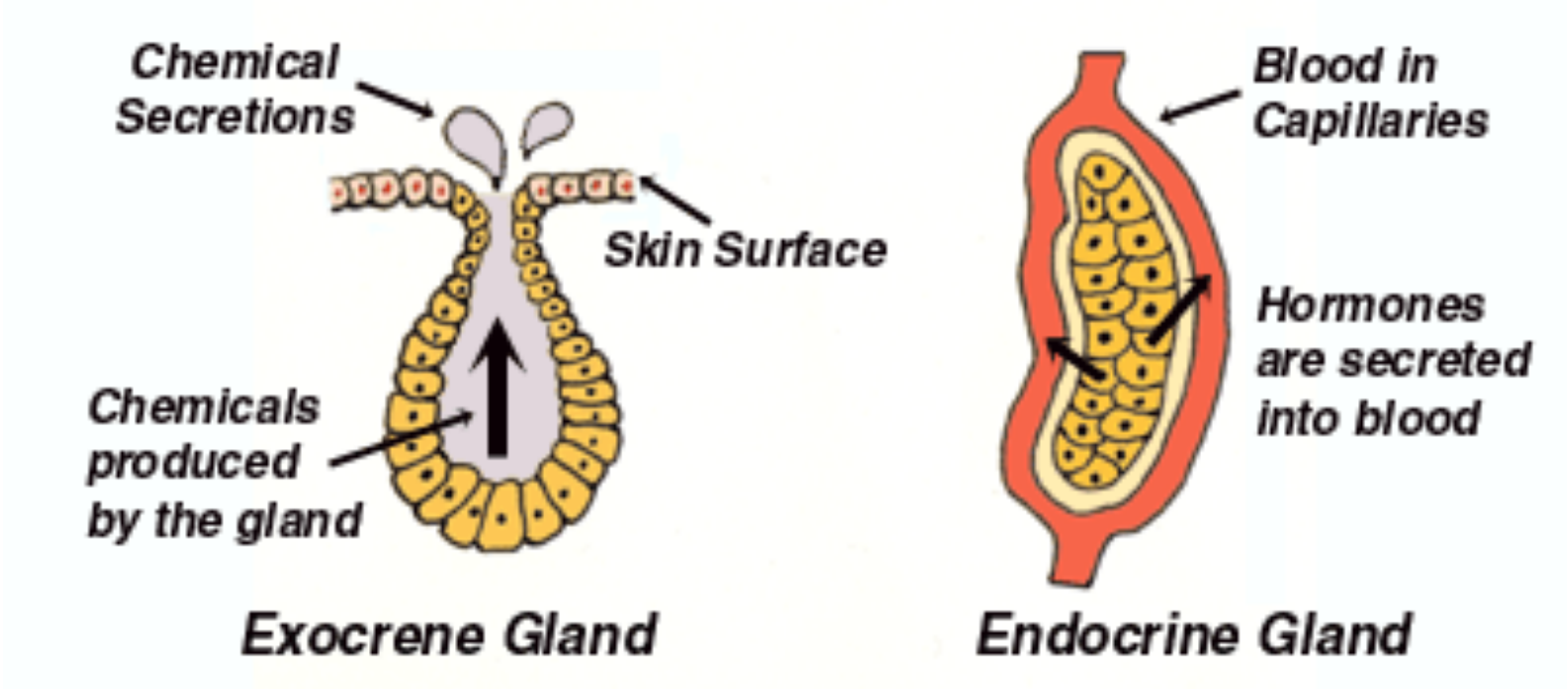
Example Adrenaline

What kind of chemical is it?	Biogenic Amine	Tyrosine Derivative
Where is it made?	Adrenal medulla	
What causes its release?	Sympathetic nervous stimulation	
What is its receptor?	Alpha/Beta-Adrenergic Receptors	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	

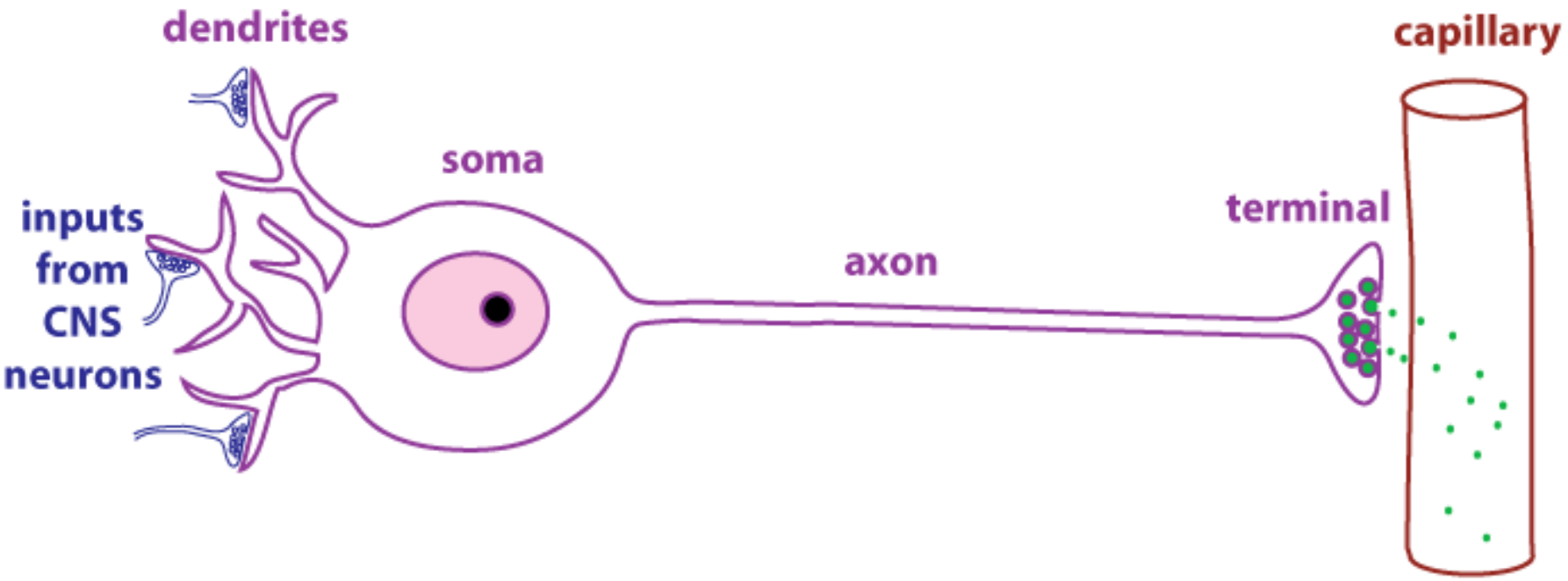
What Kinds of Hormones Are There?

Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	**Norepinephrine** 
Peptide Hormone	Short chains of linked amino acids	**Oxytocin** 
Protein Hormone	Long chains of linked amino acids	**Human Growth Hormone** 
Steroid Hormones	Derived from the lipid cholesterol	**Testosterone**  **Progesterone** 

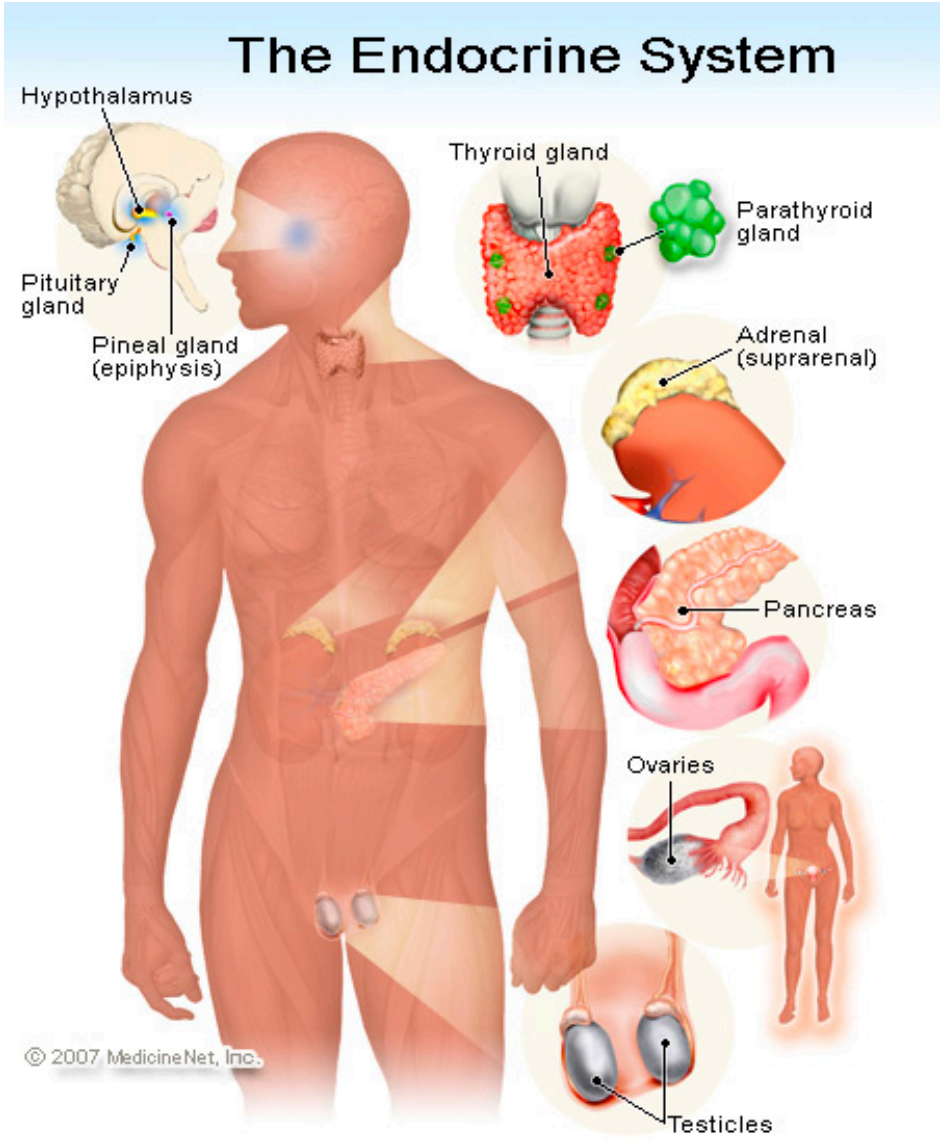
Endocrine vs Exocrine



Neuroendocrine Secretions



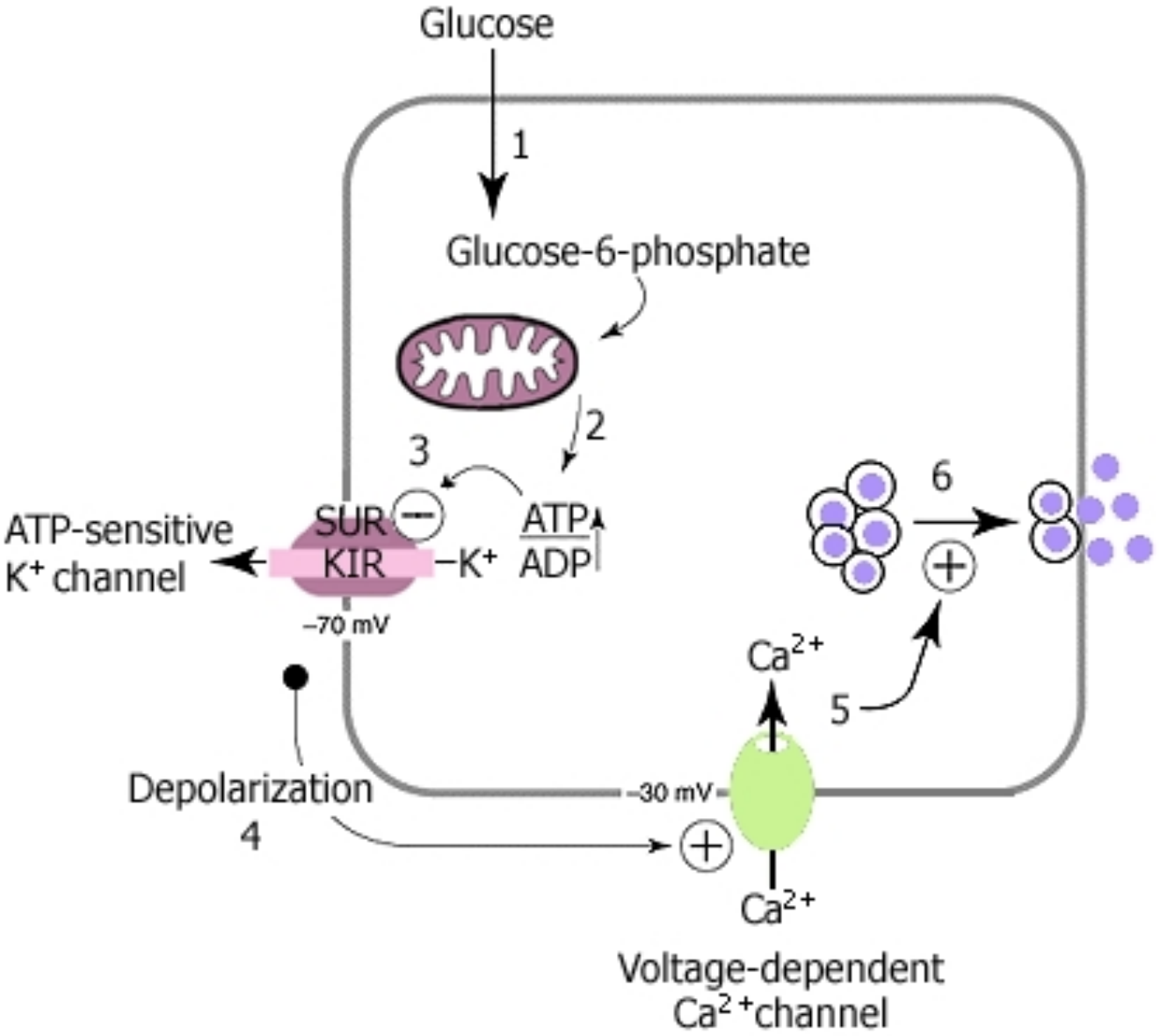
Generally, where are hormones made



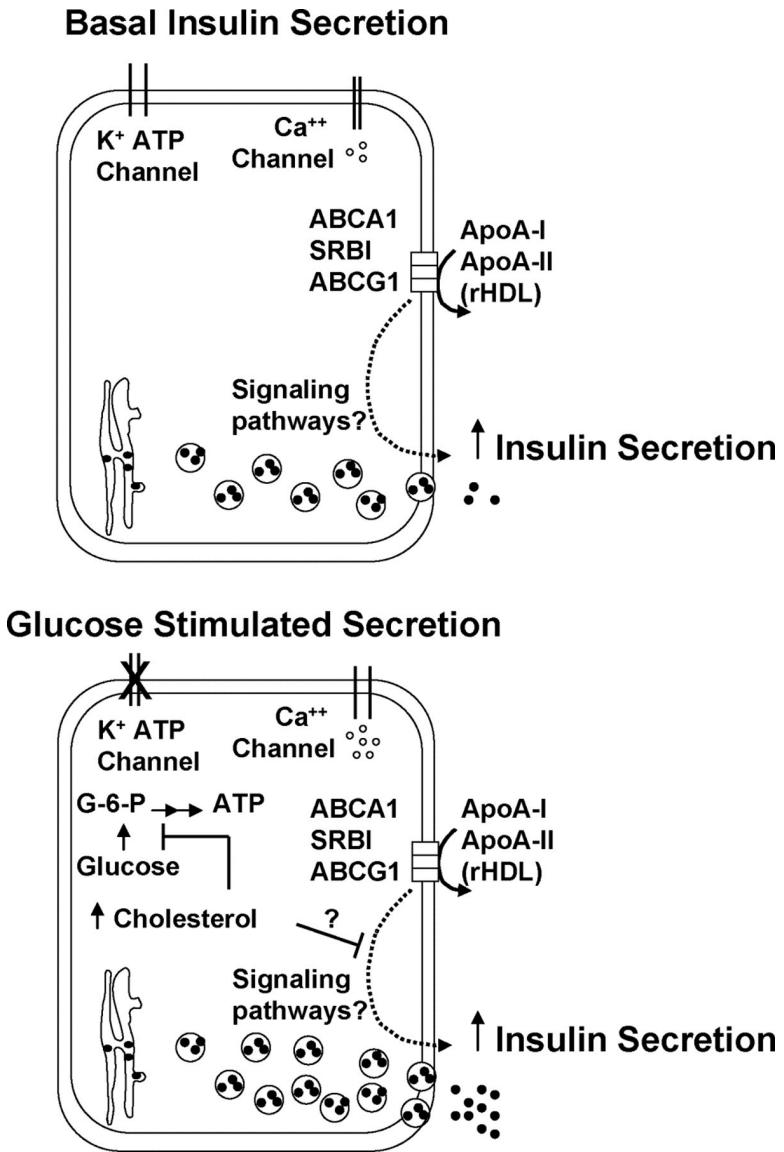
Generally how are hormones released?

- Nervous stimulation
  - Adrenaline, CRH, TSH
- In Response to Another Hormone
  - Cortisol (ACTH), Thyroid Hormones (TSH)
- In Response to A Metabolite
  - Insulin, Glucagon, Calcitonin
- In Response to Physical Changes Such As Stretch
  - Ghrelin, Renin

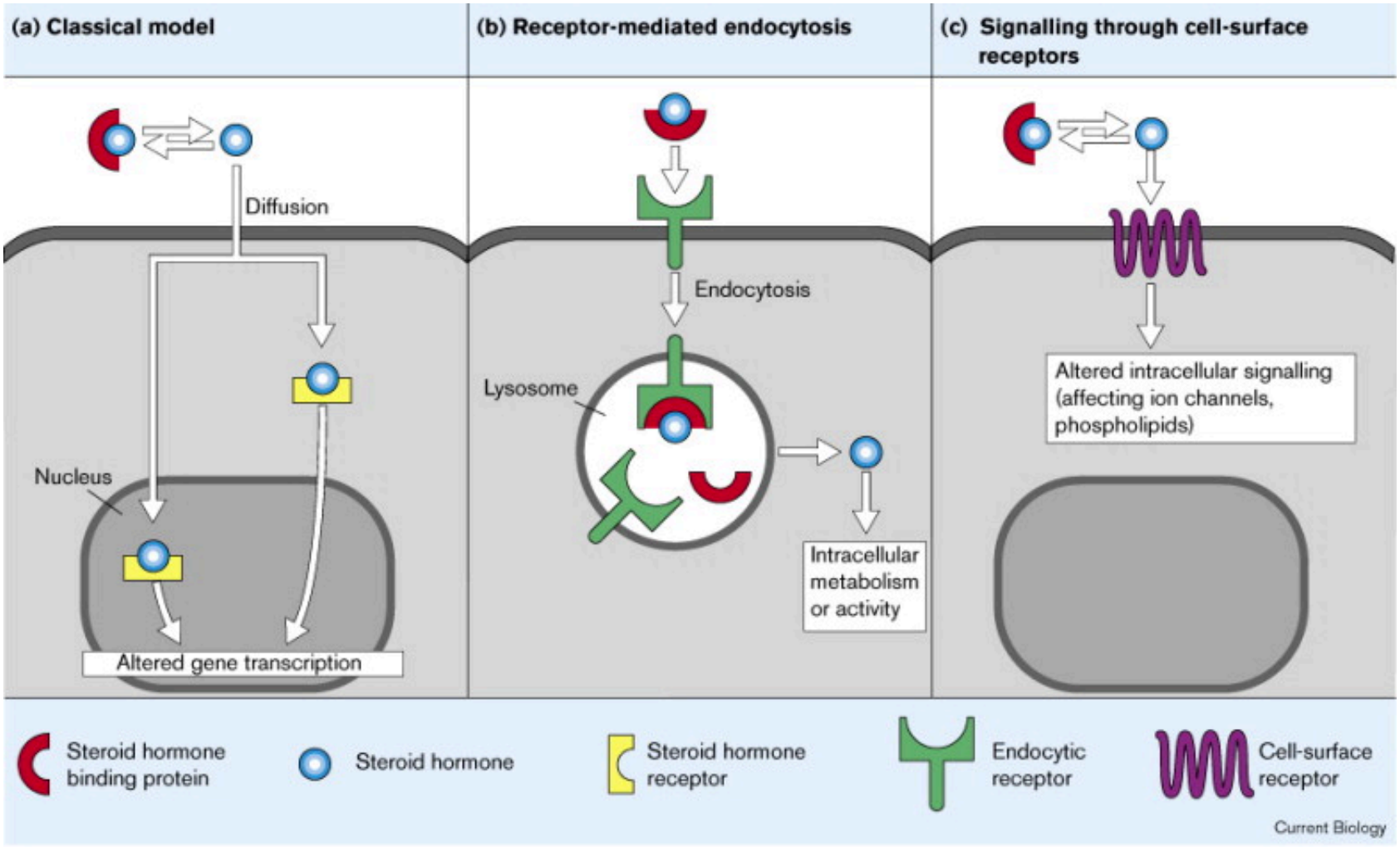
Insulin Release In Response To Glucose



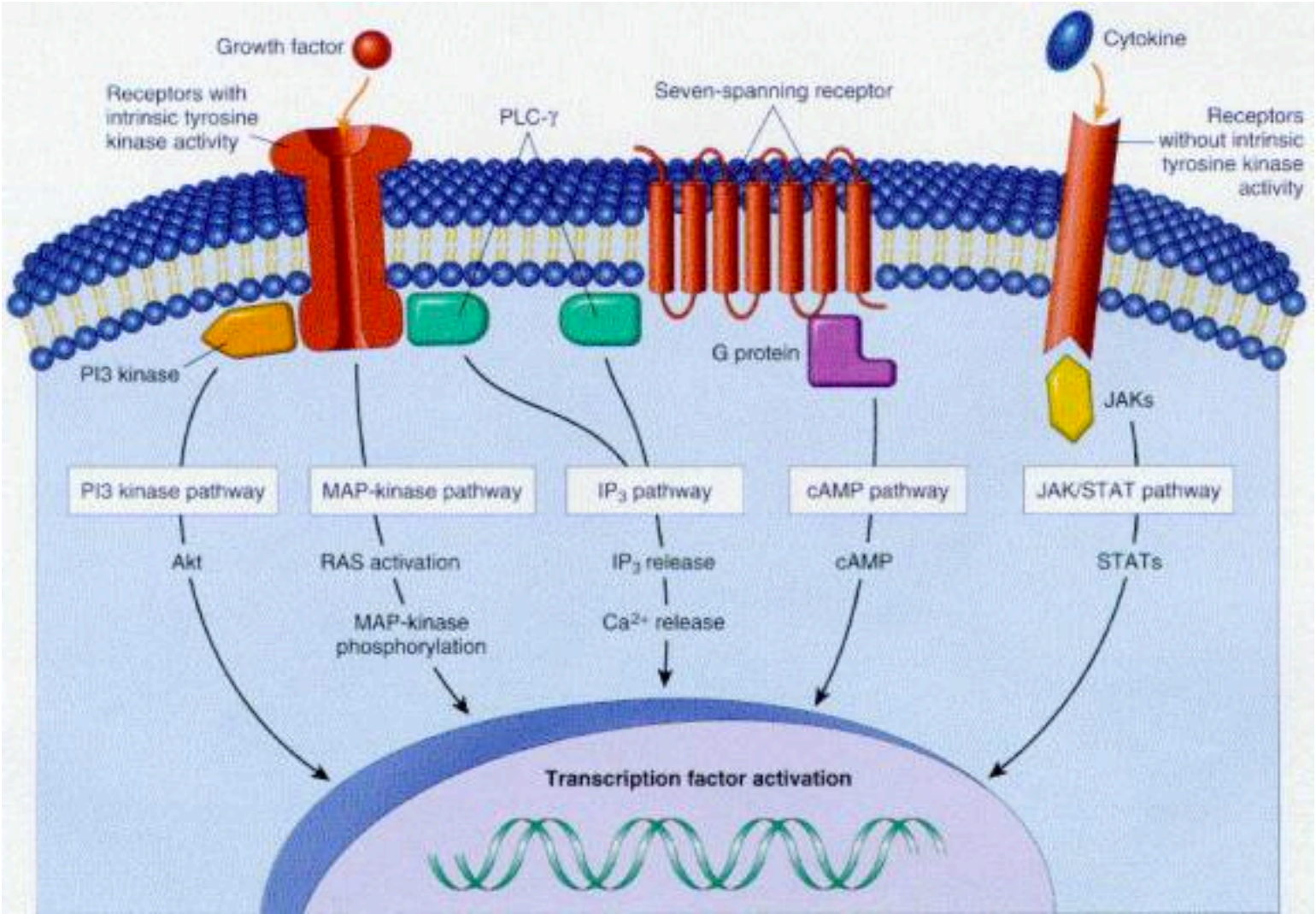
Basal vs Stimulated Secretion



What Kinds of Receptors Are There?



Cell Surface Receptors



Types of Cell Surface Receptors

GPCRs

- 7-TM
- Activates G proteins in several classes
- Can regulated cAMP, Ca, DAG and RhoGTPases
- Example β−AR

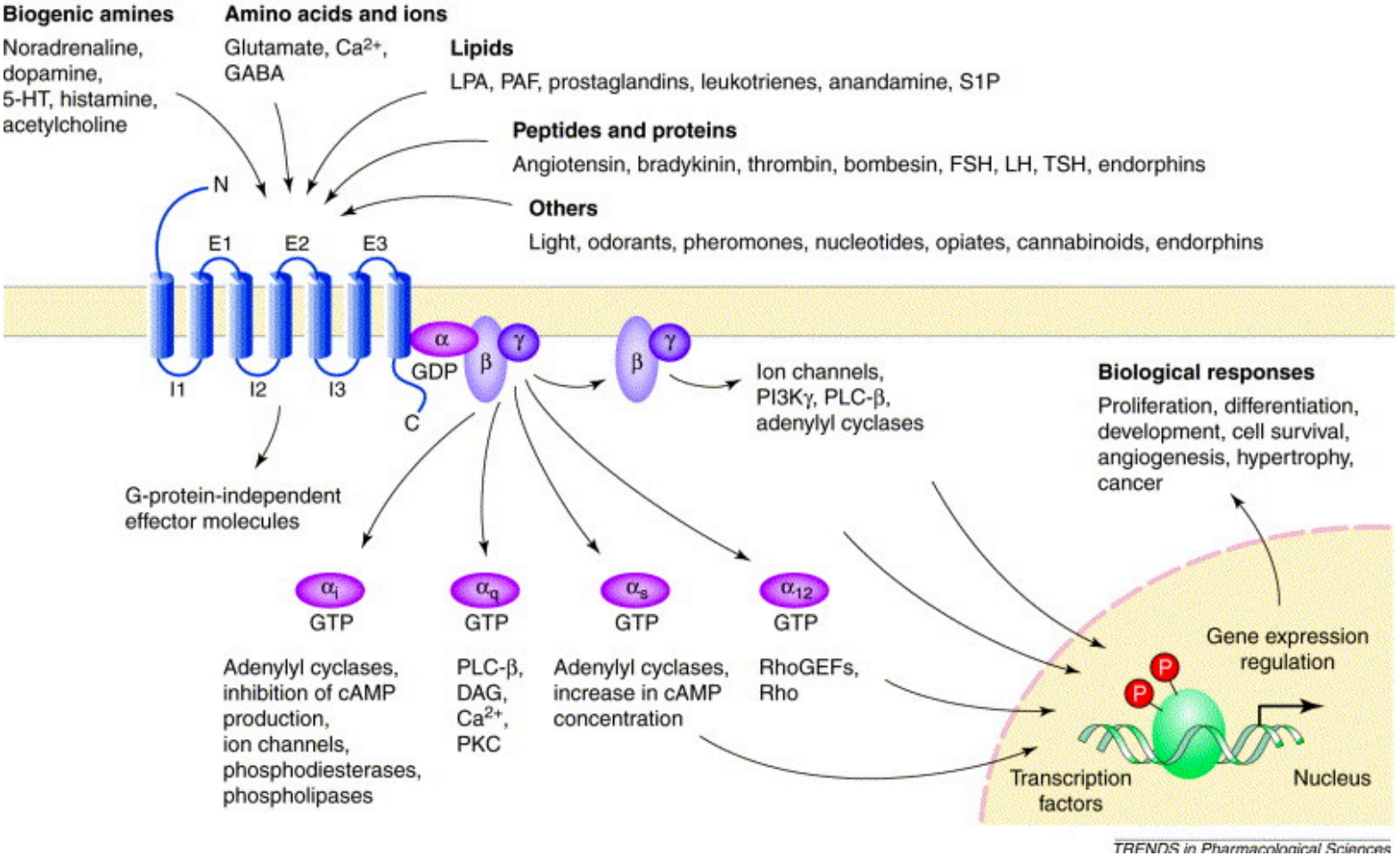
Receptor Tyrosine Kinases

- 1-TM (dimer)
- Autophosphorylate on tyrosine residues
- Recruits and activates effectors like Akt
- Example InsR

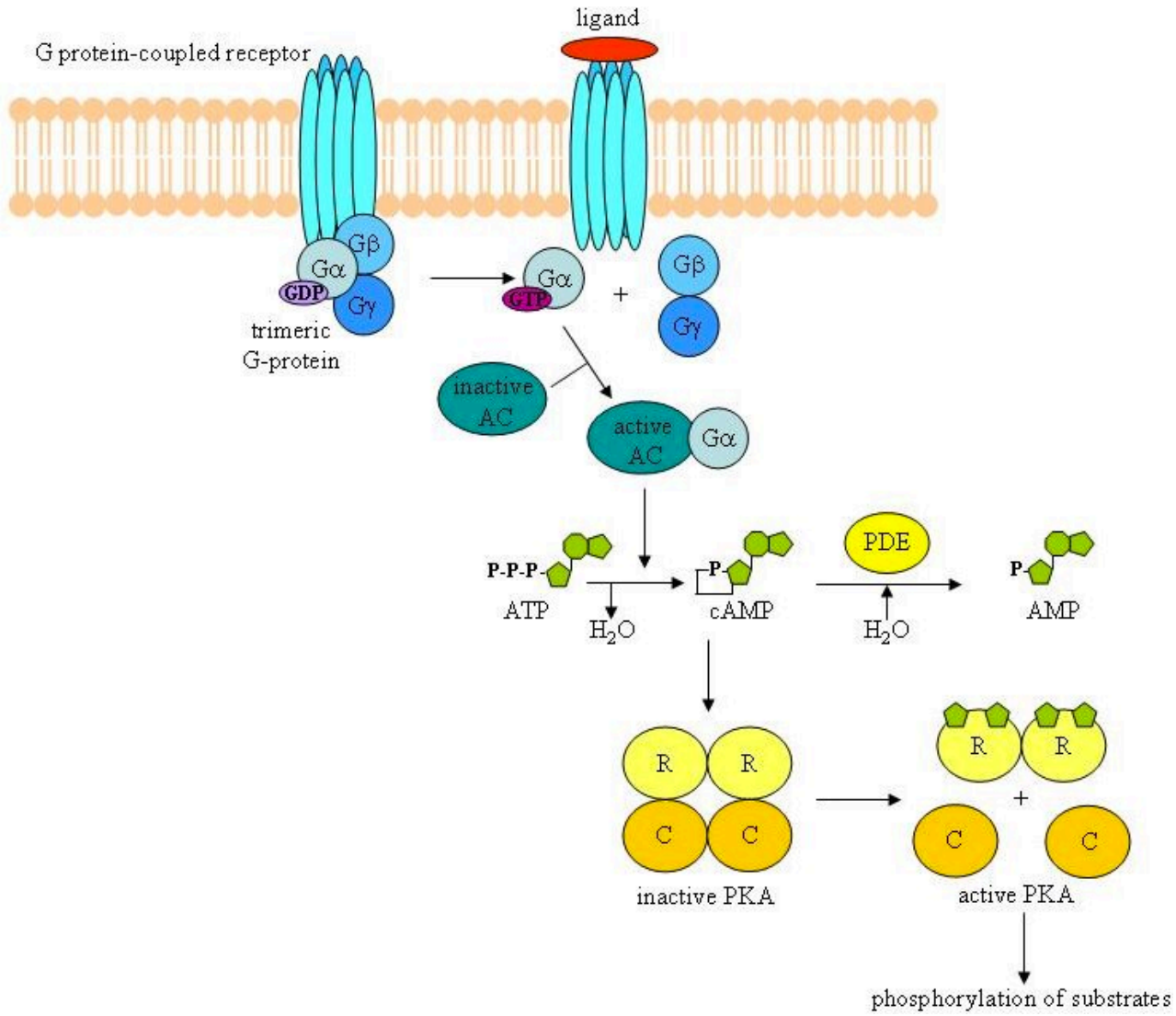
JAK/STAT Receptors

- 1-TM (dimer)
- Recruits kinase (JAK) which phosphorylates effectors (STAT)
- pSTAT activates gene transcription
- Example GH

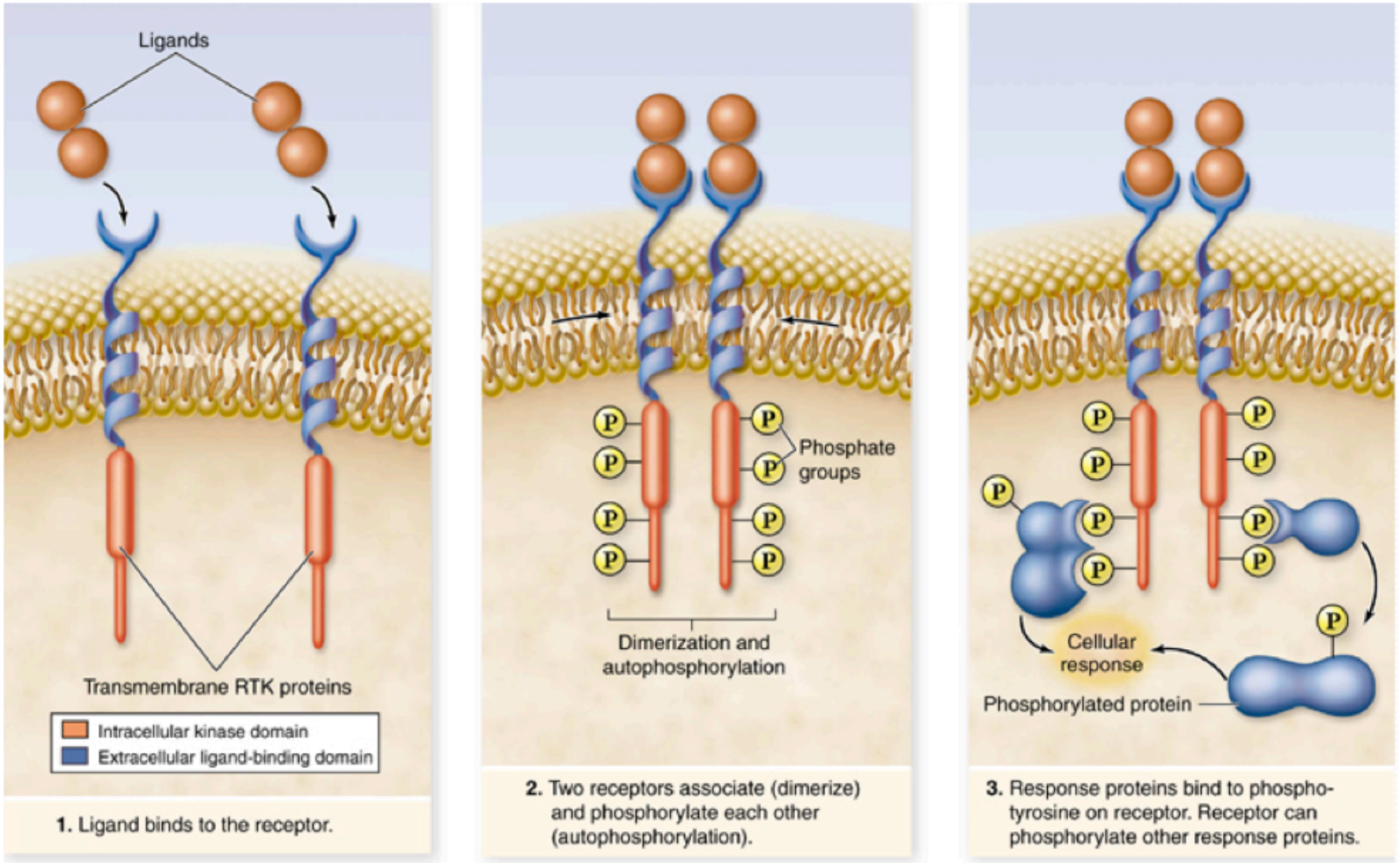
GPCRs


Biogenic amines
Noradrenaline, dopamine, 5-HT, histamine, acetylcholine
Amino acids and ions
Glutamate, Ca2+, GABA
Lipids
LPA, PAF, prostaglandins, leukotrienes, anandamine, S1P
Peptides and proteins
Angiotensin, bradykinin, thrombin, bombesin, FSH, LH, TSH, endorphins
Others
Light, odorants, pheromones, nucleotides, opiates, cannabinoids, endorphins
N
E1
E2
E3
I1
I2
I3
C
α
β
γ
GDP
Ion channels, PI3Kγ, PLC-β, adenylyl cyclases
Biological responses
Proliferation, differentiation, development, cell survival, angiogenesis, hypertrophy, cancer
G-protein-independent effector molecules
αi GTP
αq GTP
αs GTP
α12 GTP
Adenylyl cyclases, inhibition of cAMP production, ion channels, phosphodiesterases, phospholipases
PLC-β, DAG, Ca2+, PKC
Adenylyl cyclases, increase in cAMP concentration
RhoGEFs, Rho
Gene expression regulation
P
Transcription factors
Nucleus
TRENDS in Pharmacological Sciences

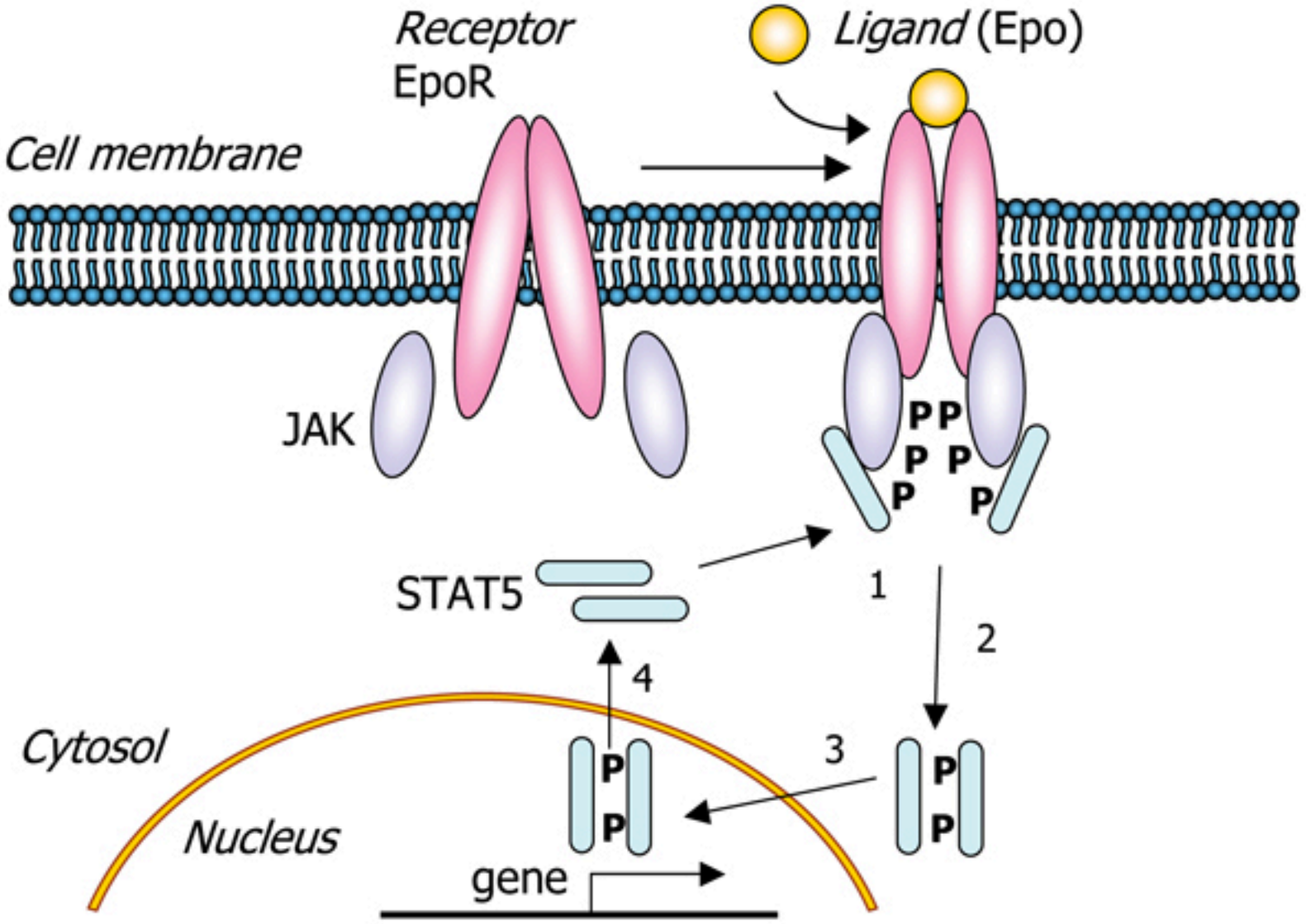
GPCRs and PKA



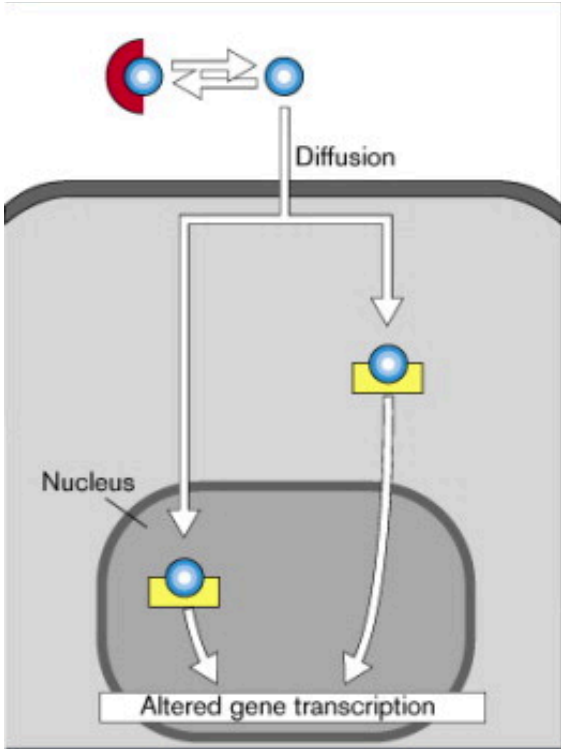
Receptor Tyrosine Kinases



Jak-Stat pathway

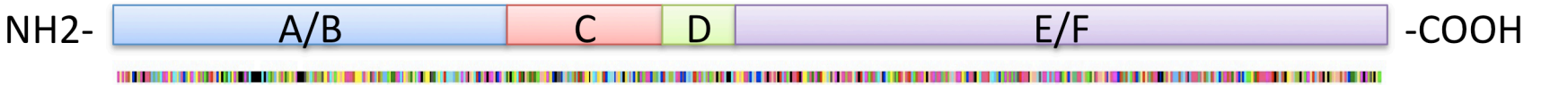


Nuclear Hormone Receptors



Structure of NRs

1°

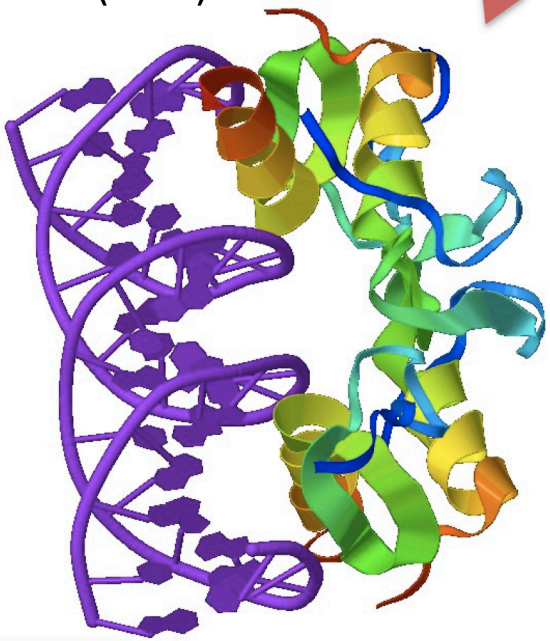


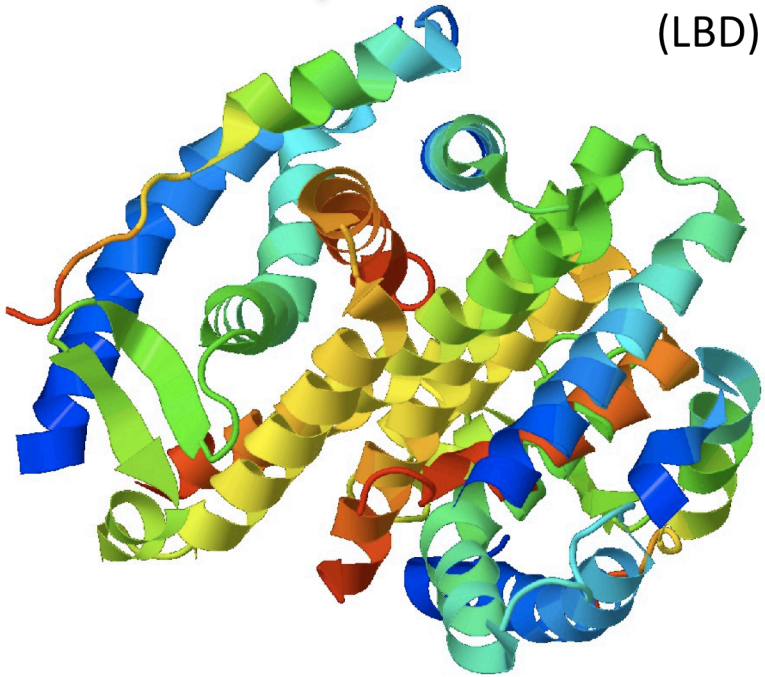
2°

DNA Binding Domain (DBD)

Ligand Binding Domain (LBD)

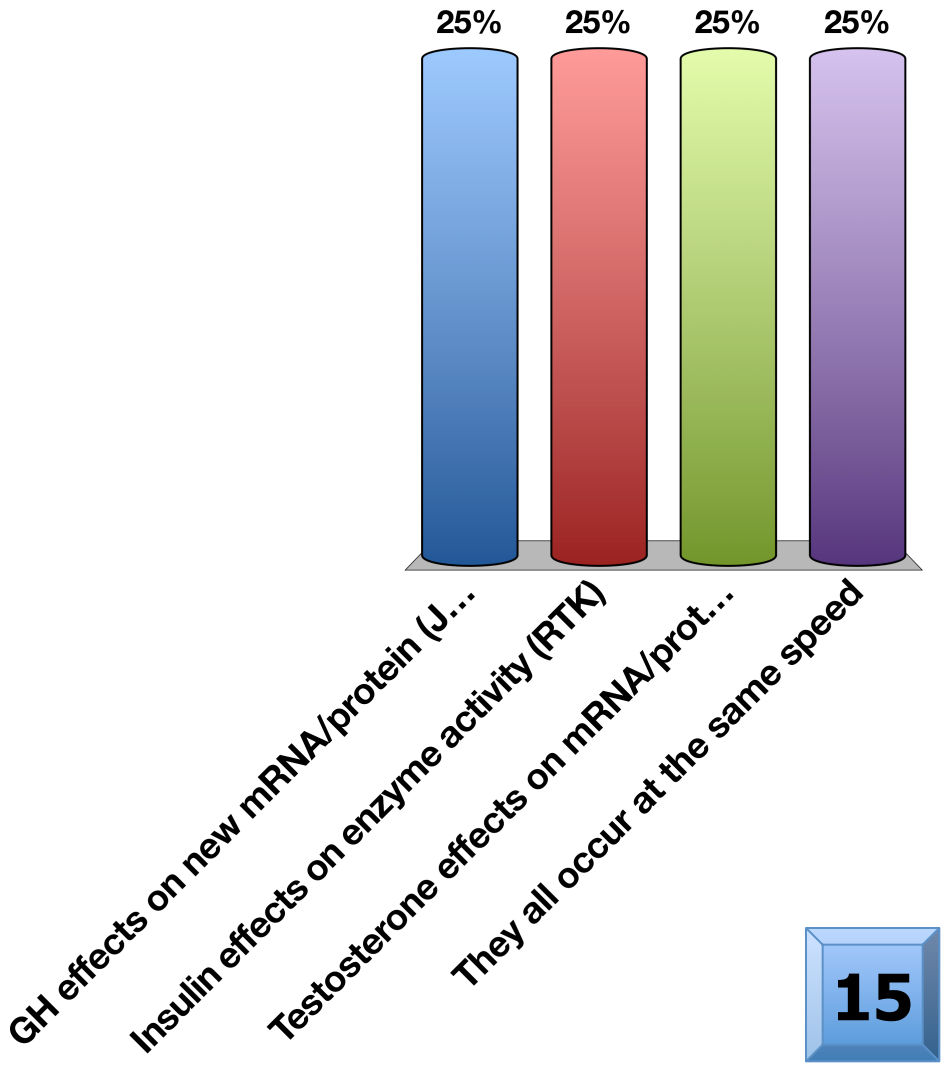
3°





Which hormonal responses will occur fastest?

A. GH effects on new mRNA/protein (JAK/ STAT)
B. Insulin effects on enzyme activity (RTK)
C. Testosterone effects on mRNA/protein (NHR)
D. They all occur at the same speed



General Concepts About Hormone Targets

- How does the hormone get from A -> B
- Is it released into the blood?
- Does it require accessory proteins to help keep it soluble?

Relative Location of Action

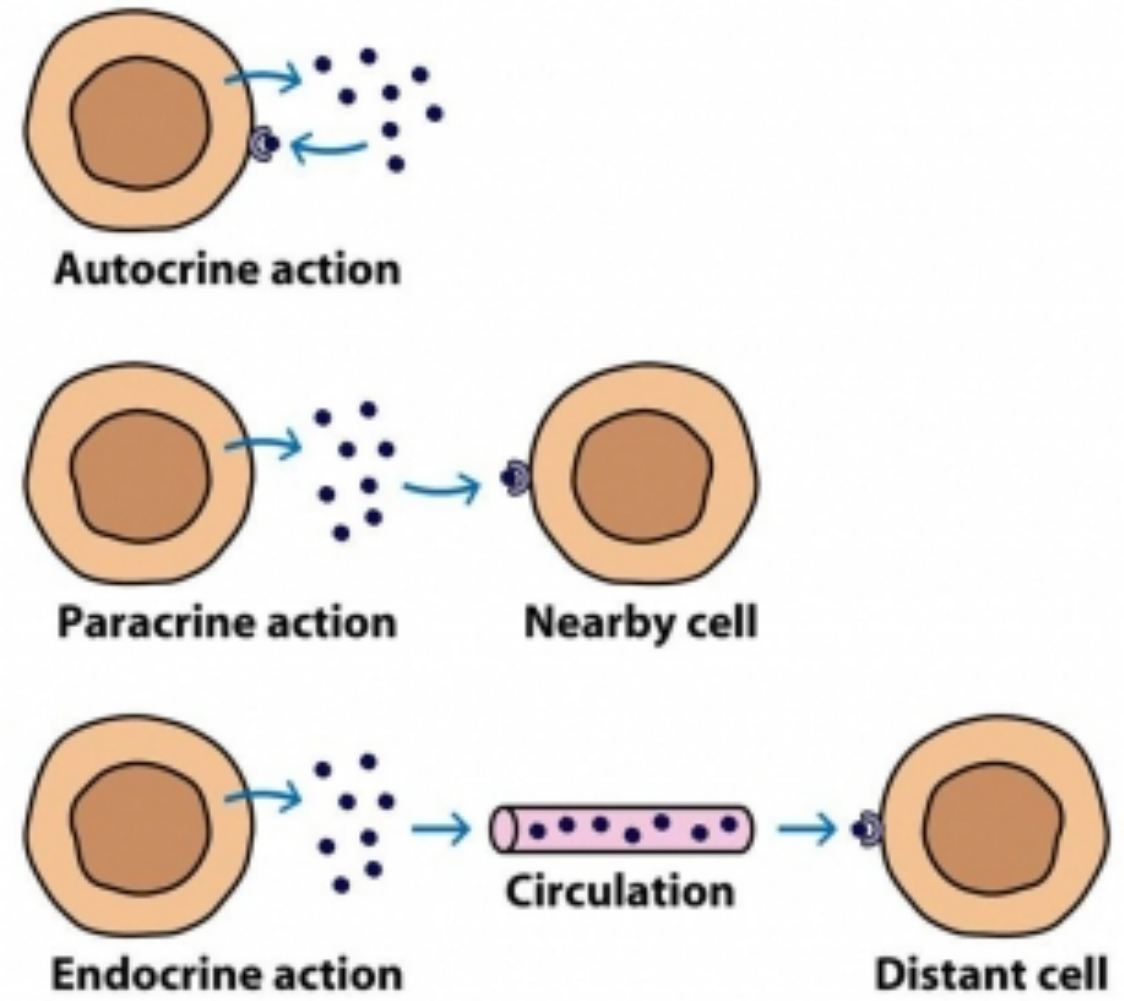
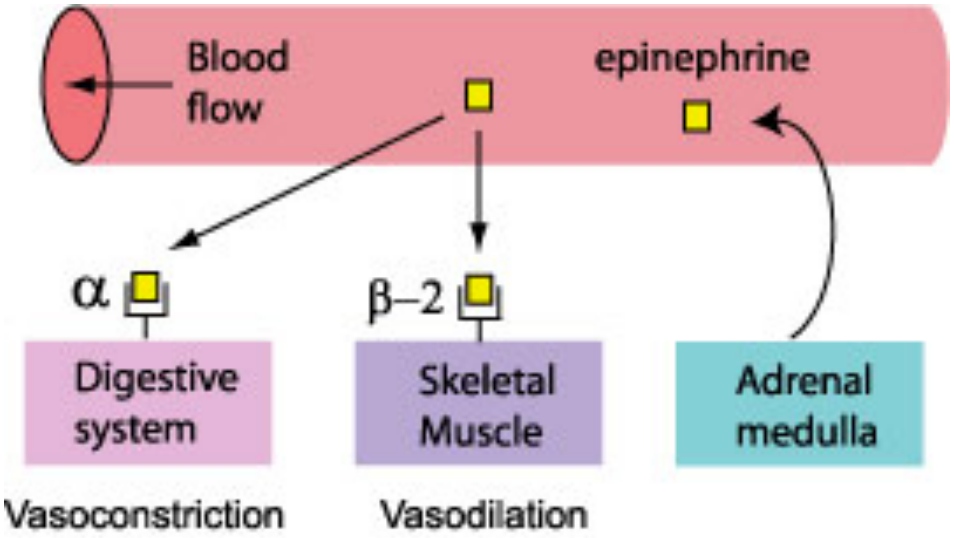


Figure 1.2-1b
Kuby IMMUNOLOGY, Sixth Edition

How To Get Hormonal Specificity?

- Restrict the location of the hormone release (ie neurotransmitters only released into synapse)
- Restrict the receptors to particular tissues
- Have the receptors mediate different processes in different cell types

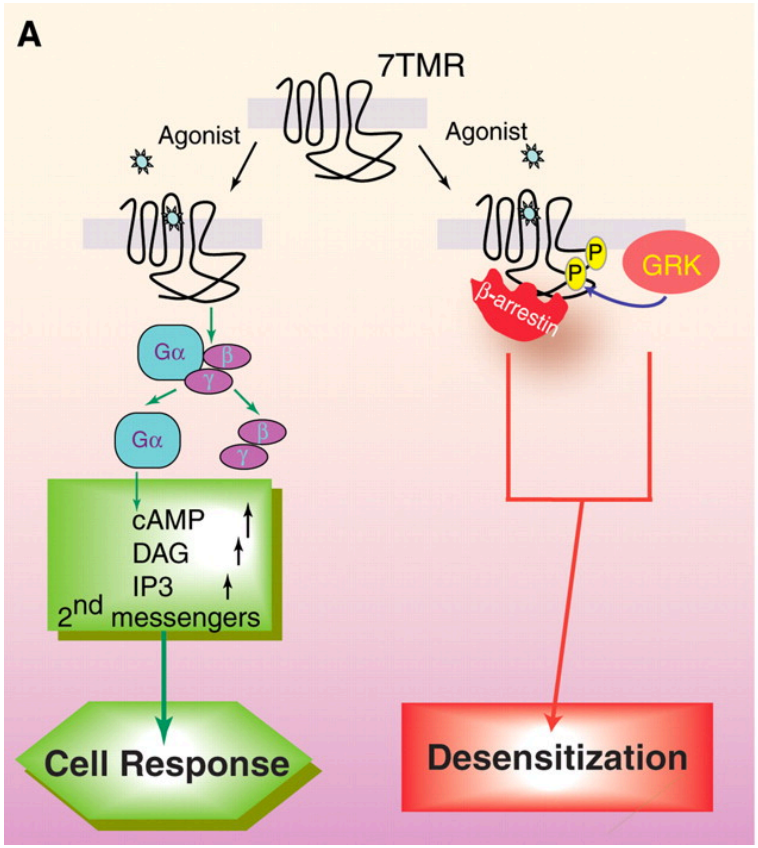


For more details see O'Connell's lectures on blood pressure regulation

Turning the Signal off

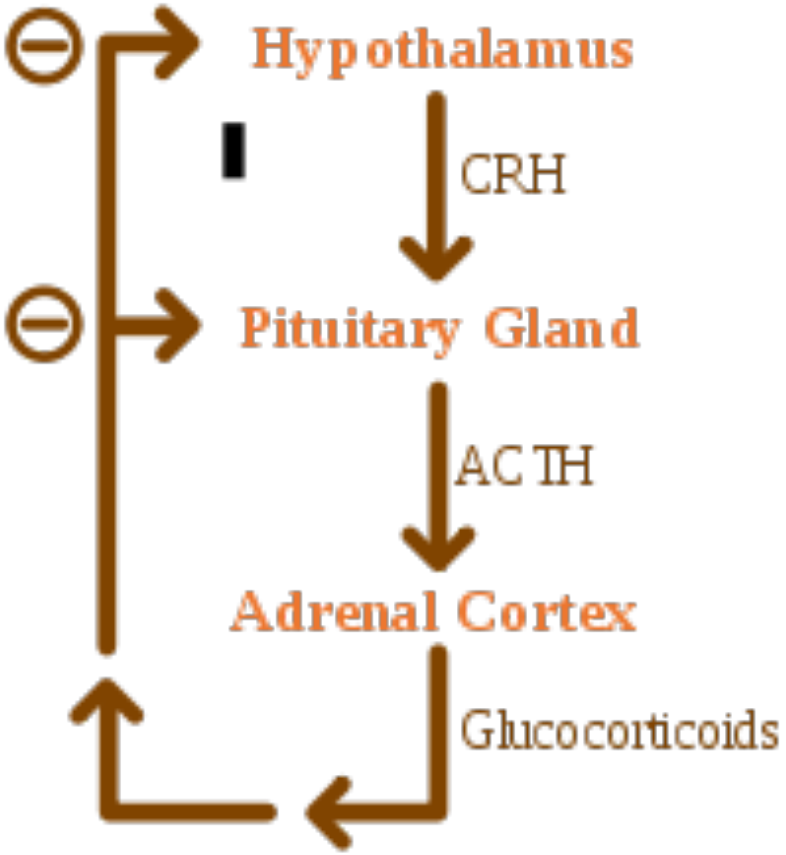
- Induce hormone resistance at the target cell
- Prevent further hormone production and/or reduce the levels

Example: Arrestins and GPCRs

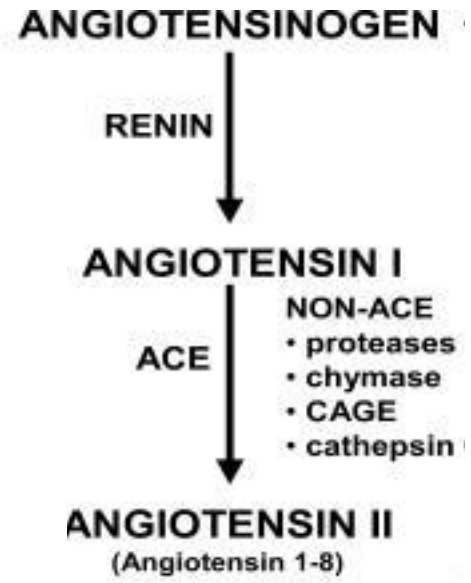


Lefkowitz RJ, Shenoy SK (2005) Transduction of receptor signals by beta-arrestins. Science 308: 512–517. doi:10.1126/science.1109237.

Example: Reduce New Hormone Secretion



Example: Degrade Existing Hormones



Group Project

1. Pick some hormone that you think you know of its function
2. Imagine a patient that has no negative feedback to that hormone. What happens and why?
3. Now imagine another patient that has way too much negative feedback to that hormone. What happens and why?

Integration of the CNS with Endocrine Signals

In Response To CNS

- Externally sensed cues (ie, look a bear!)
- Release of adrenaline
- Modify peripheral responses

To Modify CNS

- Internally sensed cues (ie, my stomach is full)
- Feeding hormones (Leptin, Ghrelin, PYY)
- Modify behavior

Learning Objectives

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- Describe negative and positive feedback system using an example.
- Explain with examples neuroendocrine integration.

Your Future

- Endocrine Control Systems
- **Neuroendocrinology and the Posterior Pituitary**
- Endocrine Control of Growth
- Adrenals and Stress Hormones
- Hypothalamus and Endocrine Control of Appetite
- Pancreatic Hormones and Metabolic Control
- Thyroid Hormones (KP)
- Calcium Homeostasis (MF)
- Reproductive Hormones (HP)

Design a hormone

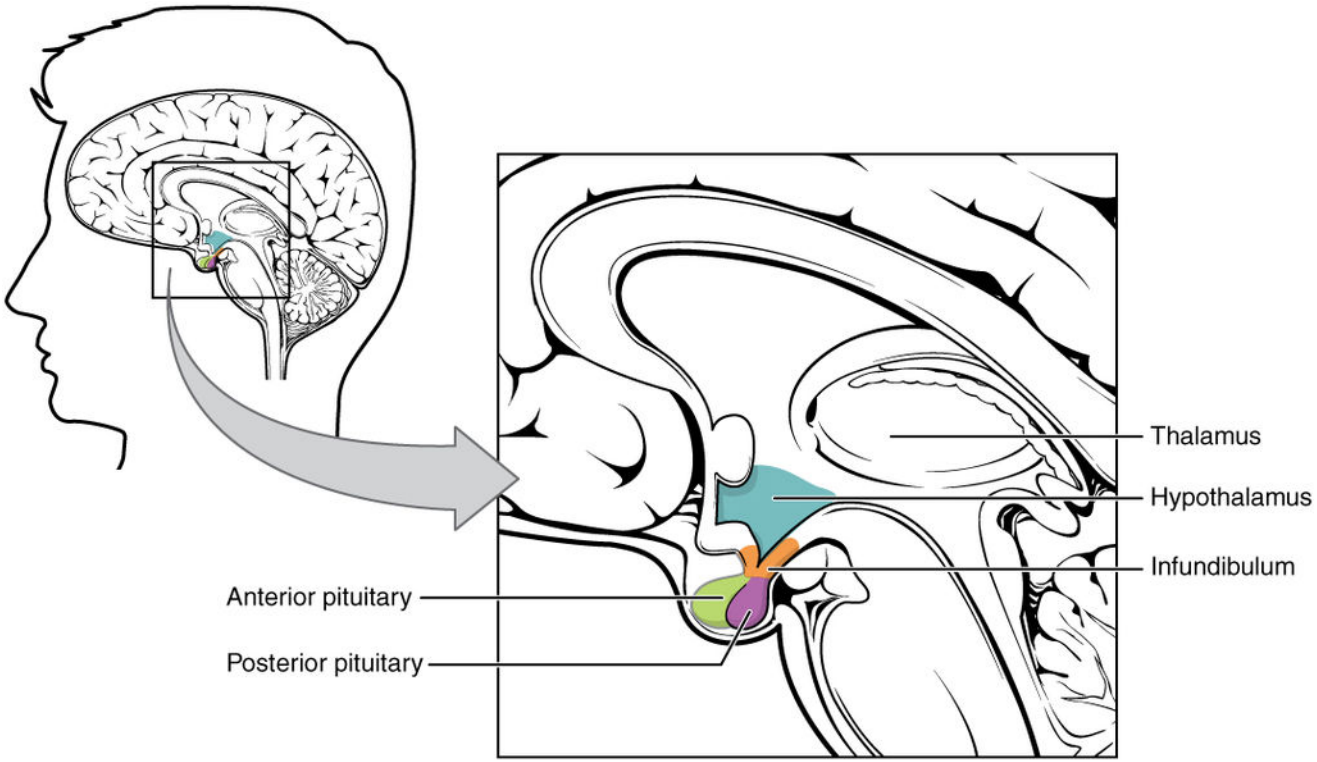
- What process does it govern?
- What signals its release? Does it result from external cues, or internal cues?
- Under what time-scale does this change occur?
- What should end the signaling event?
- What would be the pathophysiology of this hormone not existing? How about being far too active?

NEUROENDOCRINOLOGY AND THE POSTERIOR PITUITARY

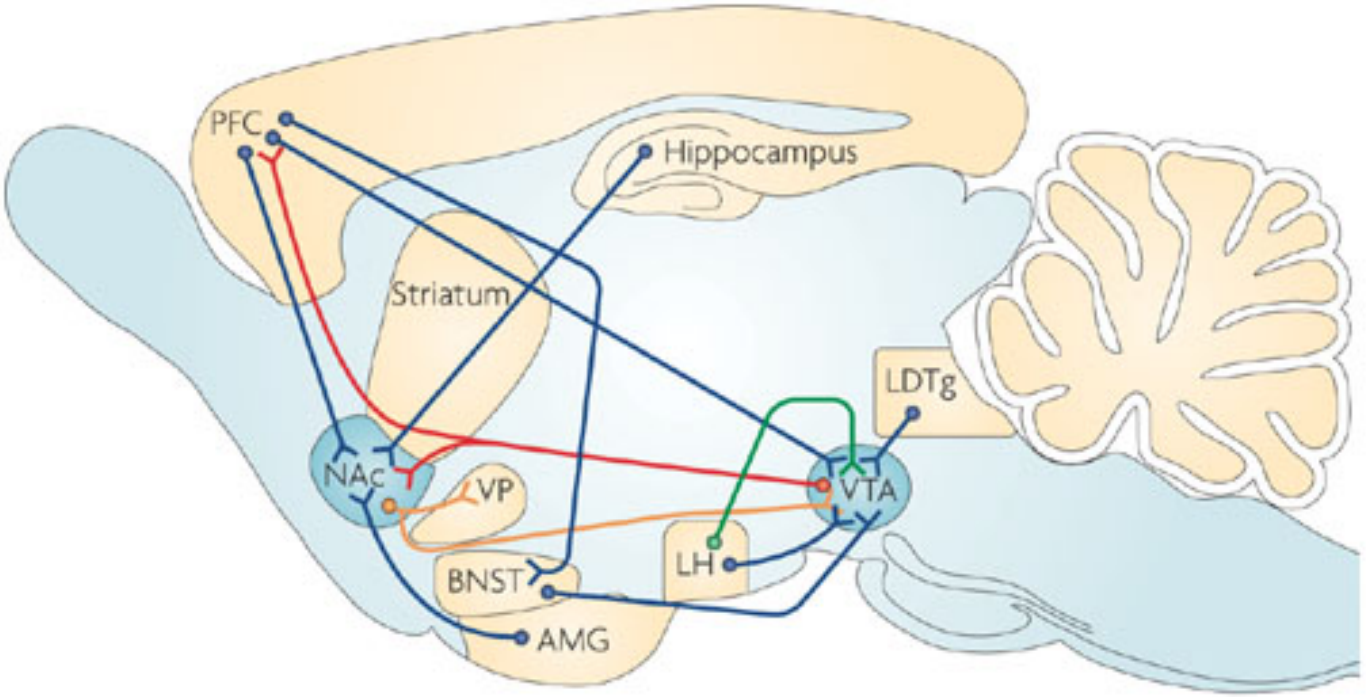
Learning Objectives

- 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 acronymns.
- 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.

The Hypothalamus Is the Main Site of Endocrine/CNS Integration

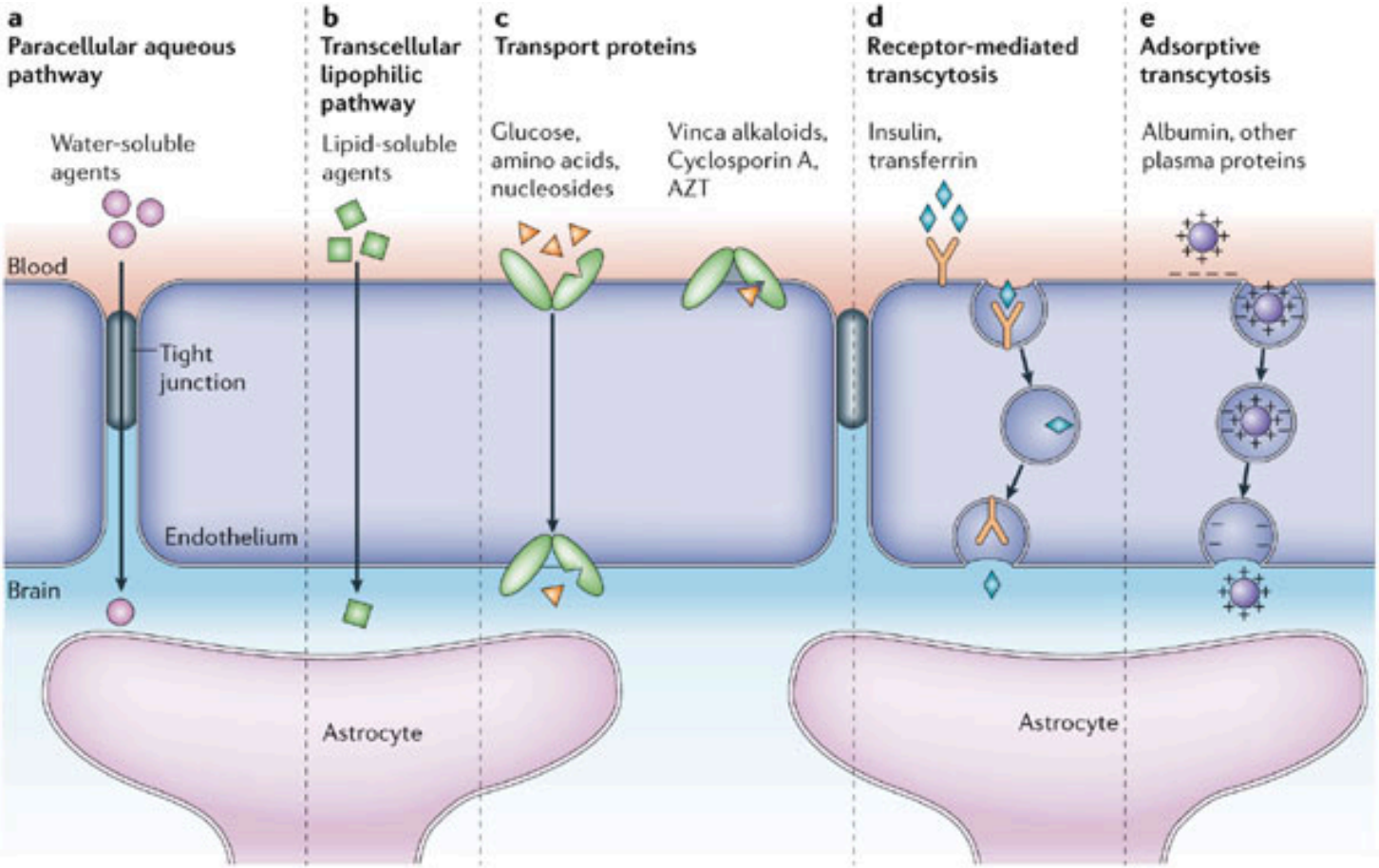


The Hypothalamus Projects to and From Other Brain Regions

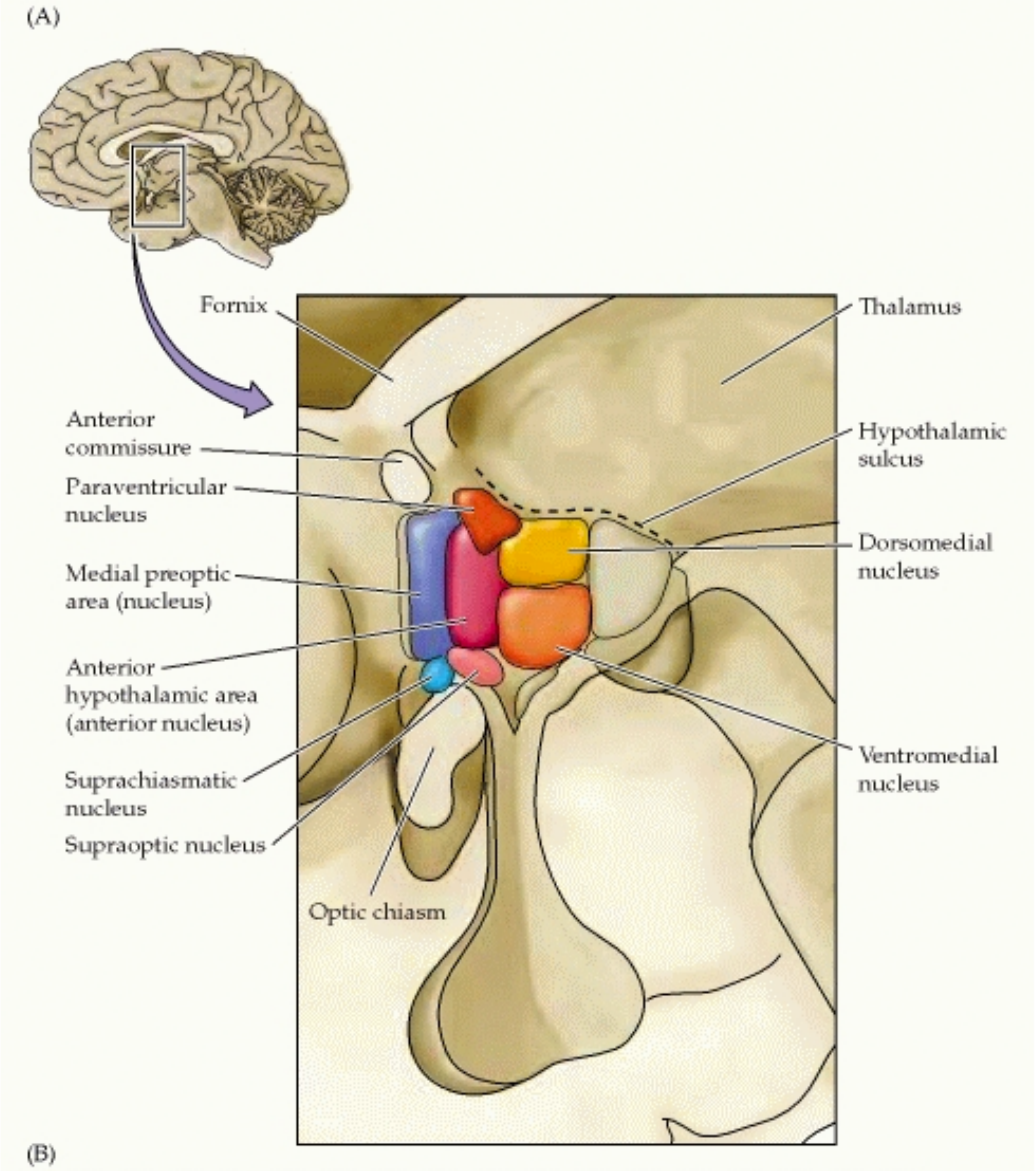


Kauer JA, Malenka RC (2007) Synaptic plasticity and addiction.
Nat Rev Neurosci 8: 844–858. doi:10.1038/nrn2234.

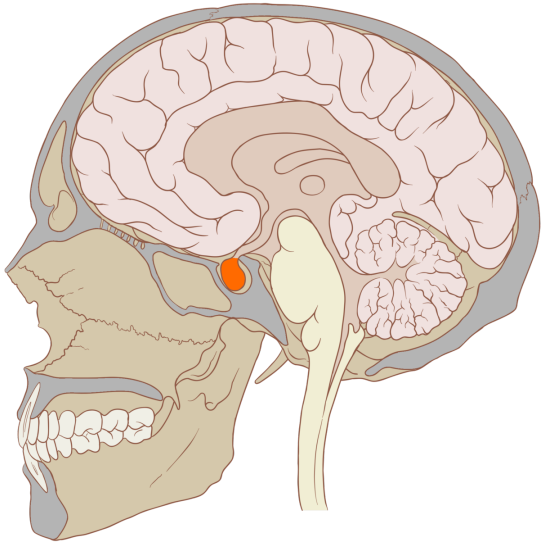
How Are Hormones Sensed by the Hypothalamus?

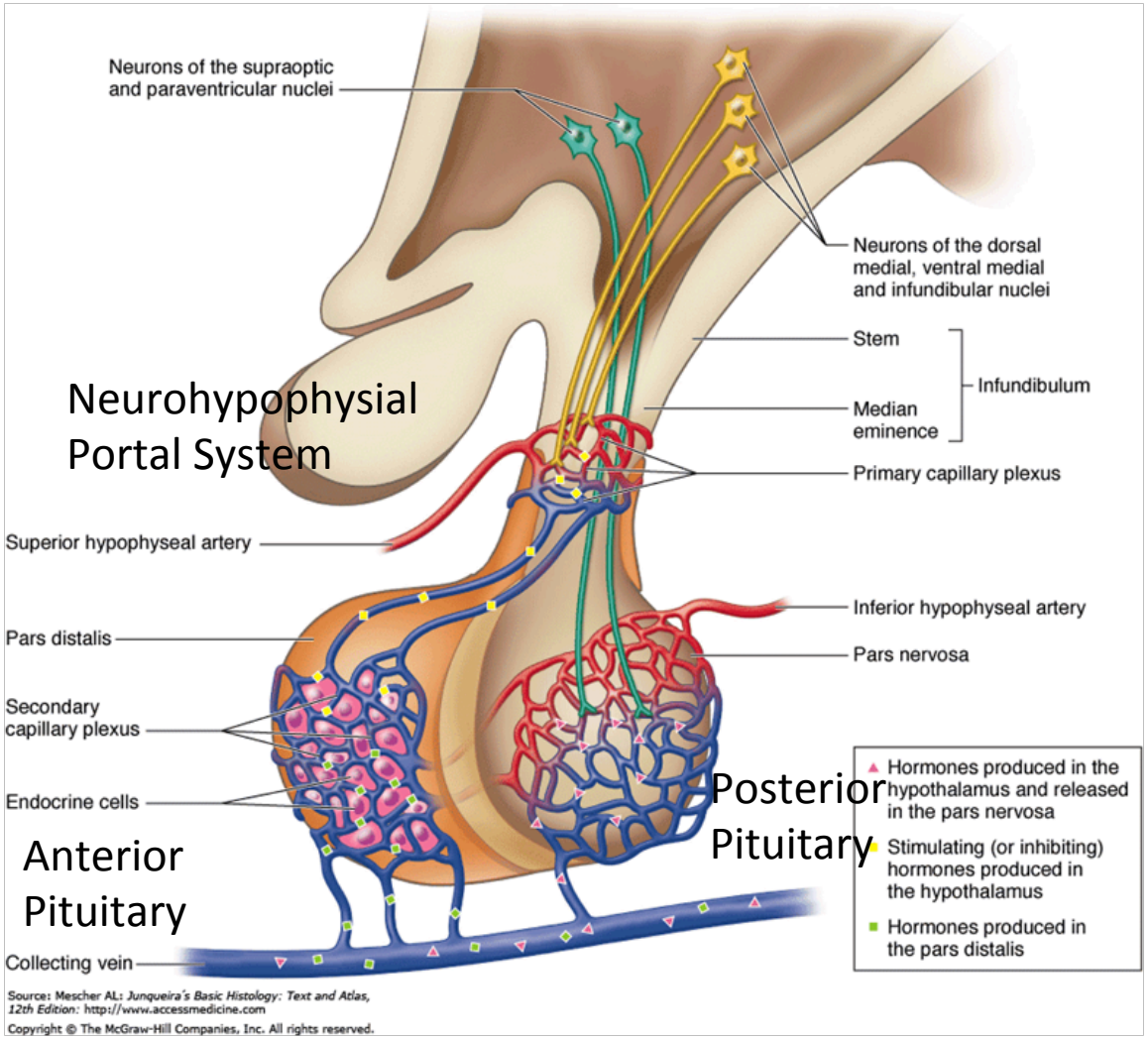


Subregions of the Hypothalamus



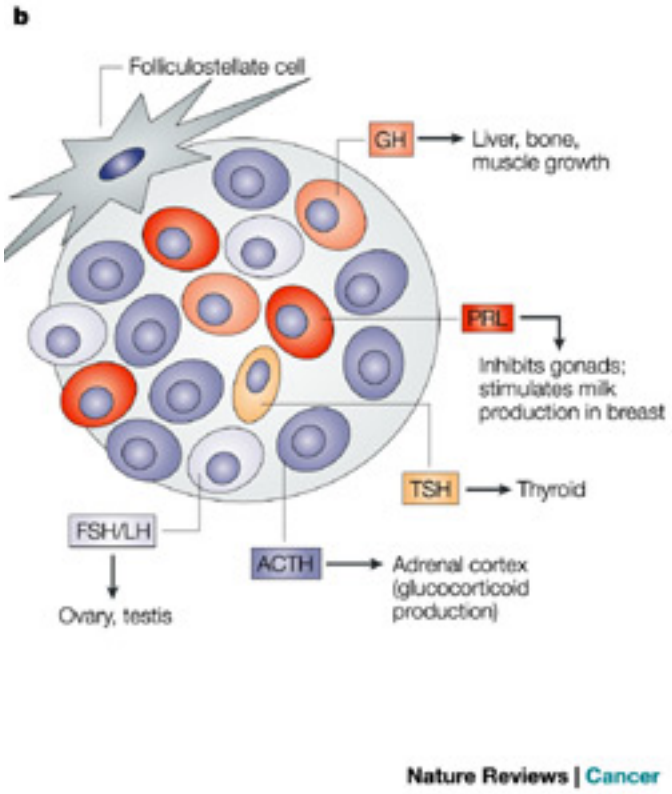
Anatomy of the Pituitary

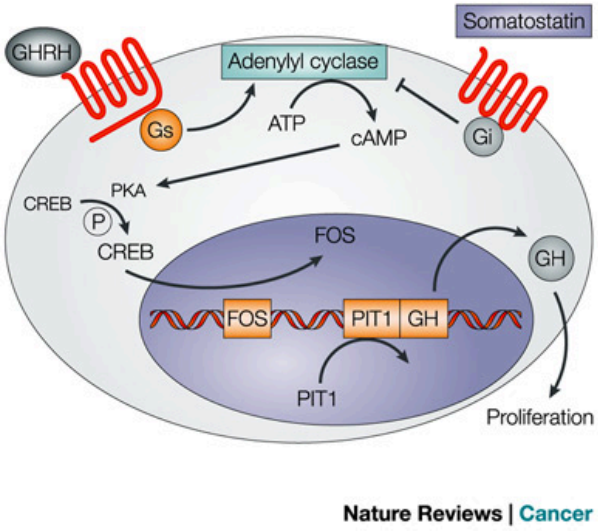




Anterior Pituitary

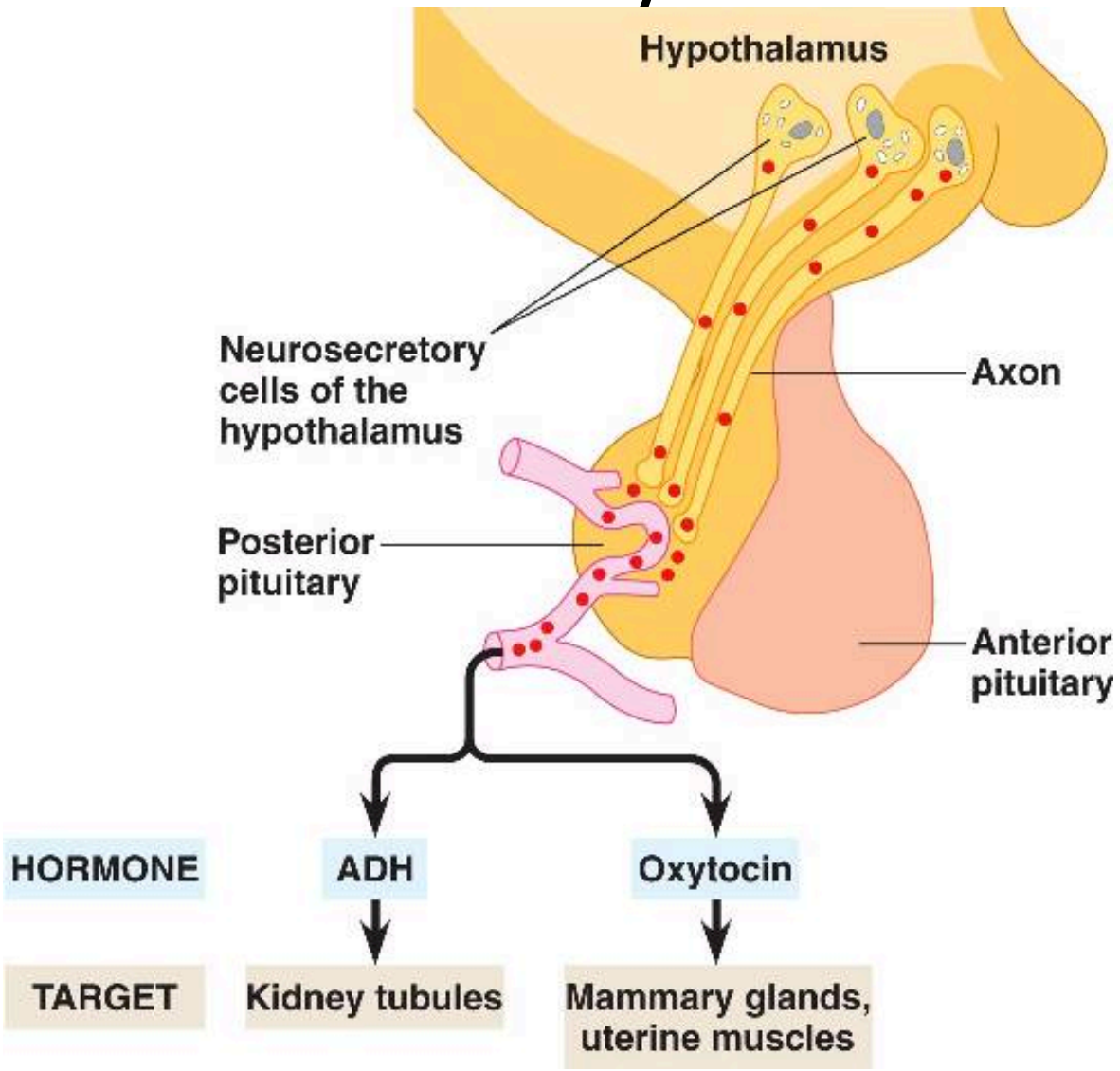
Hypothalamic	Anterior Pituitary	Cells
CRH	ACTH	Corticotropes
TRH	TSH/Prolactin	Thyrotropes/ Lactotropes
GnRH	LH/FSH	Gonadotropes
GHRH	GH (increase)	Somatotropes
Somatostatin	GH (decrease)	Somatotropes





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

The Infundibulum and the Posterior Pituitary



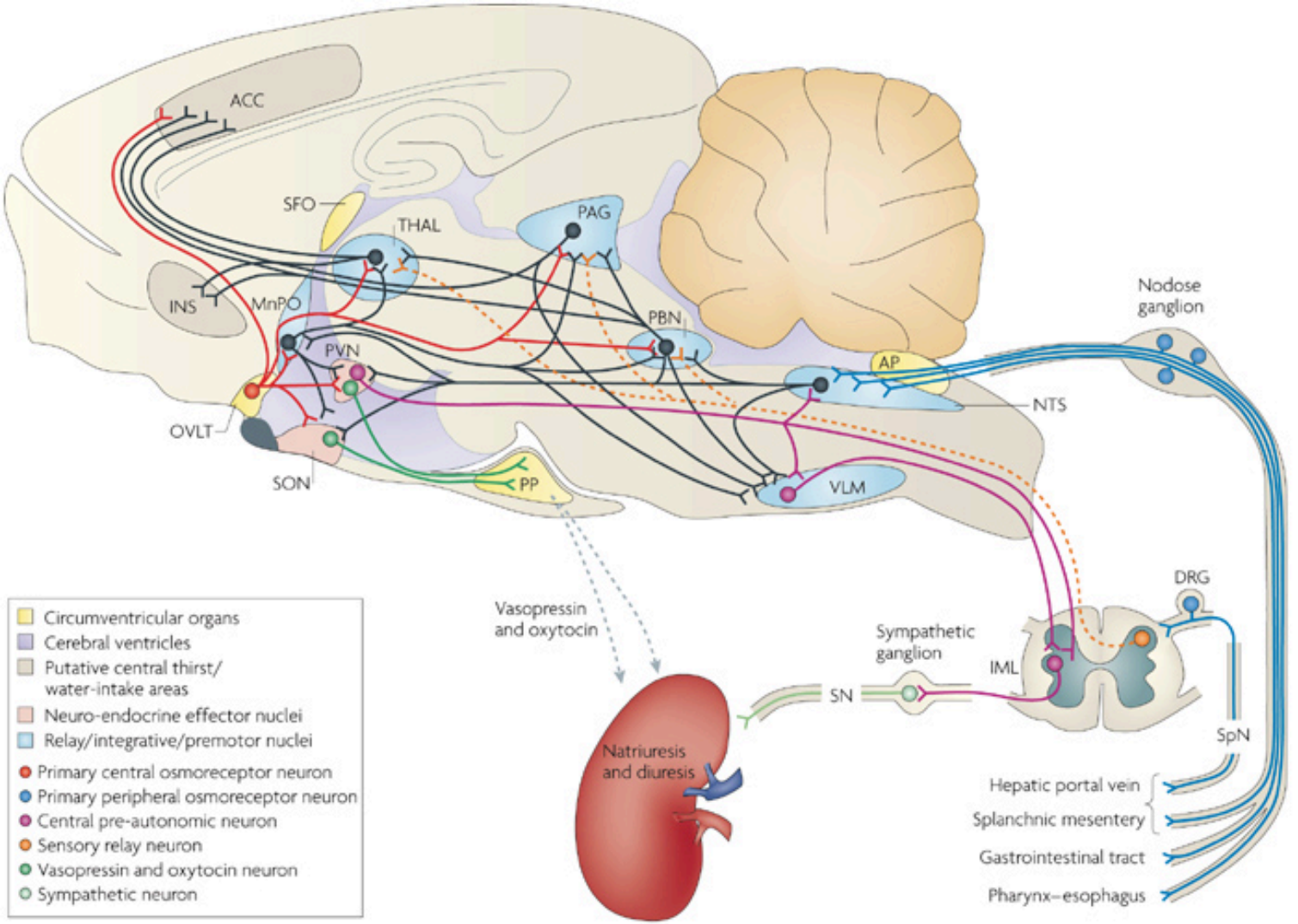
Why Regulate Water Retention?

1. Too much or too little blood volume
2. Salt concentration in blood is too high or too low

Vasopressin

What chemical type?	Peptide	9 Amino acids
Where is it made?	Posterior Pituitary	
What causes its release?	Hypothalamic osmoreceptors (PVN/SFO) and Mechanoreceptors (Carotid artery)	Increased osmotic pressure or reduced plasma volume
What are its receptors?	AVPR1-3	GPCR (Gs)
What tissues does it affect?	Kidney (Collecting Ducts)	Water Reuptake (AQP2 trafficking)
	Vascular System	Vasoconstriction
	Anterior Pituitary	ACTH Release
How does it get turned off?	Normalization of volume/ osmolality and AVPR receptor desensitization (arrestins)	

Vasopressin Release



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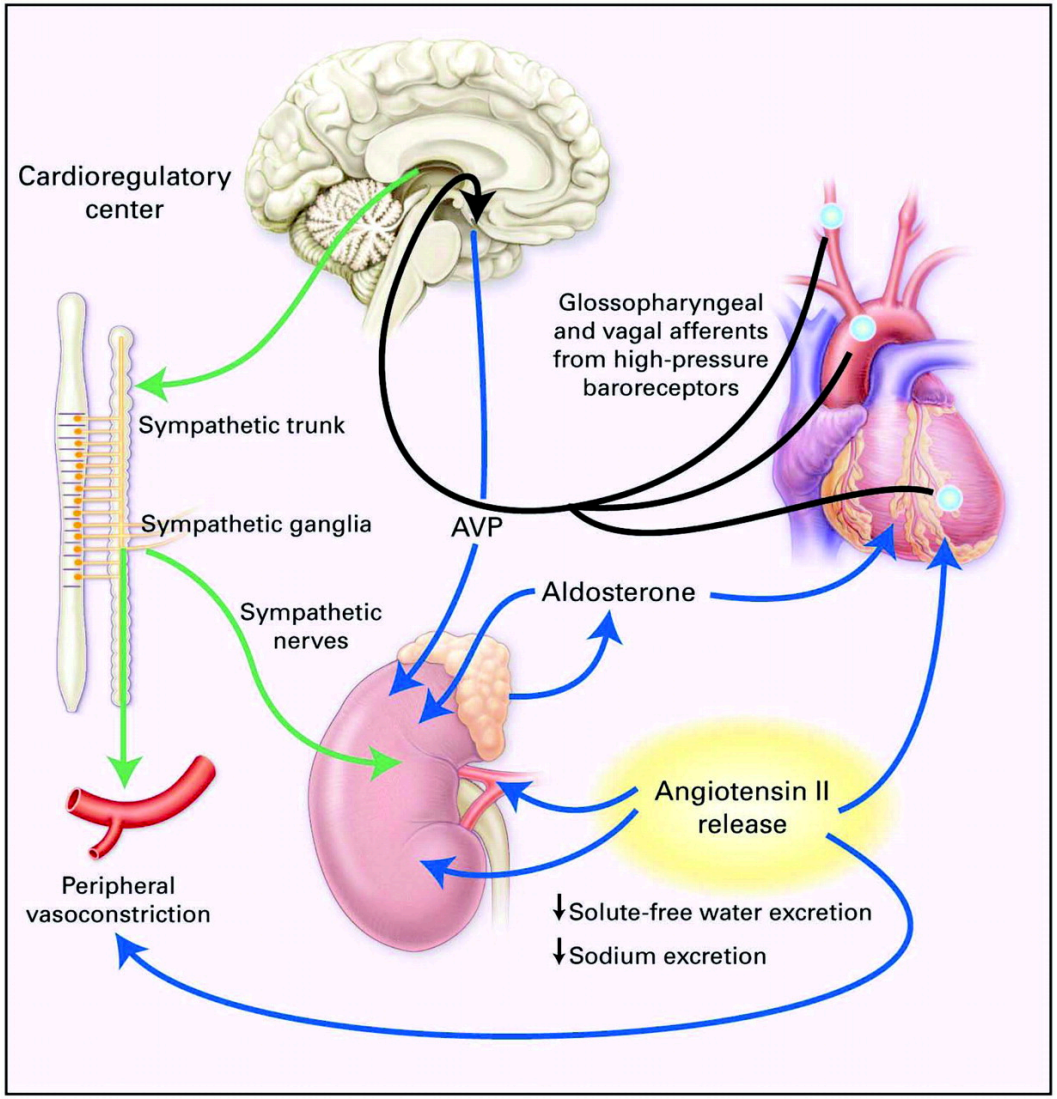
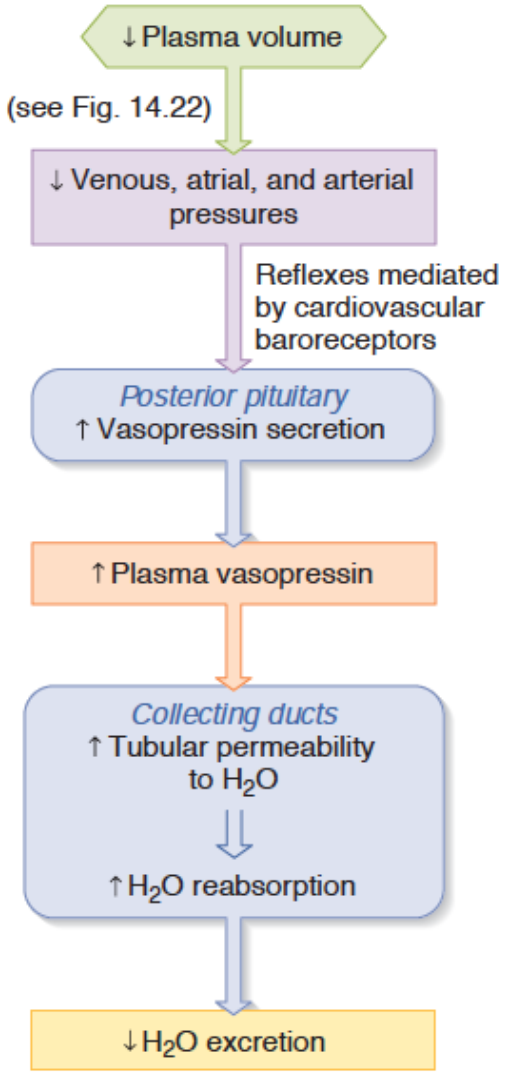
Volume, Osmolality and Vasopressin

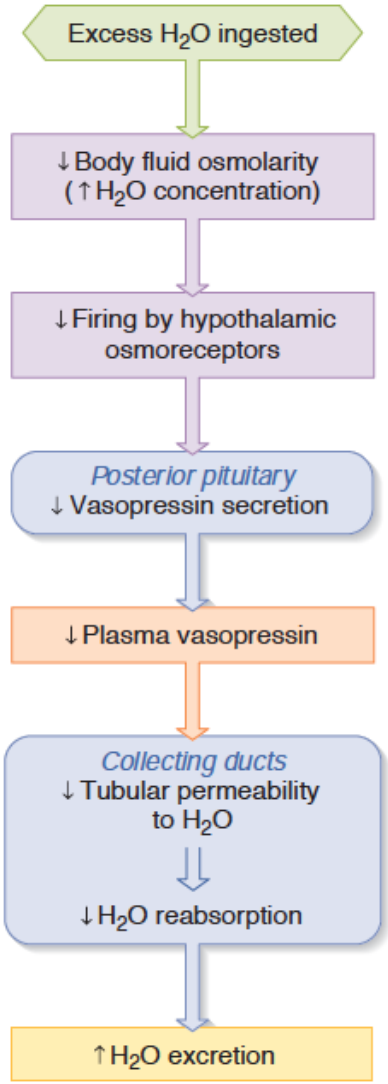
- Vasopressin is released due to **decreased blood volume** or **increased salt concentration**
  - Decreased blood volume is detected by mechanoreceptors at the carotid sinus
  - Increased salt concentration is detected by osmoreceptors in the SFO and hypothalamus
- In either case, the hormone dilutes the blood by retaining water.

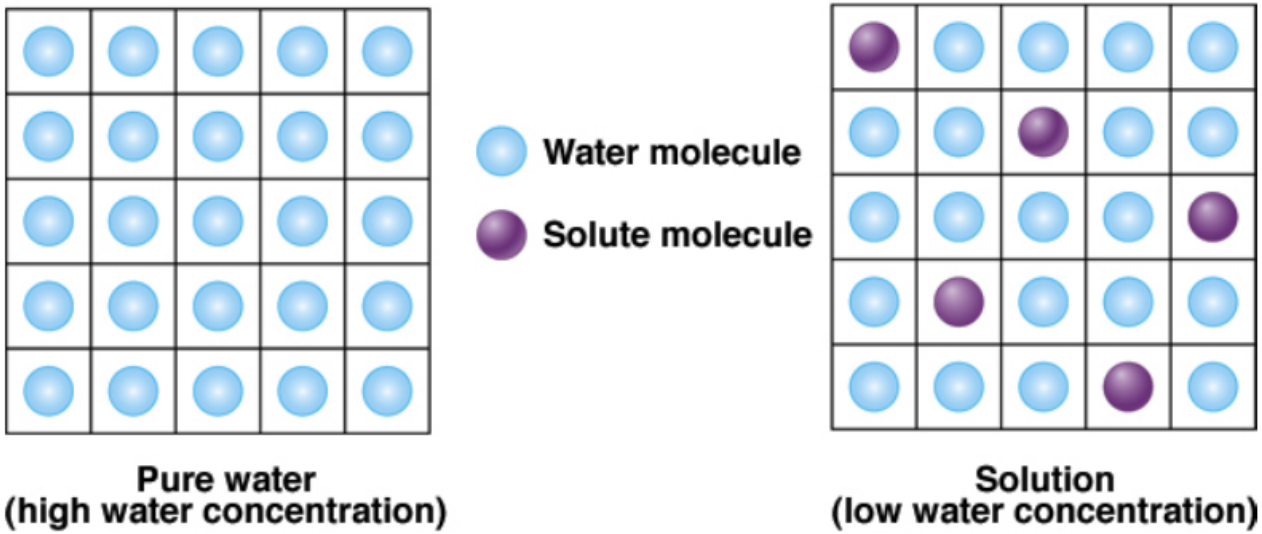
Baroreceptor Regulation of Vasopressin Release



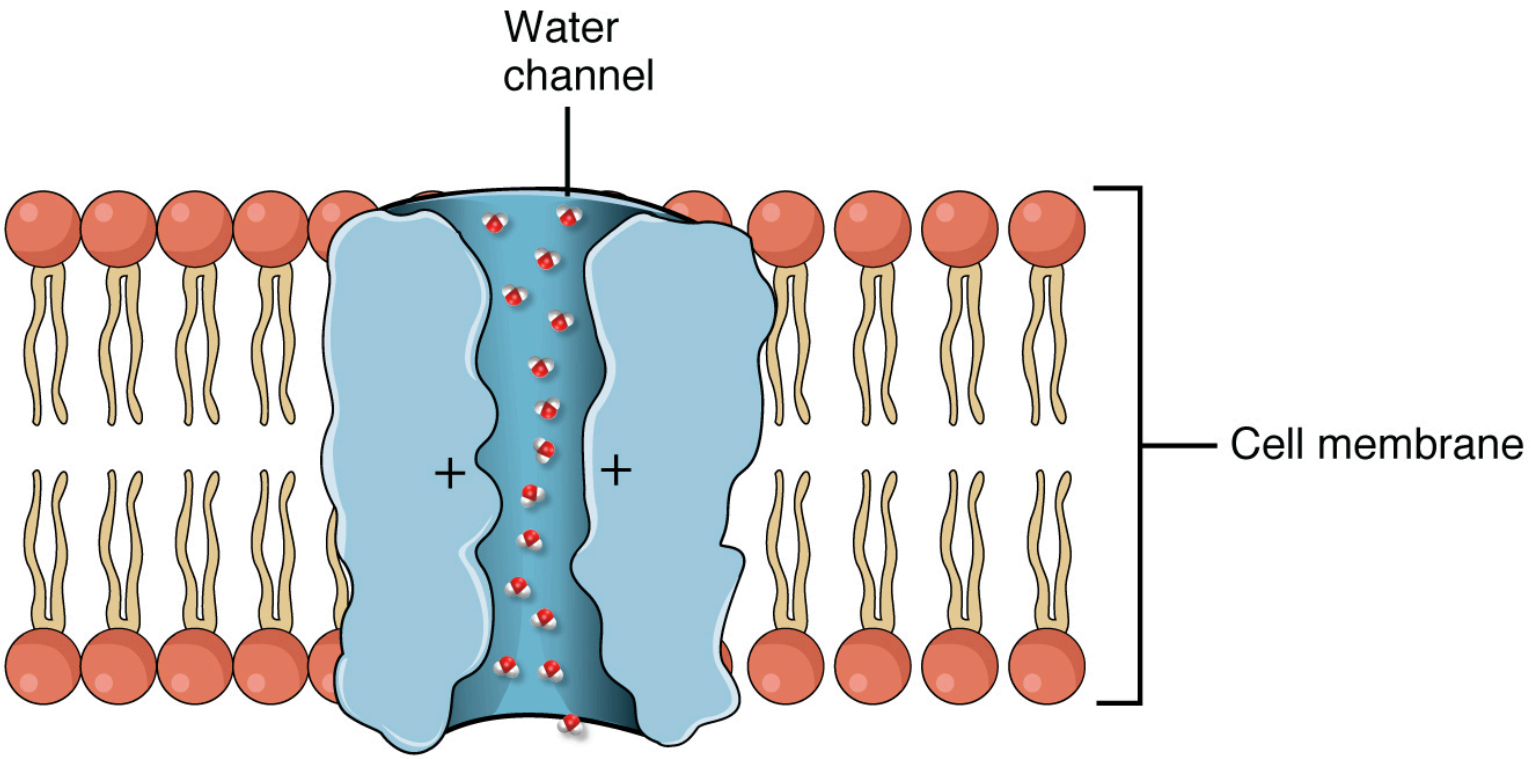


Osmoreceptor Regulation of Vasopressin Release



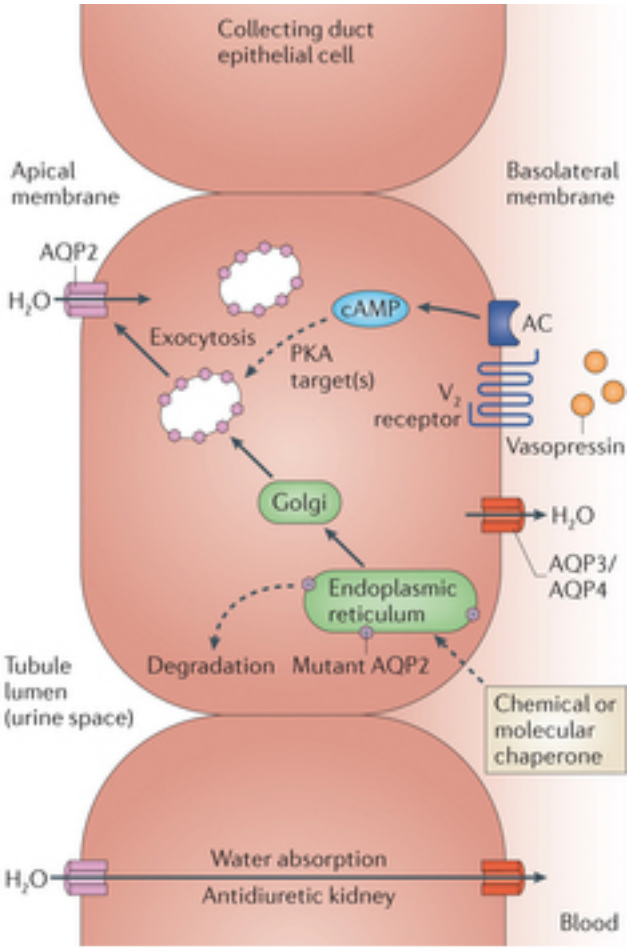


Vasopressin Regulates Aquaporin Trafficking



Effects of Vasopressin on the Kidney

Collecting Tubules



Blood

Conditions with Altered Vasopressin Function

- Lack of vasopressin signaling
- Too much vasopressin signaling

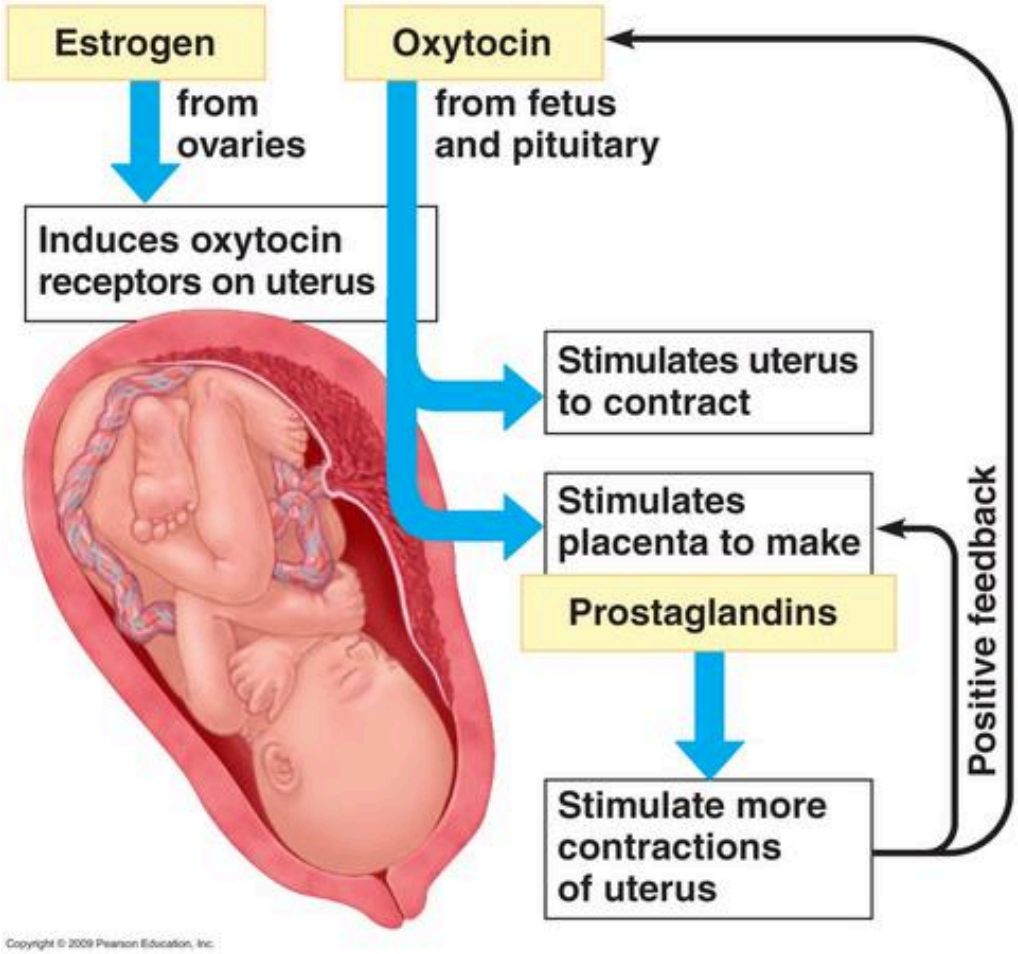
Discuss with Folks Nearby

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

Oxytocin Summary

What chemical type	Peptide	
Where is it made?	Posterior Pituitary	
What causes its release?	Synaptic activation in Hypothalamus (PVN, mechanism unclear)	
What are its receptors?	OXTR	
What tissues does it affect?	Uterus	Contractions
	Mammary Glands	Let-Down Reflex (Lactation)
	Neural	Positive Social Interactions
How does it get turned off?	Delivery (reduced input)	

Oxytocin During Delivery



Oxytocin During Lactation

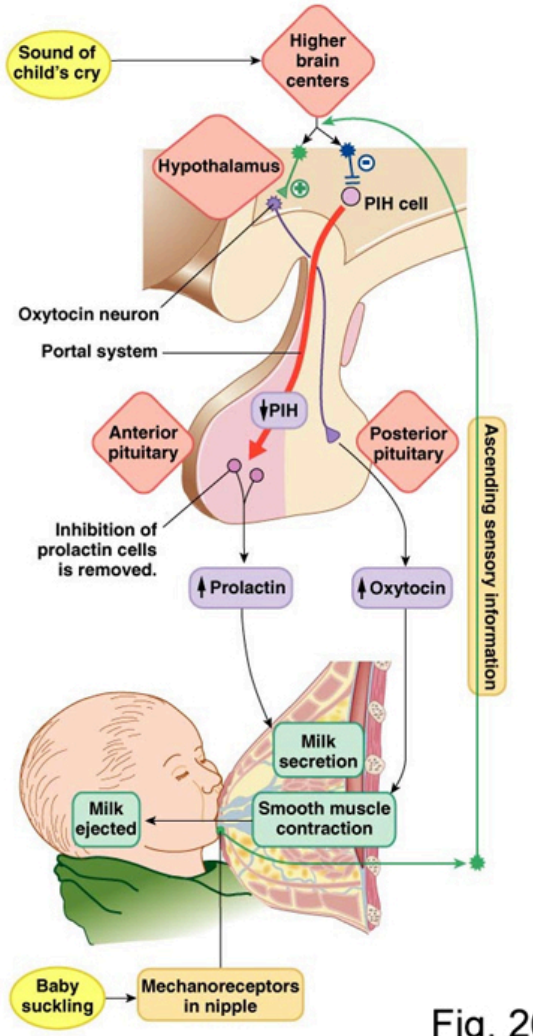


Fig. 26-23

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 acronymns.
- 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.

Your Future

- Endocrine Control Systems
- Neuroendocrinology and the Posterior Pituitary
- **Endocrine Control of Growth**
- **Adrenals and Stress Hormones**
- Hypothalamus and Endocrine Control of Appetite
- Pancreatic Hormones and Metabolic Control
- Thyroid Hormones (KP)
- Calcium Homeostasis (MF)
- Reproductive Hormones (HP)

THE END