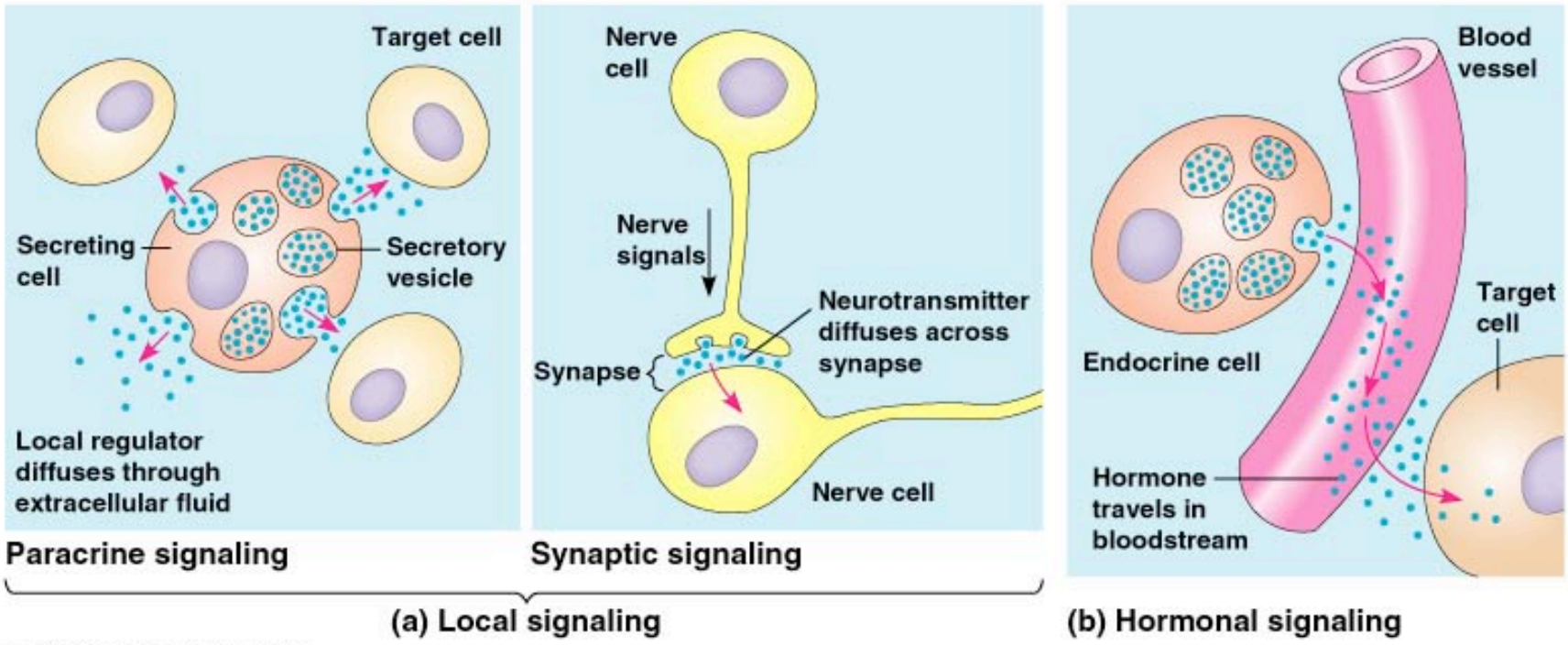
Basic Endocrinology

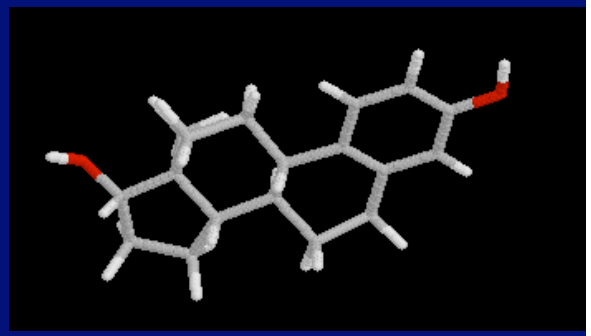
Introduction

- 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

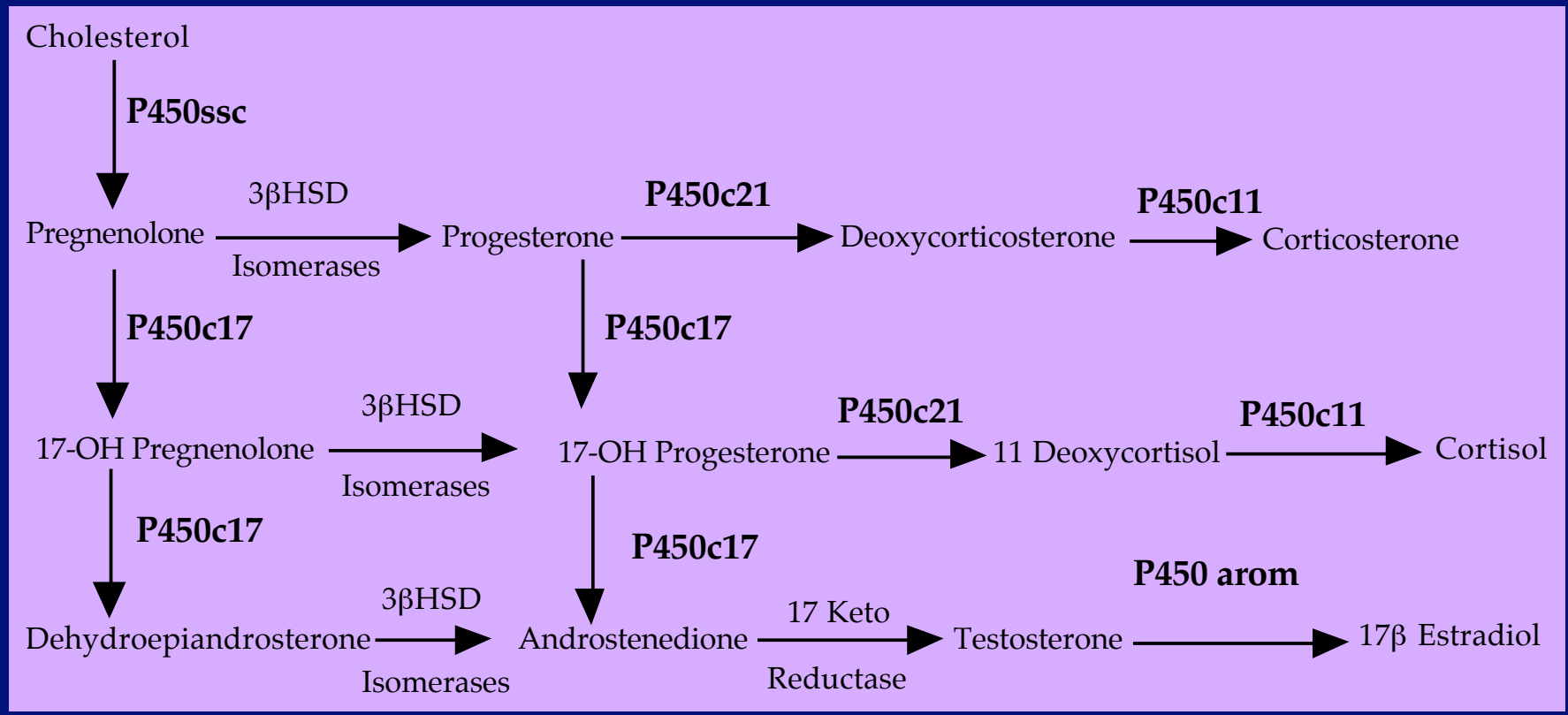


Hormones

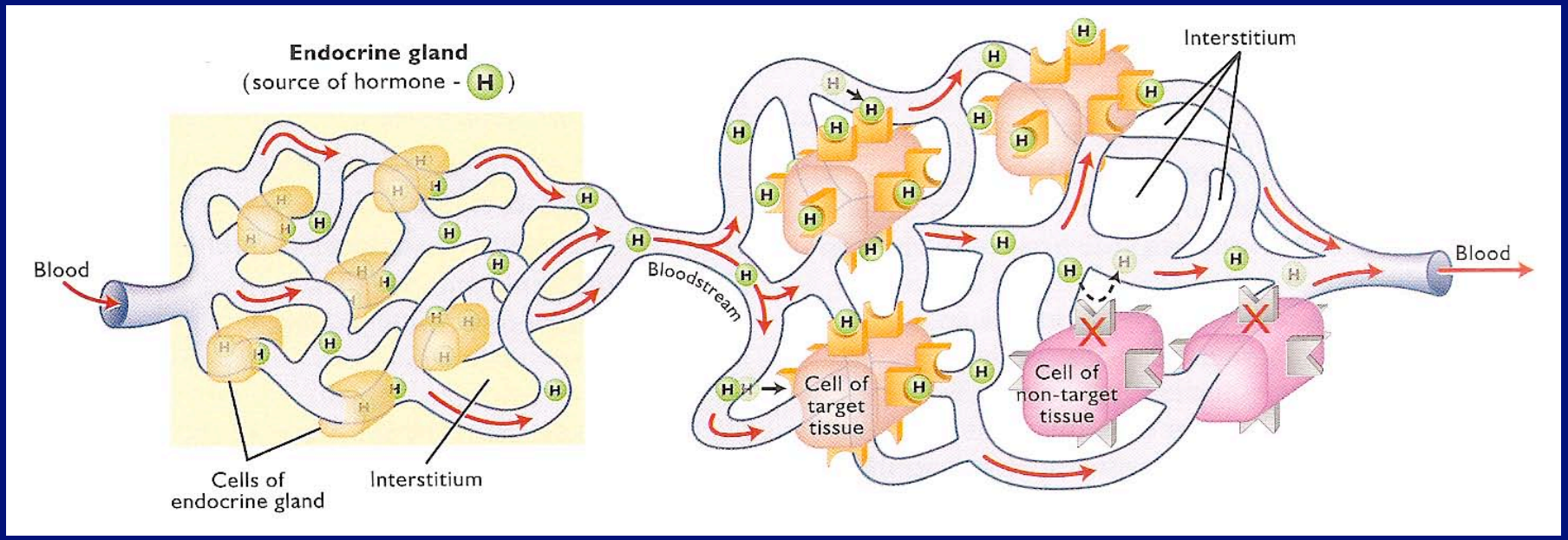
- Come in two major forms
  - peptides / proteins
    - growth hormone, insulin, oxytocin
  - Lipid-based hormones
    - steroids and prostaglandins



Steroidogenesis

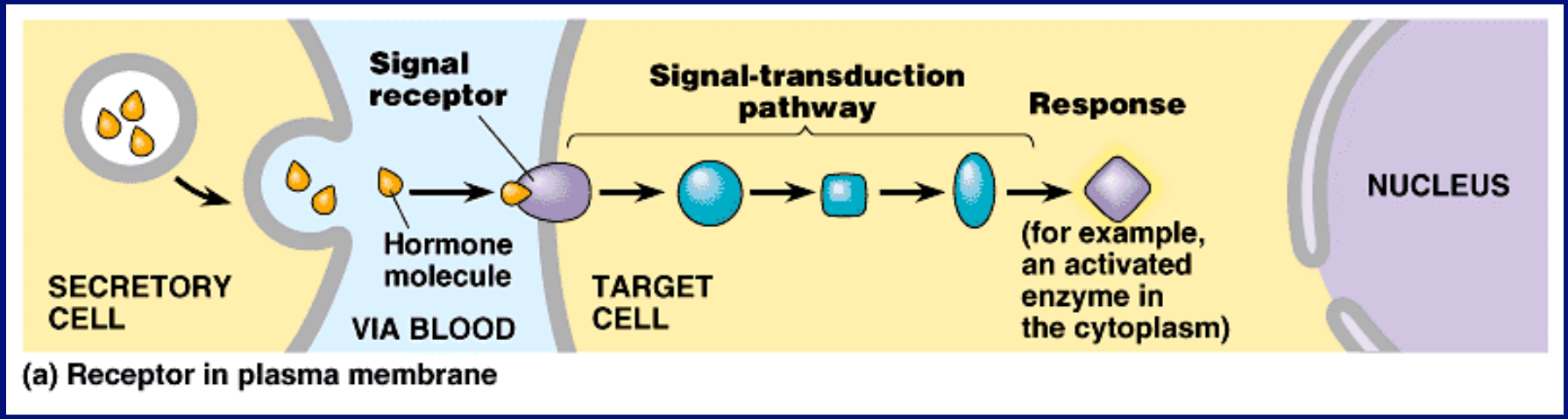


Target Tissues

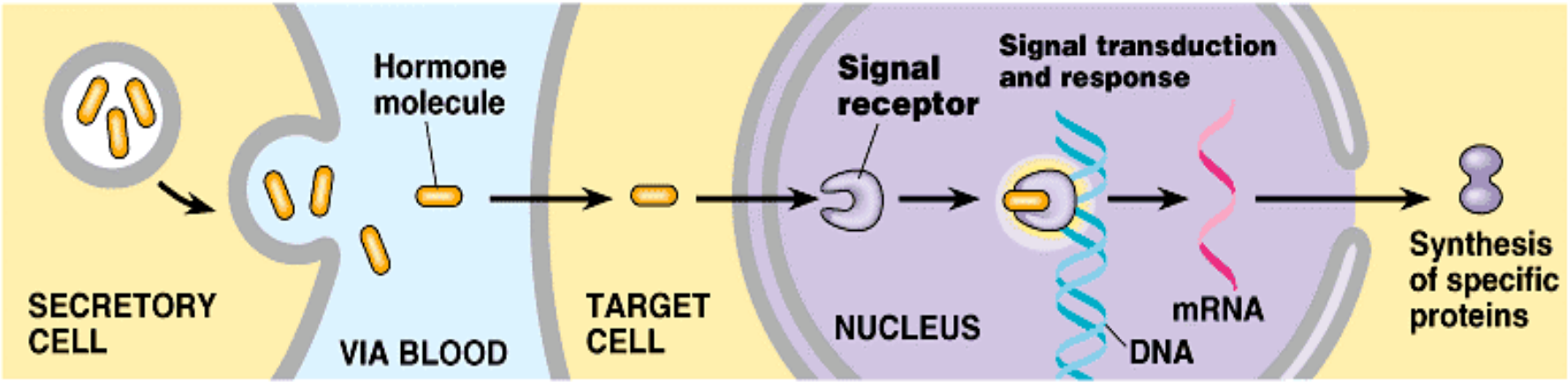


Receptors

- 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

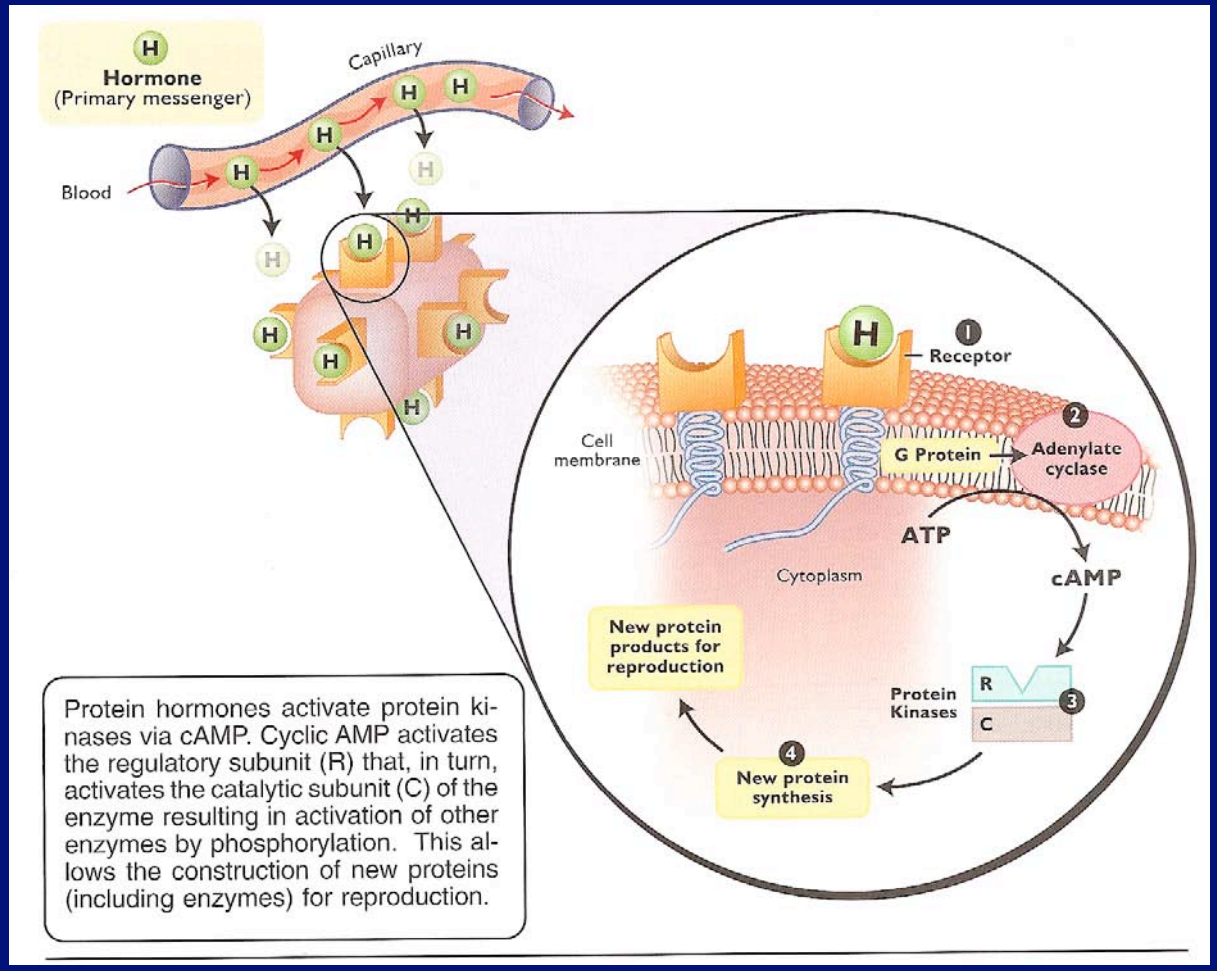


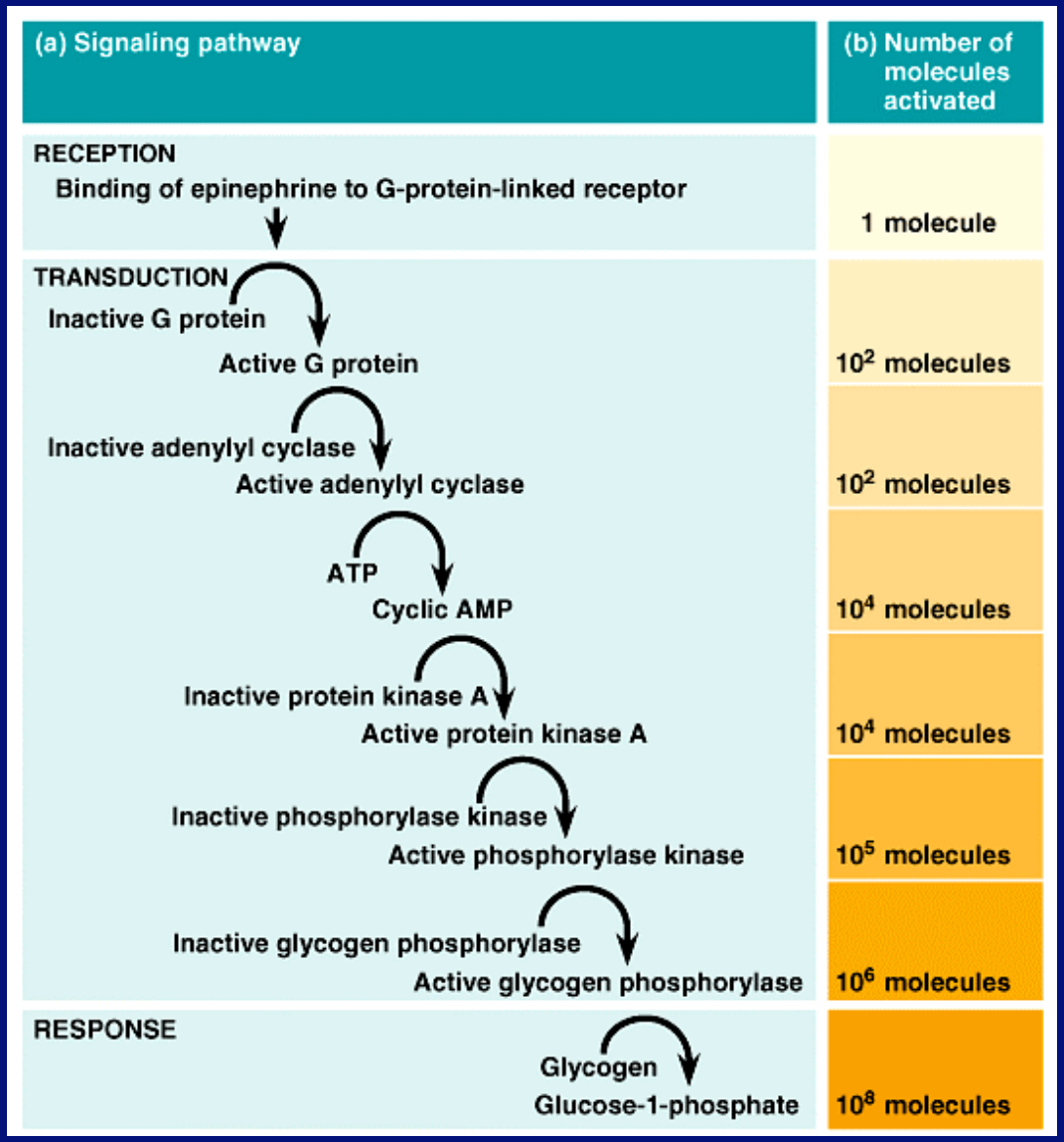
(a) Receptor in plasma membrane



(b) Receptor in cell nucleus

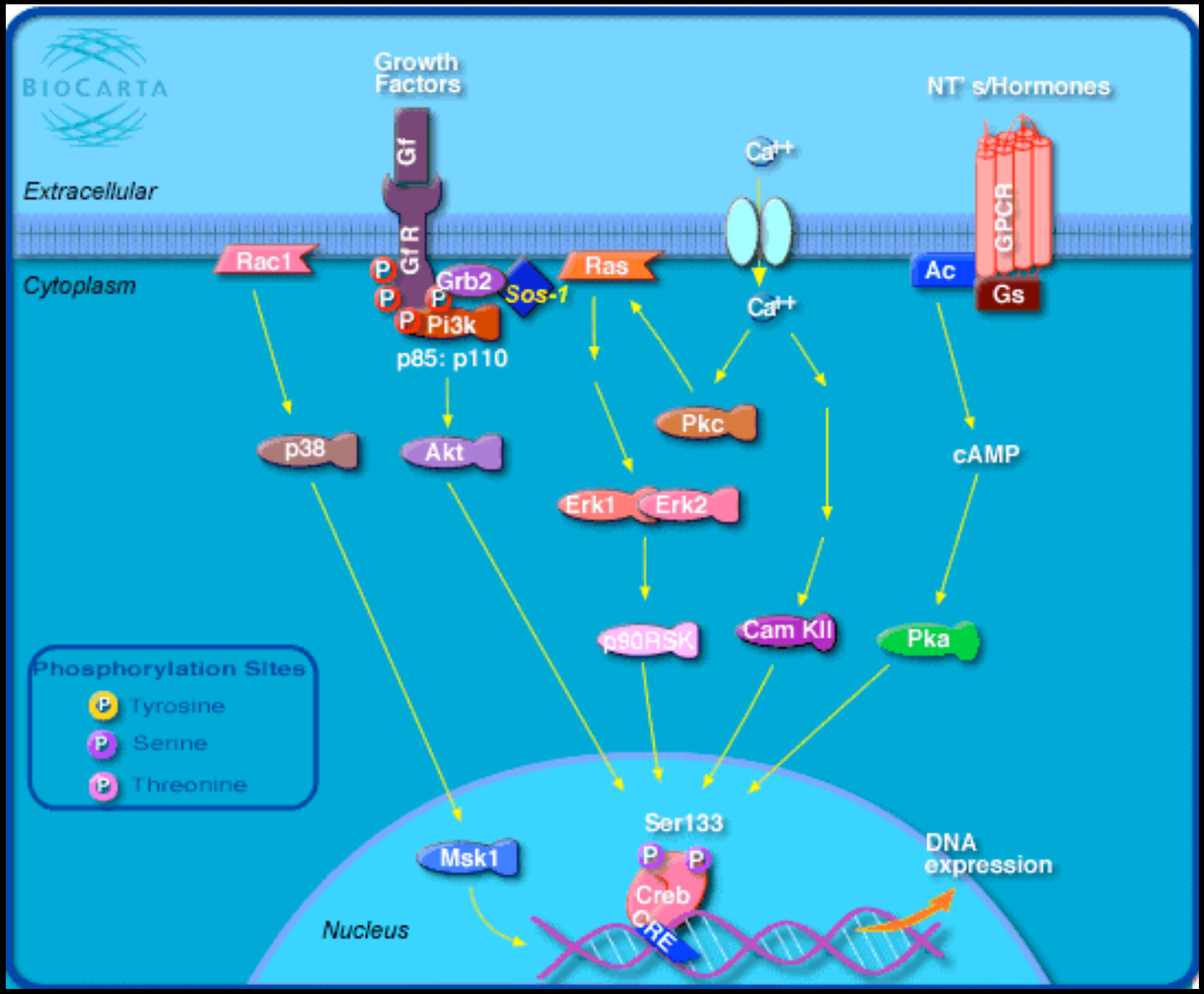
1. Membrane receptor activates G protein
2. G protein + GTP activates adenylyl cyclase
3. ATP converted to cAMP (2° messenger)
4. Results = cellular response amplified @ each step



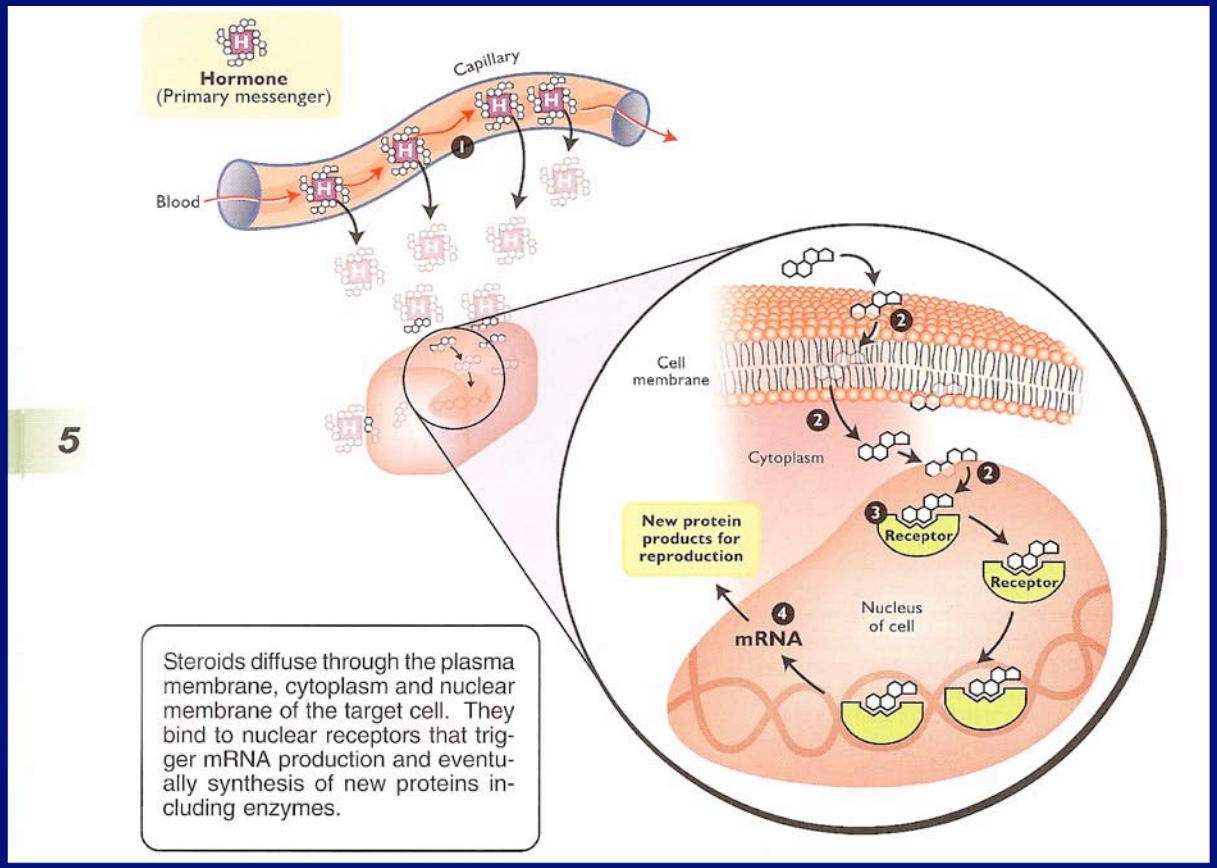


Amplification

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


BIOCARTA
Growth Factors
NT' s/Hormones
Extracellular
Cytoplasm
Gf
GfR
Grb2
Sos-1
Pi3k
p85: p110
Rac1
Ras
Ca++
Ca++
GPCR
Ac
Gs
p38
Akt
Pkc
cAMP
Erk1
Erk2
p90RSK
Cam KII
Pka
Phosphorylation Sites
Tyrosine
Serine
Threonine
Msk1
Ser133
Creb
CRE
DNA expression
Nucleus

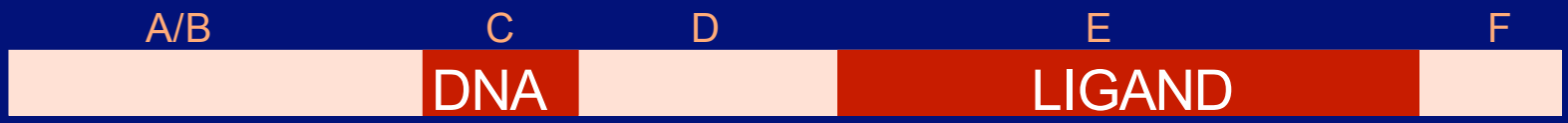
1. Steroid binds to cytoplasmic or nuclear receptor(transcription factor)
2. Receptor hormone complex binds to DNA in nucleus
3. Stimulates transcription of mRNA



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
PRα,β	progesterone
ARα,β	testosterone
ERα,β,γ	estrogen
VDR	1,25 $(OH)_2$ vit D3
TRα,β	Thyroid hormone
EcR	20-OH ecdysone

EX-orphans

RARα,β,γ	all-trans RA
RXRα,β,γ	9-*cis* RA, ?
PPARα,β,γ	fatty acids
LXRα,β	oxy-sterols
FXRα,β	bile acids
BXRα,β	benzoates

Nearly EX-orphans

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

ORPHAN RECEPTORS

Vertebrate ⟷	*Drosophila*
TR-2α,β	DHR78
NGFI-Bα,β,γ	DHR38
RORα,β,γ	DHR3
Rev-erb	E75, E78
SF-1α,β	*FTZ-F1*α,β
COUPα,β,γ	*svp*
HNF-4α,β	HNF-4
TLX	*tll*

No known homologs

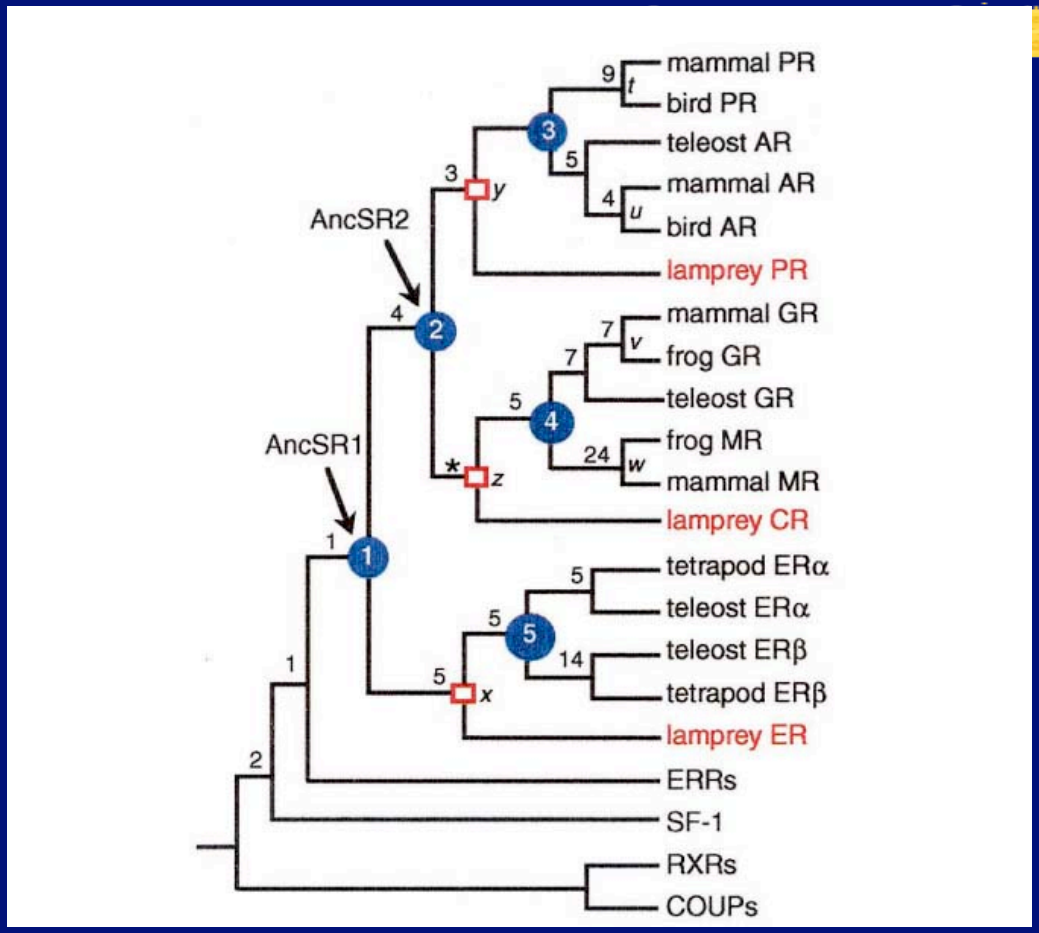
ERRα,β,γ	*knirps*
DAX-1	*knirps-related*
SHP	*egon*
GCNF	DHR96

C. elegans - 2-3% of genes are nuclear receptors ~250

Drosophila - only about 20 nuclear receptors

Blumberg, UC Irvine

Evolution of Steroid Receptors

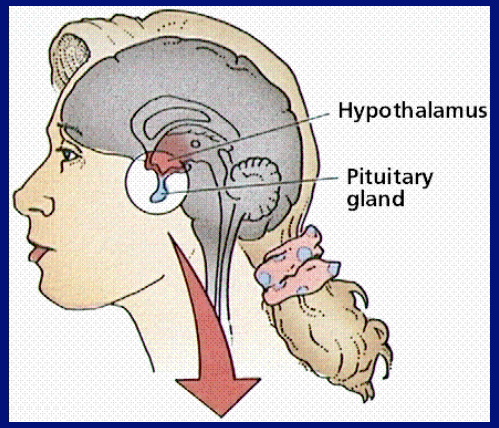


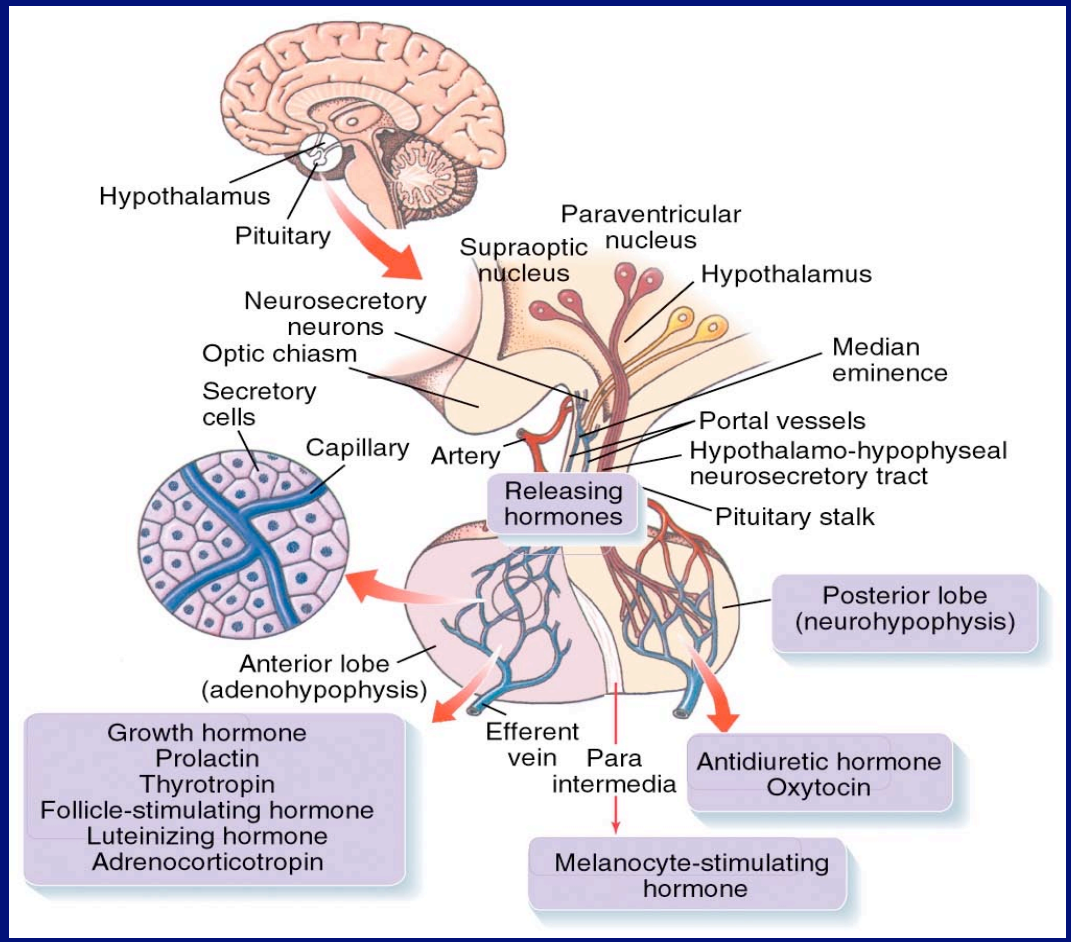
- Two serial duplications
- 1st = ER and 3-ketosteroid R
- 2nd = duplication of 3-KR
  - Corticoid receptor (CR)
  - 3-ketogonadal steroid R
    - Androgen
    - Progesterone
    - Or both
- These 3 duplicated again to form 6 common forms found today in vertebrates

Thornton (2001) PNAS 98:5671-5676

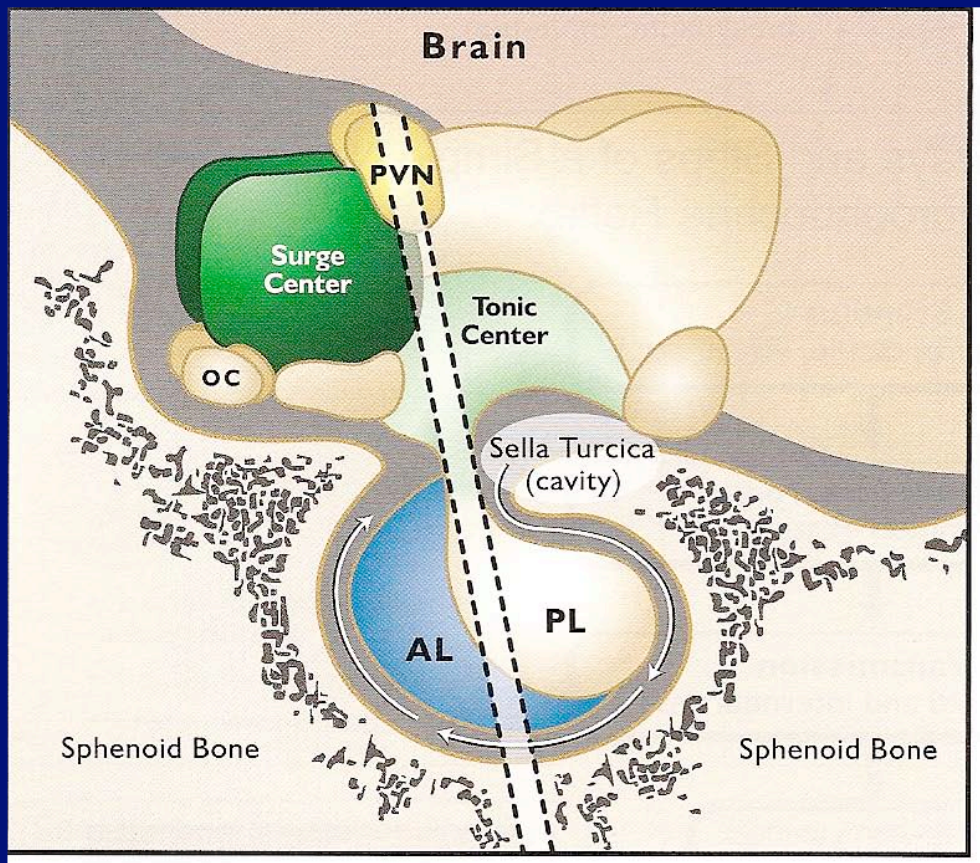
Hypothalamus - Pituitary

- considered the master organs of the endocrine system

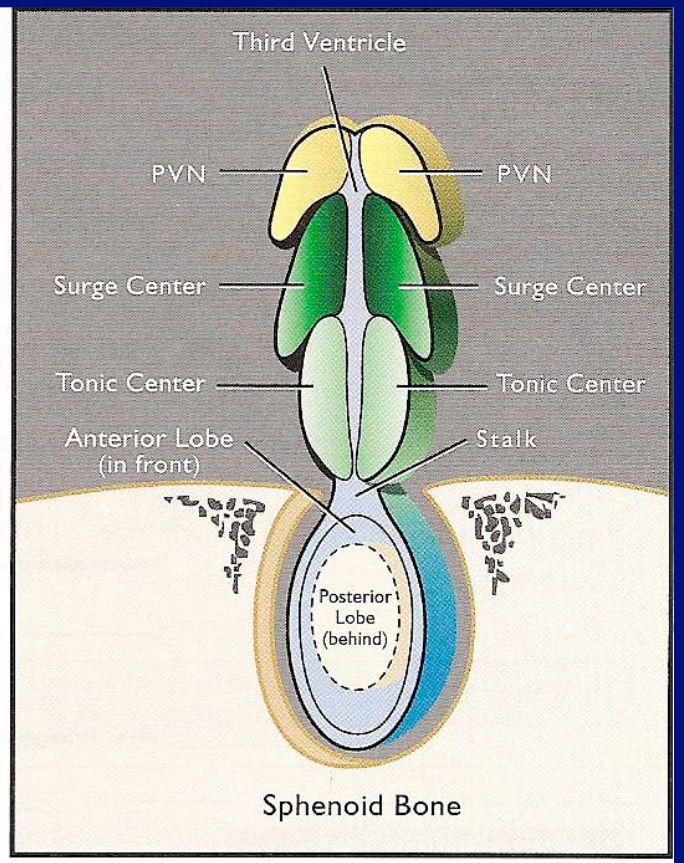




Hypothalamus

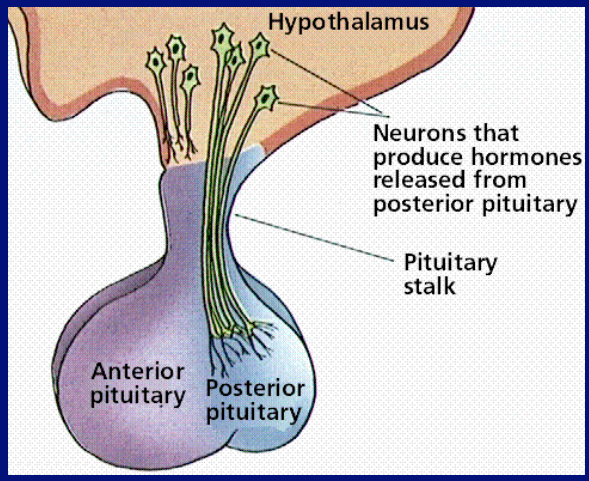


Saggital view



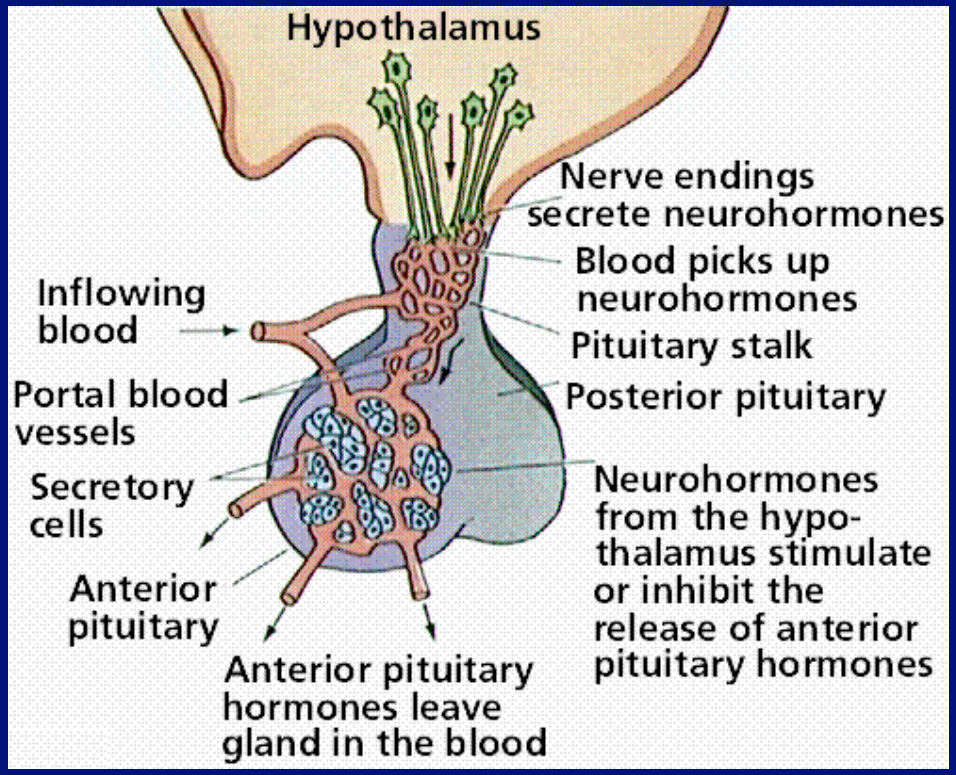
Frontal view

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 hypothalmo-hypophysial portal system
    - blood vessel system between hypothalamus and pituitary

Hypothalamo-hypophysial Portal System

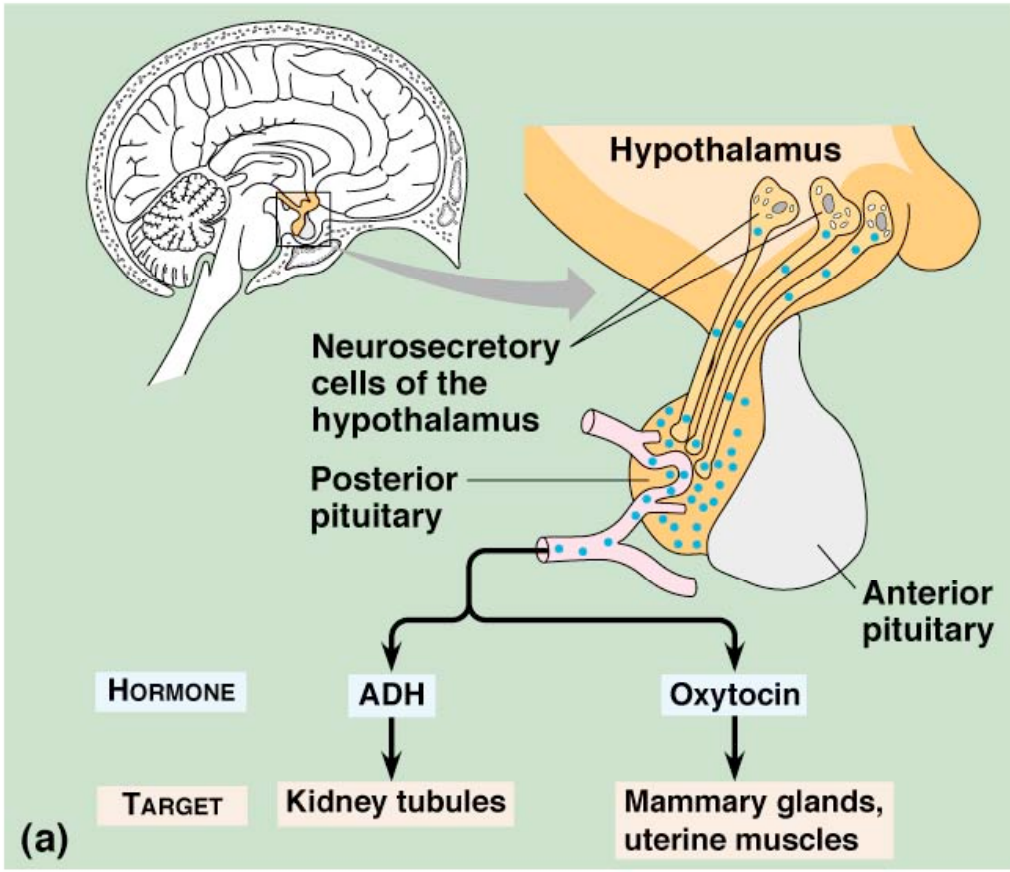


- A portal system
  - Vein - vein
  - Low pressure system
- Delivers hypothalamic factors to pituitary

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