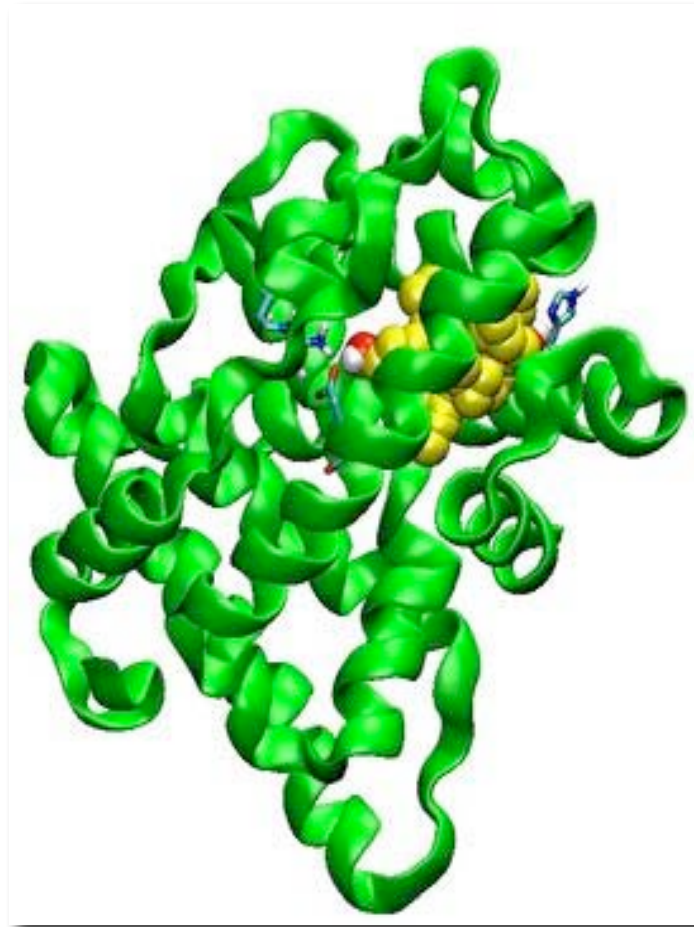


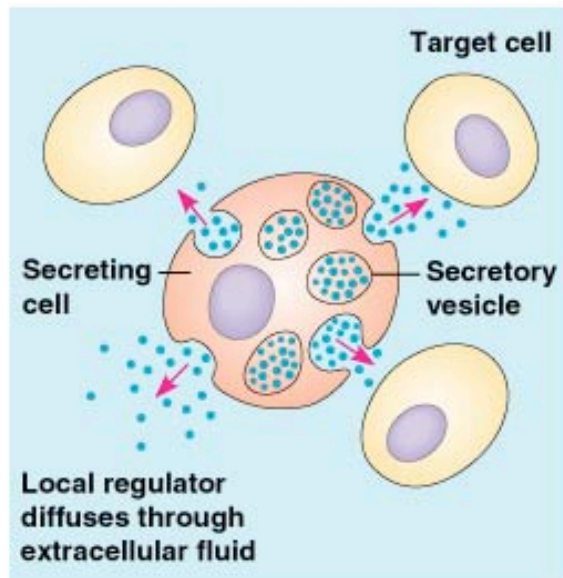
# Basic Endocrinology



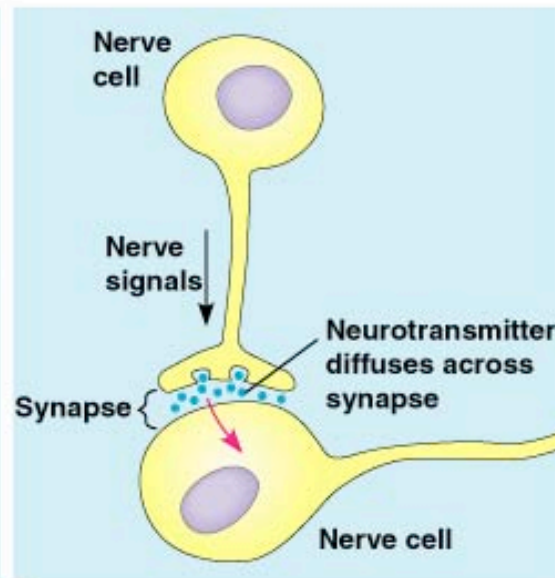
Estrogen Receptor

# Introduction

- ◆ System of ductless glands
- ◆ Produce chemical messengers called **HORMONES**
  - ◆ hormones help integrate body signals with neural and immune systems
- ◆ Hormones travel to target tissue/cell via
  - ◆ blood stream
  - ◆ intercellular space

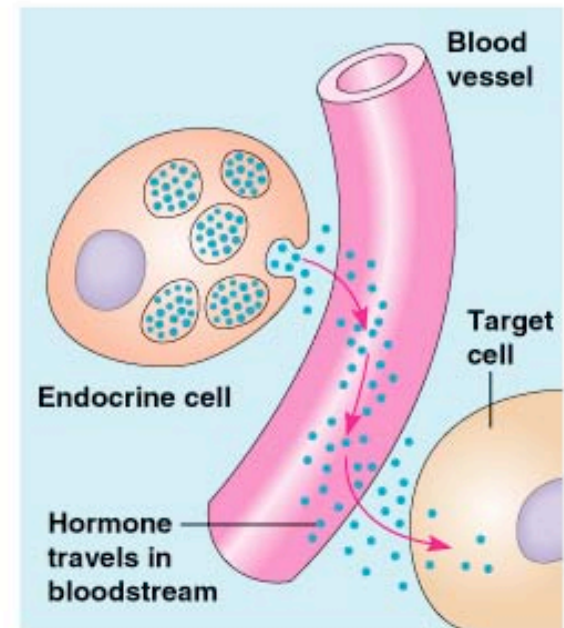


**Paracrine signaling**



**Synaptic signaling**

**(a) Local signaling**



**(b) Hormonal signaling**

# Hormones

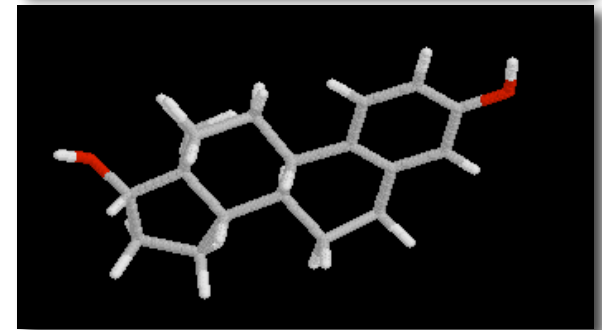
★ Come in two major forms

★ peptides / proteins

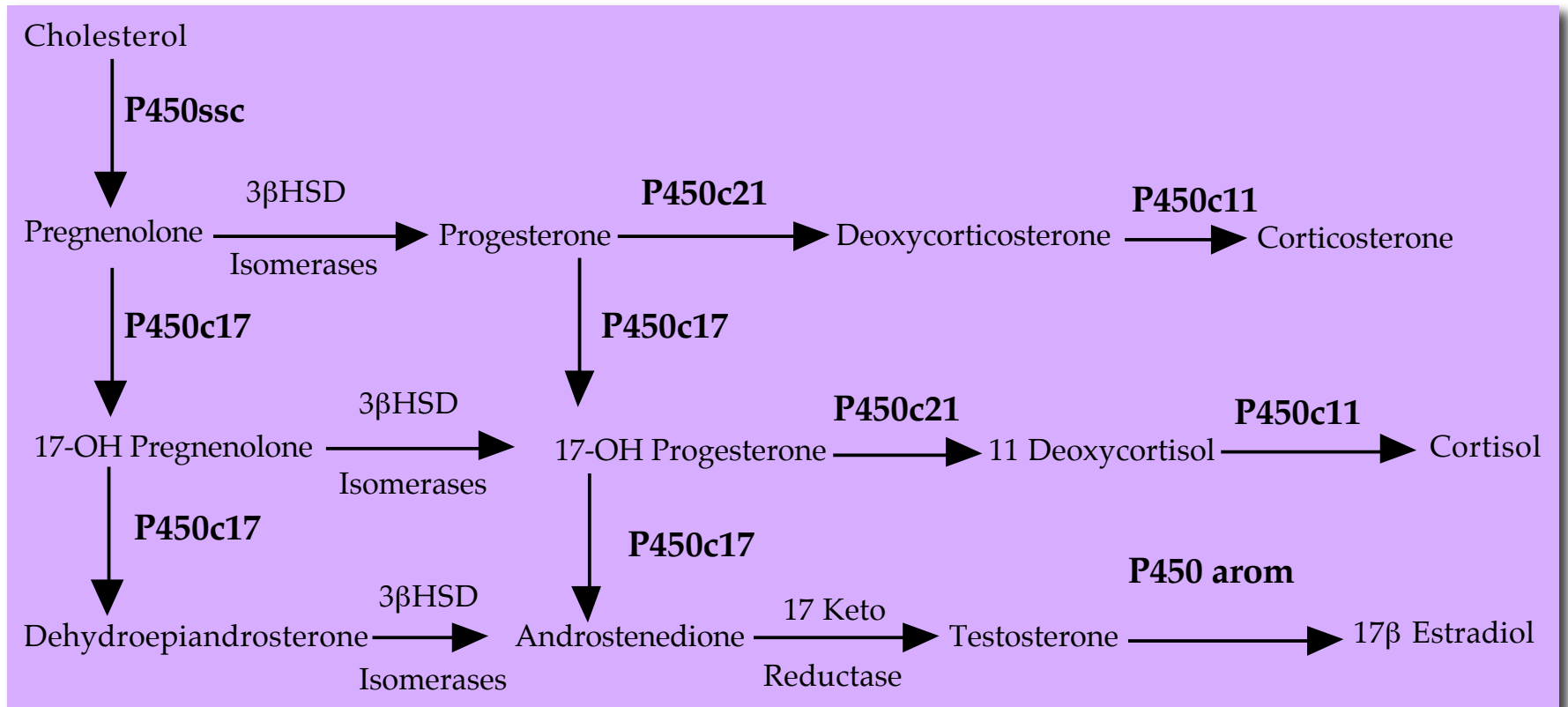
★ growth hormone, insulin, oxytocin

★ Lipid-based hormones

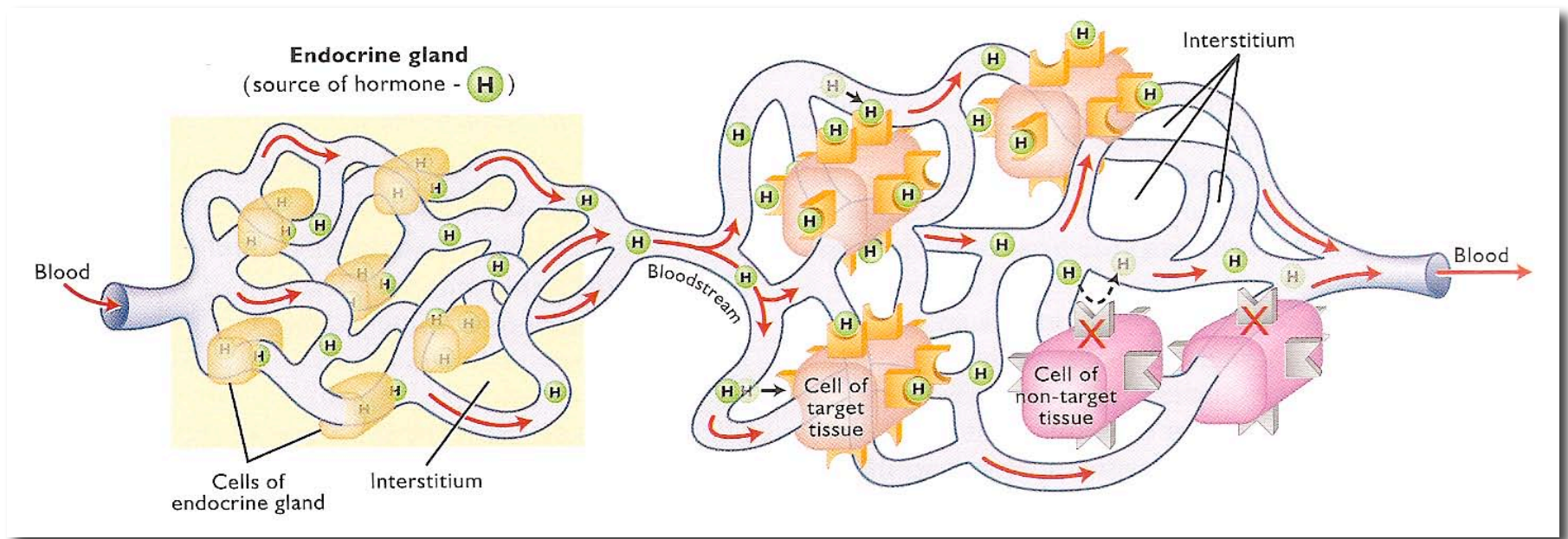
★ steroids and prostaglandins



# Steroidogenesis



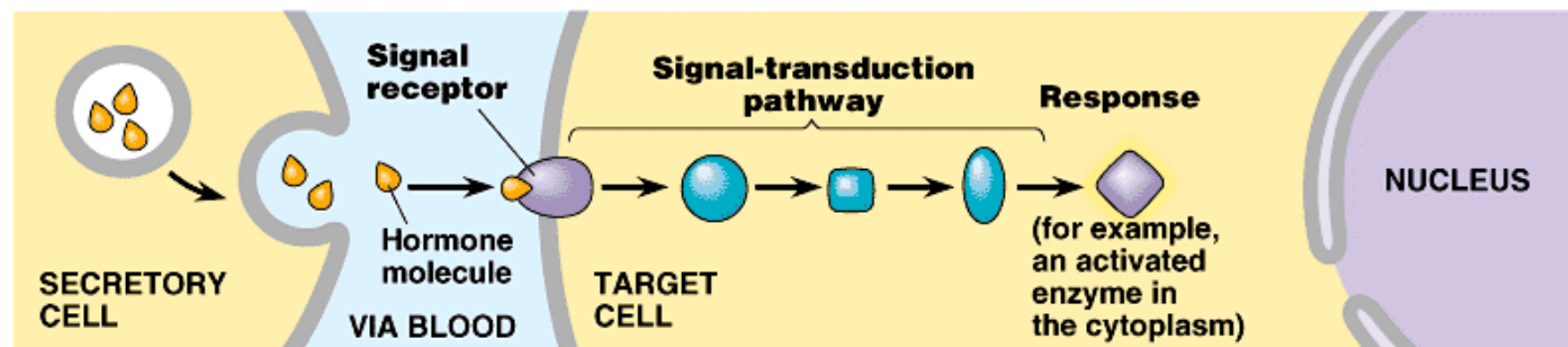
# Target Tissues



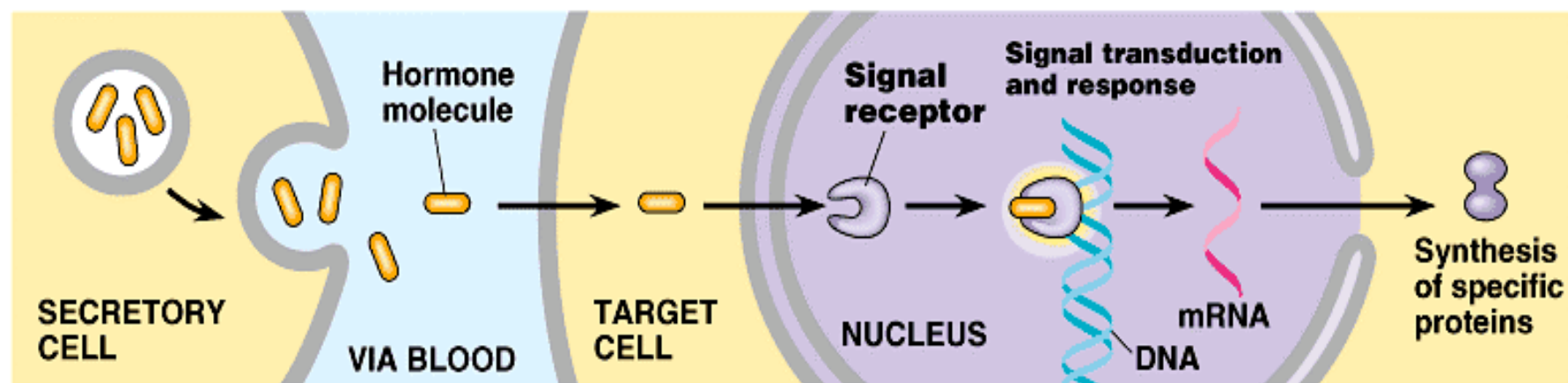
# Receptors

- at the target cell, a hormone interacts with a RECEPTOR
- peptide hormones usually interact with membrane receptor
- steroid hormones interact with nuclear receptor
  - many steroid receptors are transcription factors





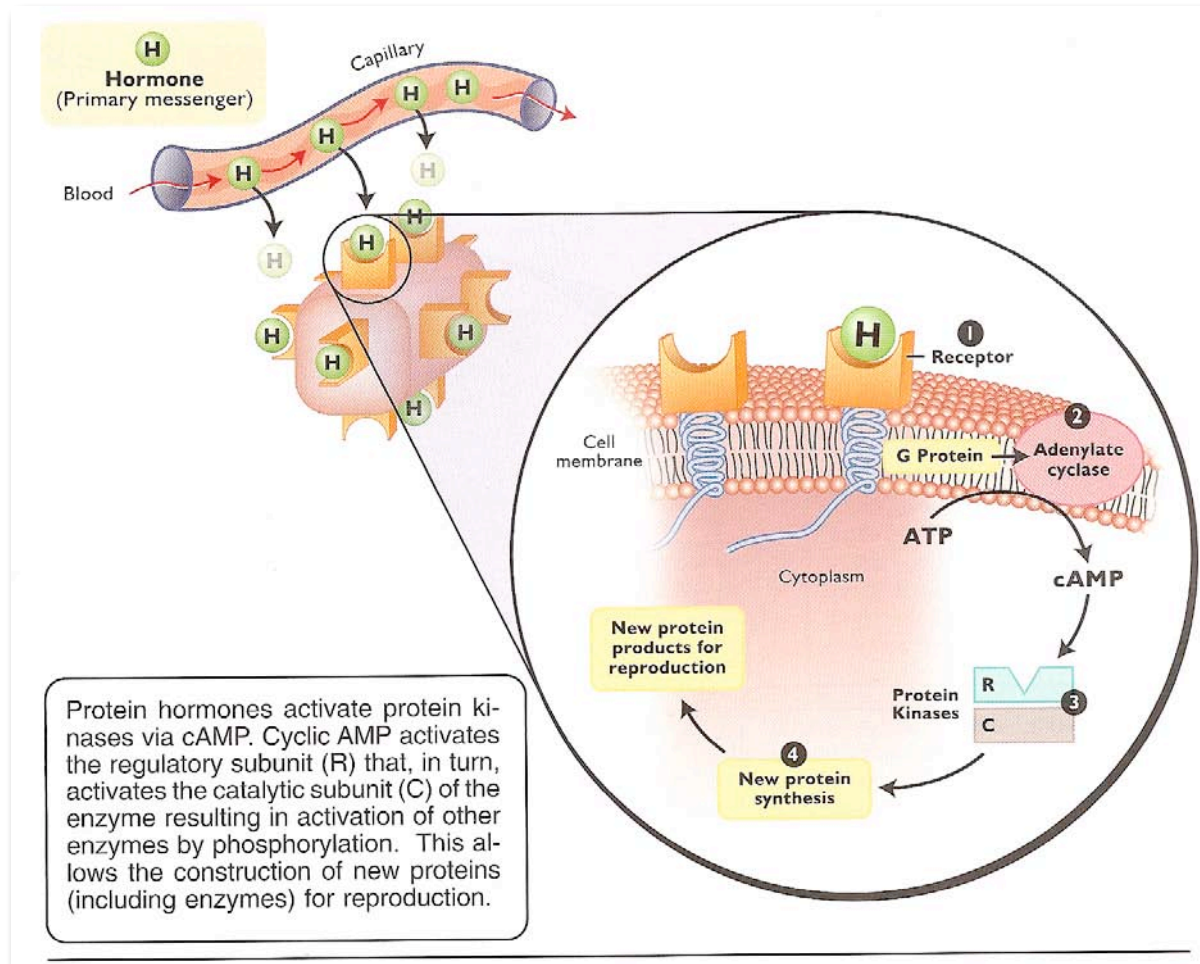
(a) Receptor in plasma membrane



(b) Receptor in cell nucleus



1. Membrane receptor activates G protein
2. G protein + GTP activates adenyl cyclase
3. ATP converted to cAMP (2° messenger)
4. Results = cellular response amplified @ each step



(a) Signaling pathway	(b) Number of molecules activated
<b>RECEPTION</b> Binding of epinephrine to G-protein-linked receptor	1 molecule
<b>TRANSDUCTION</b> Inactive G protein → Active G protein	$10^2$ molecules
Inactive adenylyl cyclase → Active adenylyl cyclase	$10^2$ molecules
ATP → Cyclic AMP	$10^4$ molecules
Inactive protein kinase A → Active protein kinase A	$10^4$ molecules
Inactive phosphorylase kinase → Active phosphorylase kinase	$10^5$ molecules
Inactive glycogen phosphorylase → Active glycogen phosphorylase	$10^6$ molecules
<b>RESPONSE</b> Glycogen → Glucose-1-phosphate	$10^8$ molecules

## Amplification

Signal-transduction pathways allow for small amounts of a hormone to have a large effect

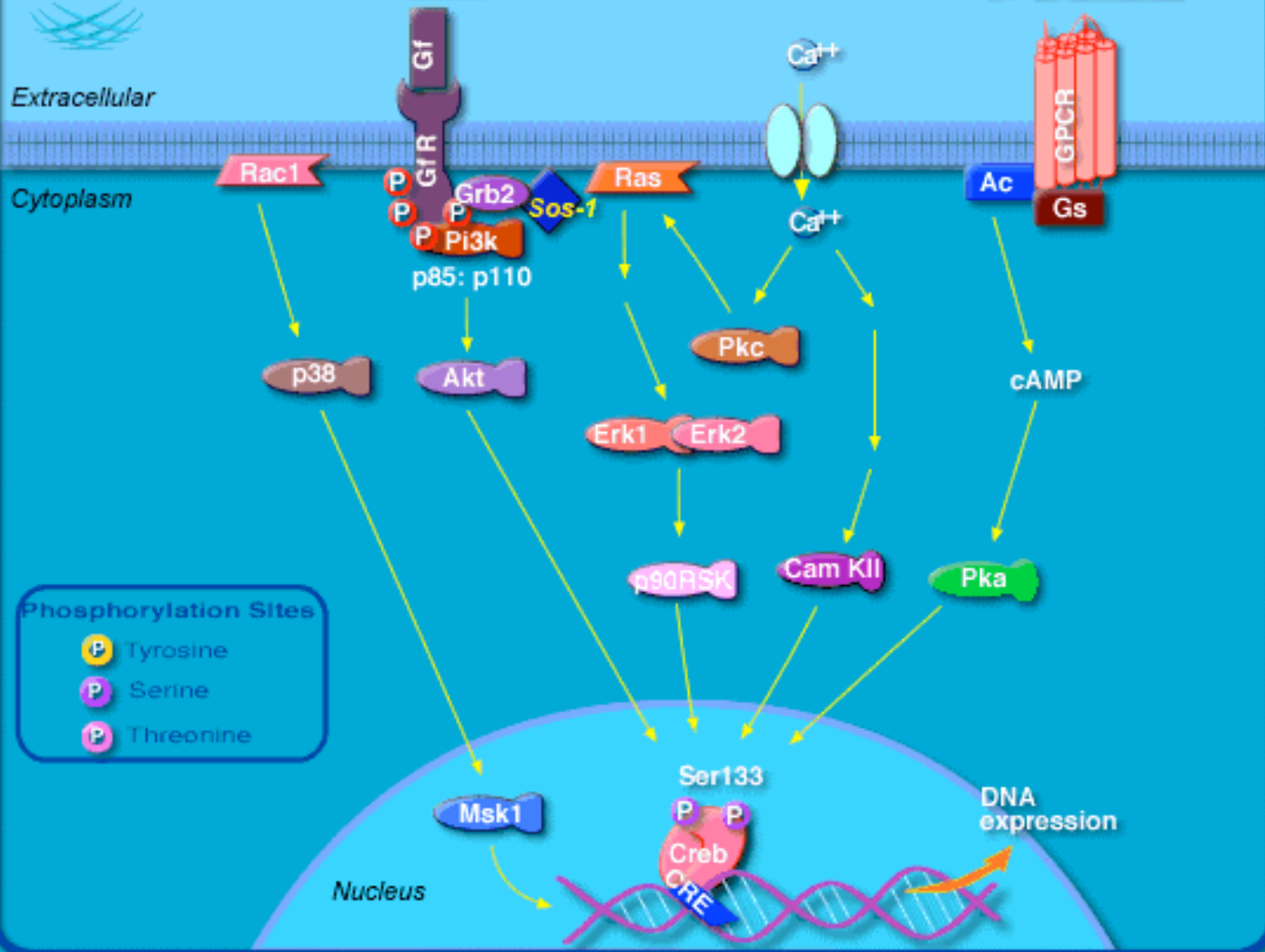


Extracellular

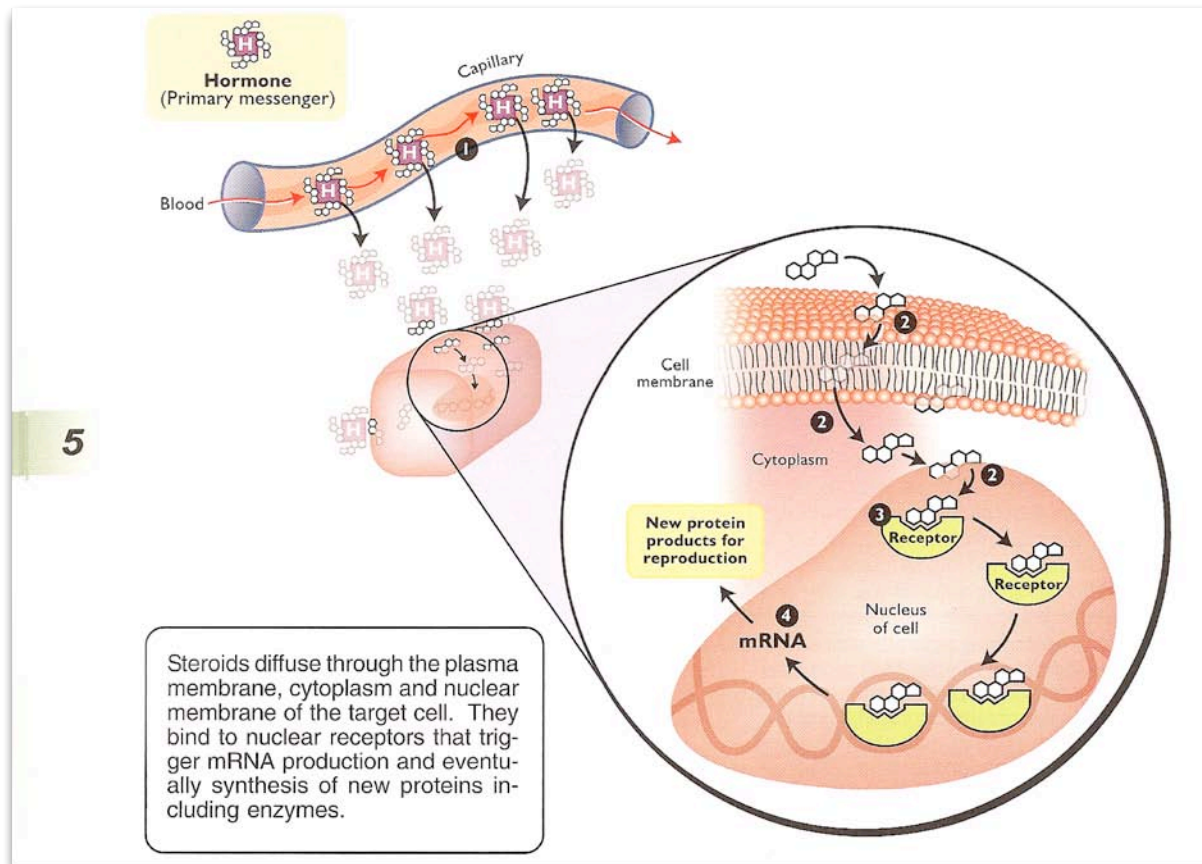
Cytoplasm

Growth Factors

NT's/Hormones



1. Steroid binds to cytoplasmic or nuclear receptor(transcription factor)
2. Receptor hormone complex binds to DNA in nucleus
3. Stimulates transcription of mRNA



# Nuclear Receptor Evolution

- Steroid receptors
  - Transcription factors
  - Large family of related molecules
    - Gene duplication
    - Ancestral form unknown

# The Nuclear Receptor Superfamily



## KNOWN RECEPTORS

### Classical receptors (from biochemistry)

GR	cortisol
MR	aldosterone
PR $\alpha,\beta$	progesterone
AR $\alpha,\beta$	testosterone
ER $\alpha,\beta,\gamma$	estrogen
VDR	1,25 (OH) <sub>2</sub> vit D3
TR $\alpha,\beta$	Thyroid hormone
EcR	20-OH ecdysone

### EX-orphans

RAR $\alpha,\beta,\gamma$	all-trans RA
RXR $\alpha,\beta,\gamma$	9- <i>cis</i> RA, ?
PPAR $\alpha,\beta,\gamma$	fatty acids
LXR $\alpha,\beta$	oxy-sterols
FXR $\alpha,\beta$	bile acids
BXR $\alpha,\beta$	benzoates

### Nearly EX-orphans

CAR	androstans, xenobiotics
SXR	steroids, xenobiotics
PXR.1,2	pregnanes, xenobiotics

## ORPHAN RECEPTORS

### Vertebrate $\longleftrightarrow$ *Drosophila*

TR-2 $\alpha,\beta$	DHR78
NGFI-B $\alpha,\beta,\gamma$	DHR38
ROR $\alpha,\beta,\gamma$	DHR3
Rev-erb	E75, E78
SF-1 $\alpha,\beta$	<i>FTZ-F1<math>\alpha,\beta</math></i>
COUP $\alpha,\beta,\gamma$	<i>svp</i>
HNF-4 $\alpha,\beta$	HNF-4
TLX	<i>tll</i>

### No known homologs

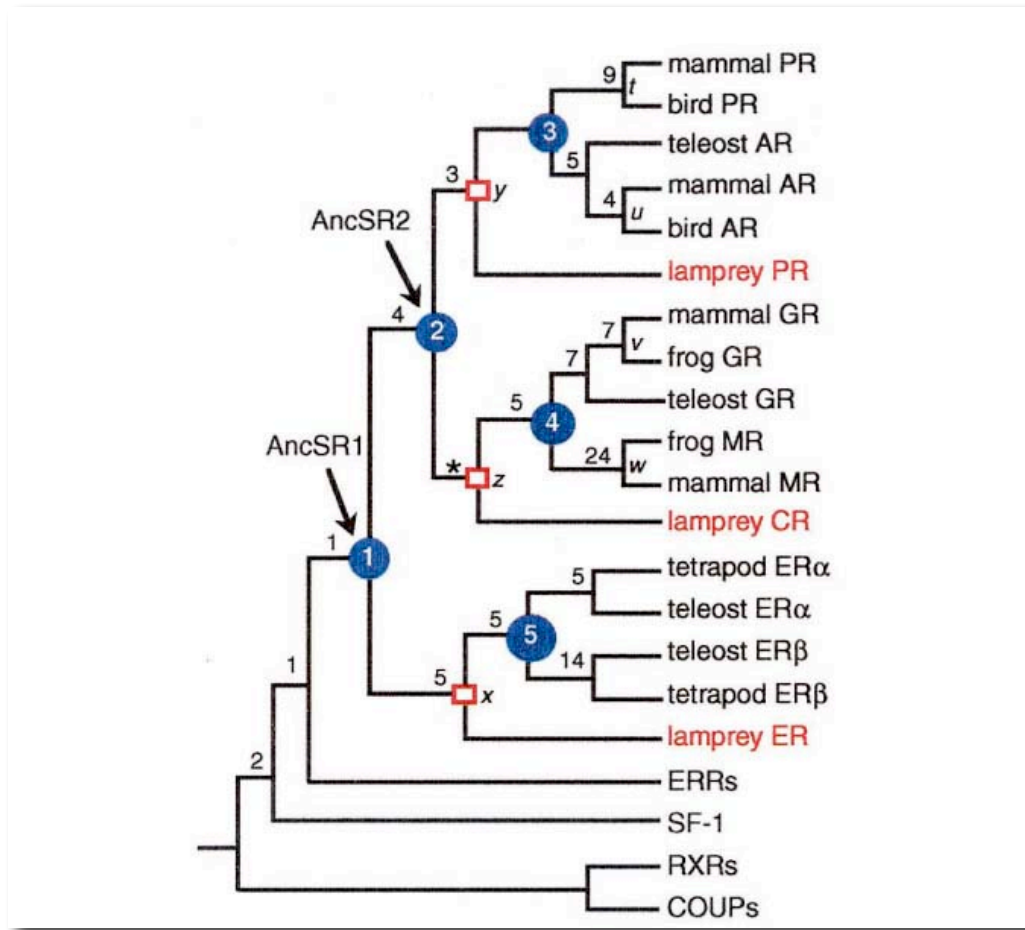
ERR $\alpha,\beta,\gamma$	<i>knirps</i>
DAX-1	<i>knirps-related</i>
SHP	<i>egon</i>
GCNF	DHR96

*C. elegans* - 2-3% of genes are nuclear receptors ~250  
*Drosophila* - only about 20 nuclear receptors

Blumberg, UC Irvine



# Evolution of Steroid Receptors



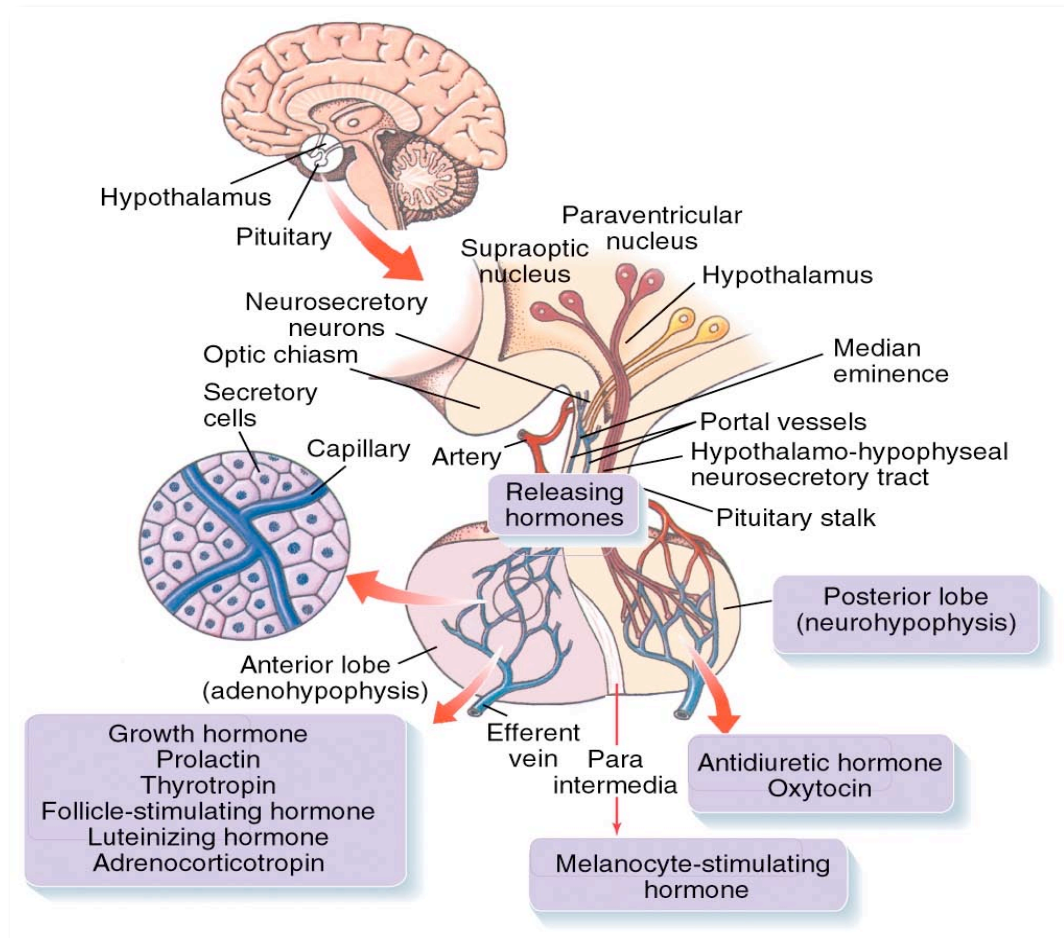
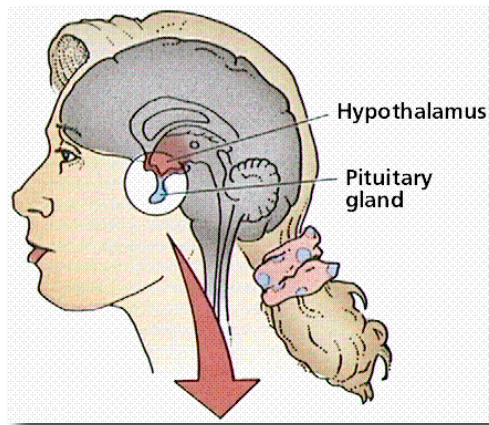
- Two serial duplications
- 1st = ER and 3-ketosteroid R
- 2nd = duplication of 3-KR
  - Corticoid receptor (CR)
  - 3-ketogonadal steroid R
    - Androgen
    - Progesterone
    - Or both
- These 3 duplicated again to form 6 common forms found today in vertebrates

Thornton (2001) PNAS 98:5671-5676

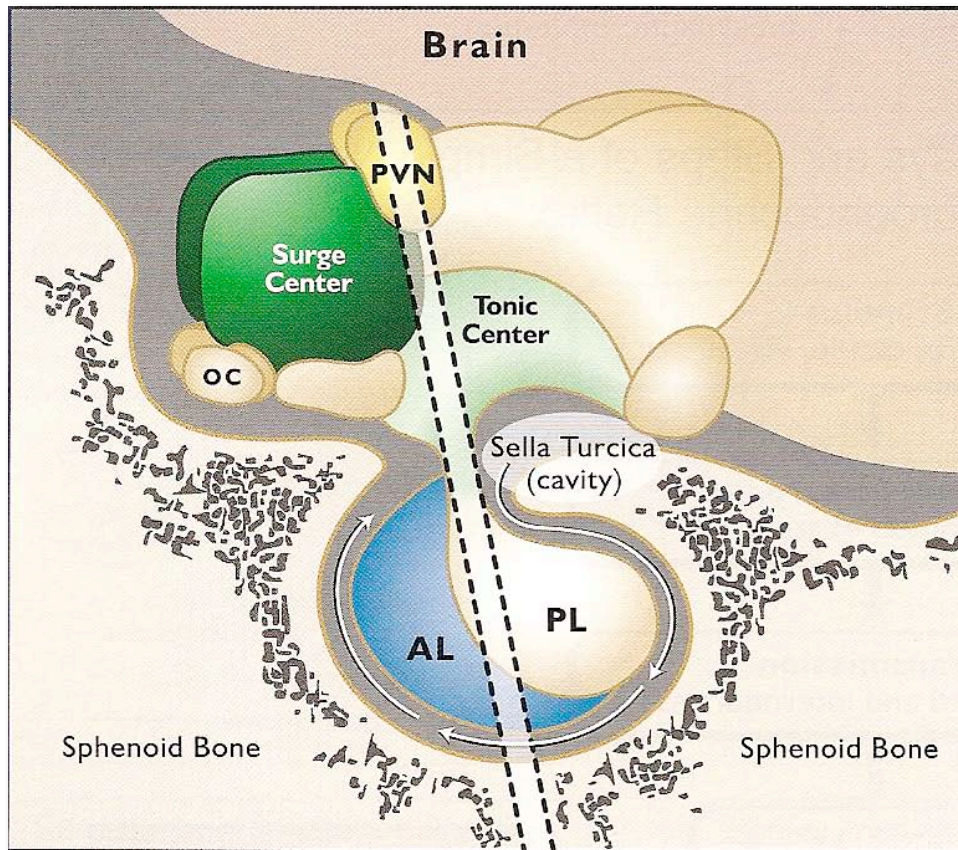


# Hypothalamus - Pituitary

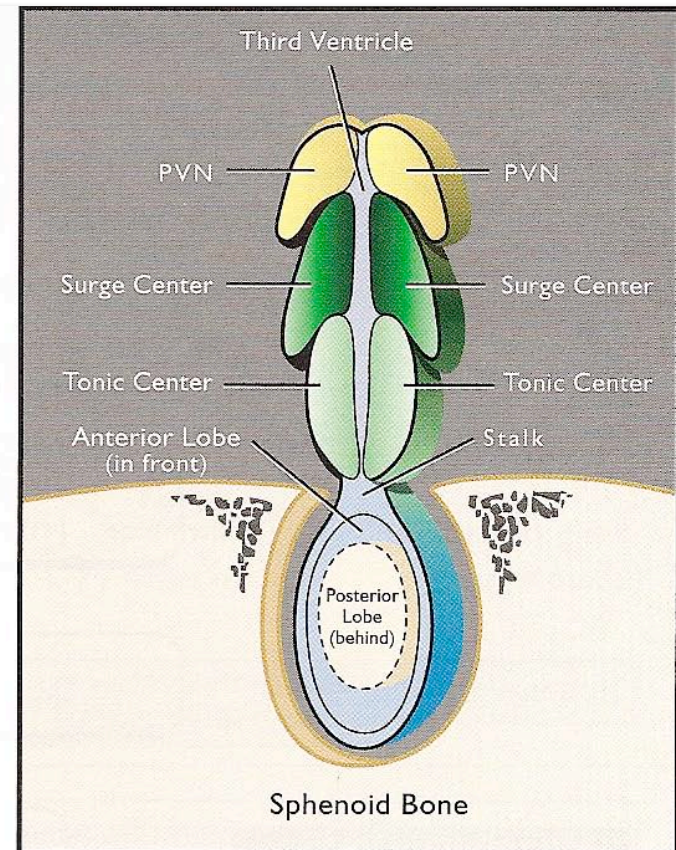
- considered the master organs of the endocrine system



# Hypothalamus



**Sagittal view**

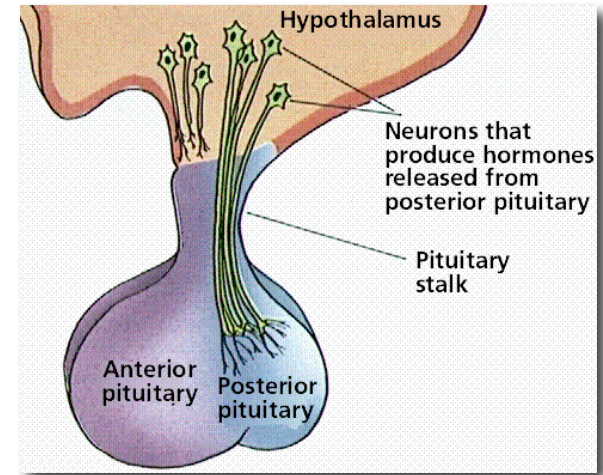


**Frontal view**



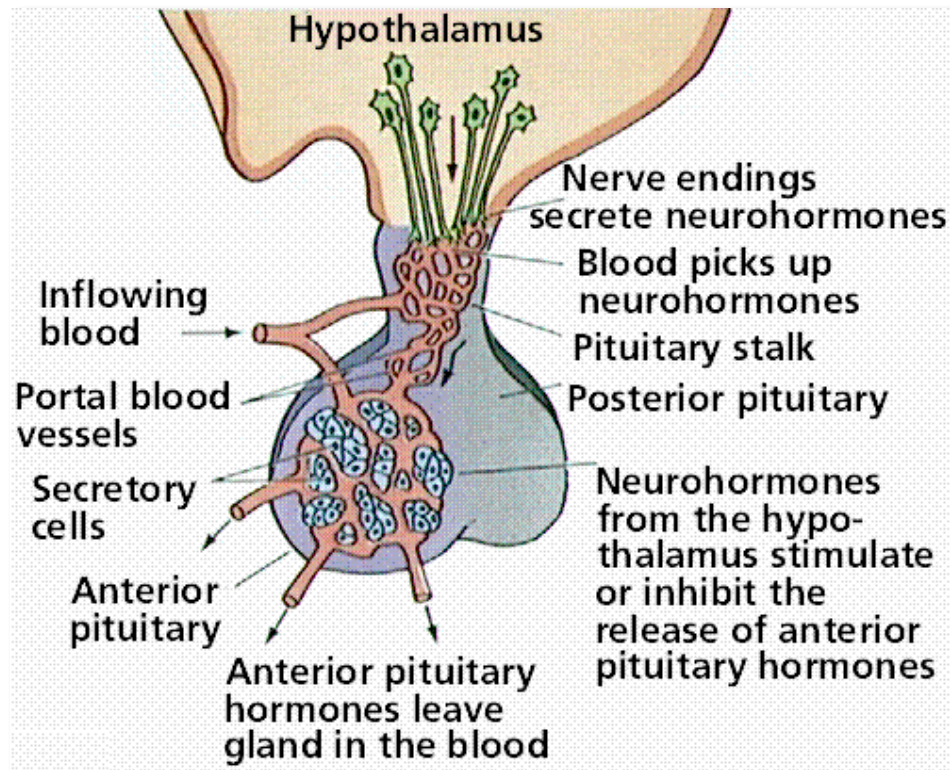
# Hypothalamus

- bottom of 3rd ventricle of brain
- secretes



- neurohormones that influence synthesis and release of pituitary hormones
- examples:
  - gonadotropin releasing hormone (GnRH)
  - thyrotropin releasing hormone (TRH)
  - dopamine - Prolactin releasing inhibiting factor
- released into hypothalamo-hypophysial portal system
  - blood vessel system between hypothalamus and pituitary

# Hypothalamo-hypophysial Portal System

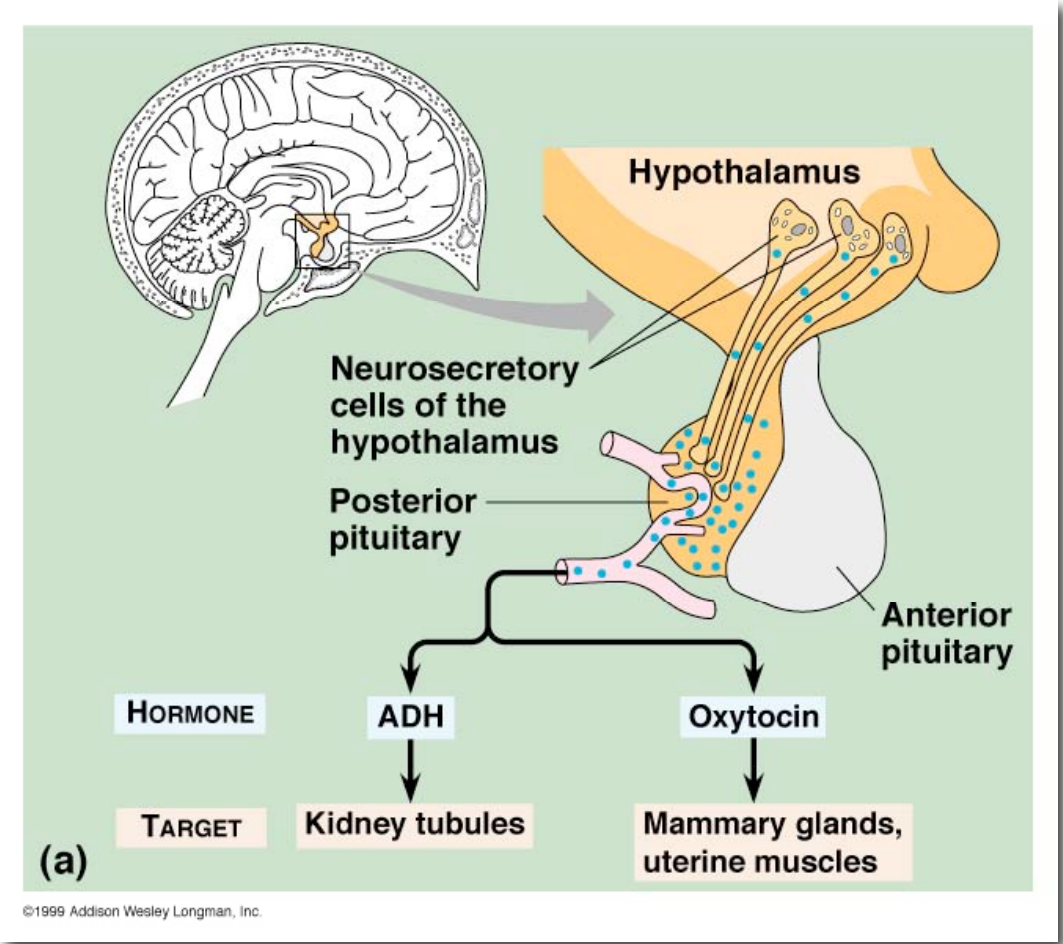


- A portal system
  - Vein - vein
  - Low pressure system
- Delivers hypothalamic factors to pituitary

# Pituitary - Hypophysis

- center of the soul in classical times
- derived from two tissues embryologically
  - **adenohypophysis** (anterior pituitary) - derived from outpocketing of mouth - Rathke's pouch
  - **neurohypophysis** (posterior pituitary) - derived from outpocketing of third ventricle and hypothalamus
- these two extensions meet, interact and form pituitary with two distinct regions as noted

# Neurohypophysis



# Adenohypophysis

