Vaclav Hampl

Regulation of homeostasis

- Nerves
  - ✓ fast
  - ✓ governing
- Hormones
  - ✓ mainly metabolism, growth, differentiation, reproduction

Hormone

- Substance produced by a specific cell type usually accumulated in one (small) organ
- Transport by blood to target tissues
- Stereotypical response (receptors)

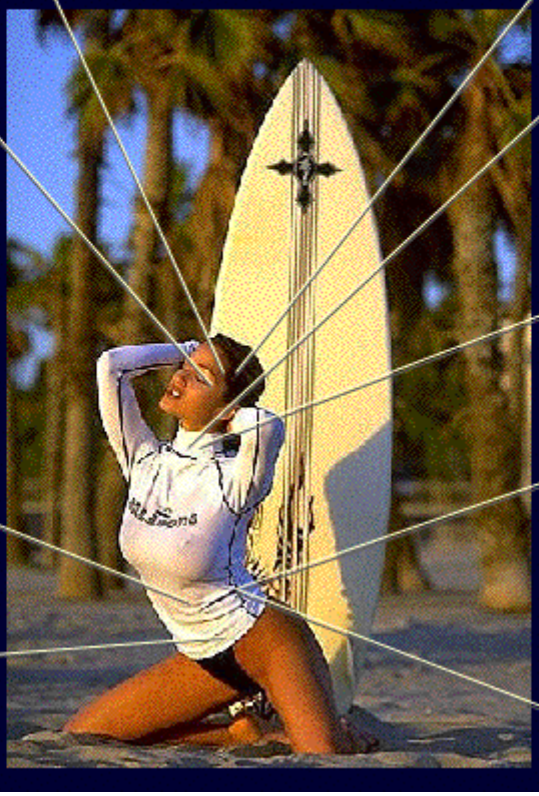
Hormone production: "Classic" glands

Hypothalamus:
- GHRH, CRH, TRH, GnRH
- Somatostatin
- ADH

Pituitary:
- Growth hormone
- Prolactin
- ACTH, MSH
- TSH
- FSH & LH
- Oxytocin
- ADH

Pancreas:
- Insulin
- Glucagon

Ovaries:
- Estrogens
- Progesterone



Epiphysis:
- Melatonin

Thyroid gland:
- T3, T4
- Calcitonin

Parathyroid glands:
- Parathyroid h.

Adrenal cortex:
- Cortisol
- Aldosterone
- Androgens

Adrenal medulla:
- Catecholamines

Hormone production: Less traditional sources

Endothelium:
- Endothelins
- NO
- Prostanoids,...

Immune system:
- Cytokines

Platelets, mesenchyme:
- Growth factors

Placenta:
- All hormones

Adipocytes:
- Leptin

Cardiocytes:
- ANP

Kidney:
- Erythropoietin
- RAS

GIT:
- Gastrin
- Cholecystokinin
- Secretin,...

Gonads:
- Inhibins
- Activins

Hormones, cytokines, growth factors

- Common aspects:
  - ✓ small quantities
  - ✓ regulate other cells
  - ✓ act through receptors
- Tight interactions between immune and endocrine systems

	Hormones	Cytokines	Growth factors
Production	Only specialized cells	Many cell types	
	Few places	Many places	
Action	Long-range	Mostly short-range	Short-range
Pleiotropy	Low	High	Medium
Redundance	Low	High	Medium
Regulation	Tight	Loose	
Function	Homeostasis Ontogenesis	Defence	Remo-deling

Endocrine and nervous systems

- Many common aspects:
  - ✓ small quantities
  - ✓ regulate other cells & tissues
  - ✓ act through receptors
  - ✓ functional overlap between some hormones & neurotransmitters
  - ✓ excitability
  - ✓ both can secrete into blood

Types of humoral signalization

- Endocrine
  - from gland via blood to a distance
- Neurocrine
  - via axonal transport and then via blood
- Paracrine
  - neighboring cells of different types
- Autocrine
  - neighboring cells of the same type or the secreting cell itself

Chemical characteristics of hormones

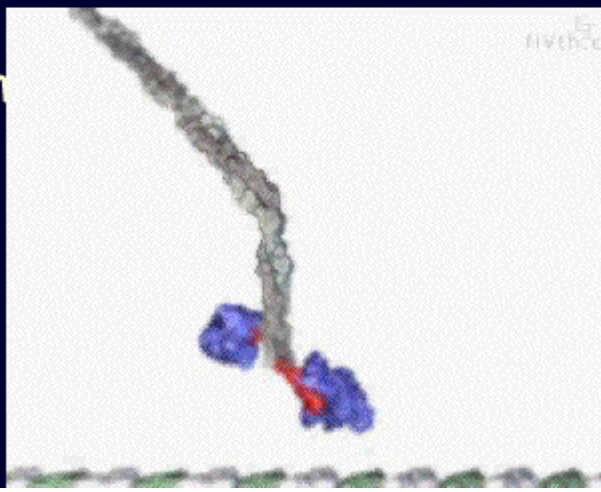
- Amines (from tyrosine)
  - hydroxylation - catecholamines
  - iodination - thyroid hormones
- Peptides/proteins
- Steroids (from cholesterol)
  - adrenocortikoids
  - sex hormones
  - active metabolites of vitamin D

Genetic disorders

- Peptides/proteins:
  - ✓ Often gene coding the hormone
    - -> ↓ activity (e.g. insulin)
- Amines & steroids:
  - ✓ gene coding enzyme catalyzing the synthesis
    -> ↓ hormone level
    - and/or ↑ precurzor level
      - e.g. ↑ androgens in deficient estrogen synthesis

Hormone release

- Proteins & catecholamines:
  - ✓ secretory granules, exocytosis
    - for incorporation into granules often special sequences cleaved off in granules or after release
    - stimulus → ↑ $[Ca^{2+}]_i$ (influx, reticulum → granules travel along microtubules towards cell membrane (kinesins, myosins) → fusion

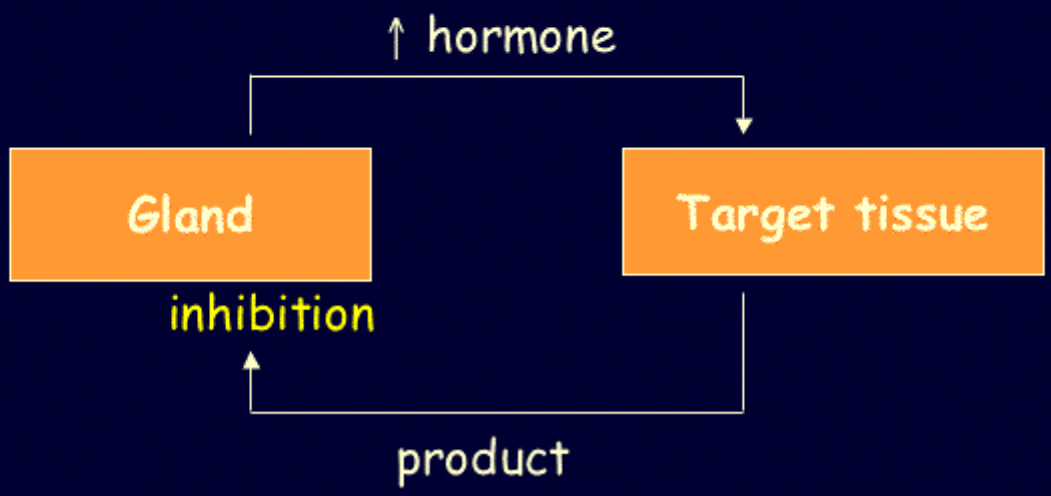


Hormone release

- Thyroid hormones:
  - ✓ made as part of thyroglobulin
  - ✓ stored in folicles
  - ✓ T3 & T4 secreted by enzymatic cleavage
- Steroid hormones:
  - leave the cell across cell membrane right after synthesis (no storage)

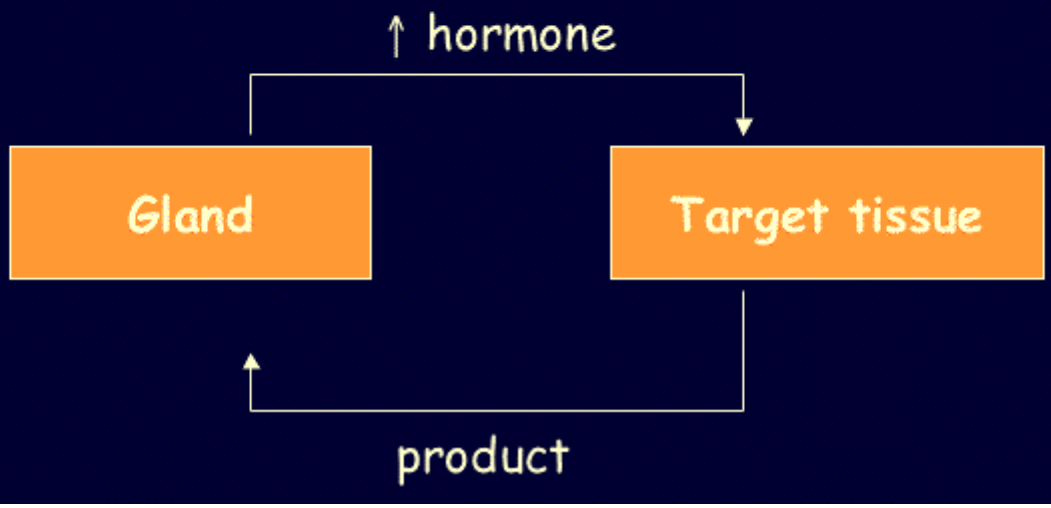
Regulation of hormone release

- Feedback
  - ✓ Negative



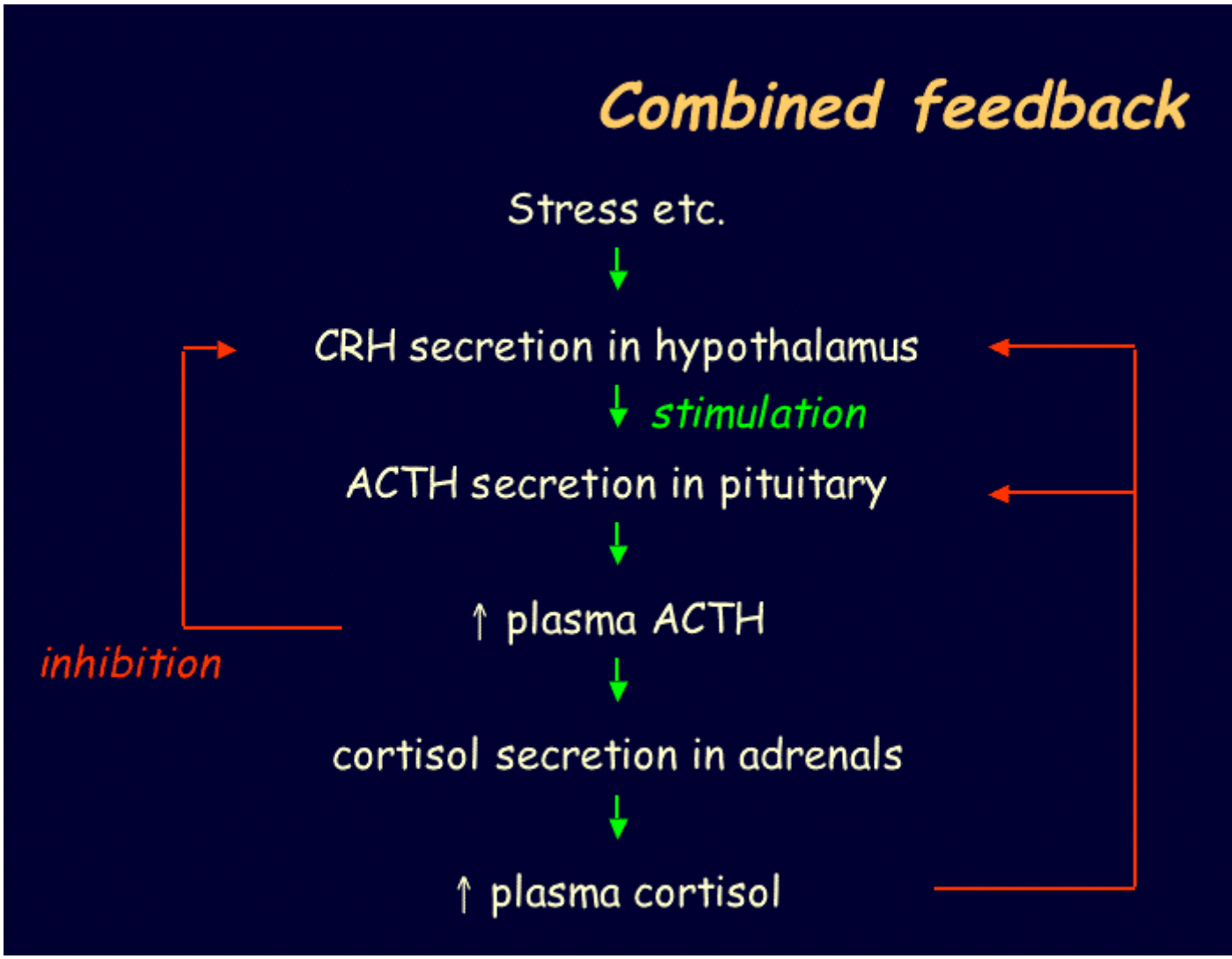
Regulation of hormone release

- Feedback
  - ✓ Negative
  - ✓ Positive (only narrow dose range)



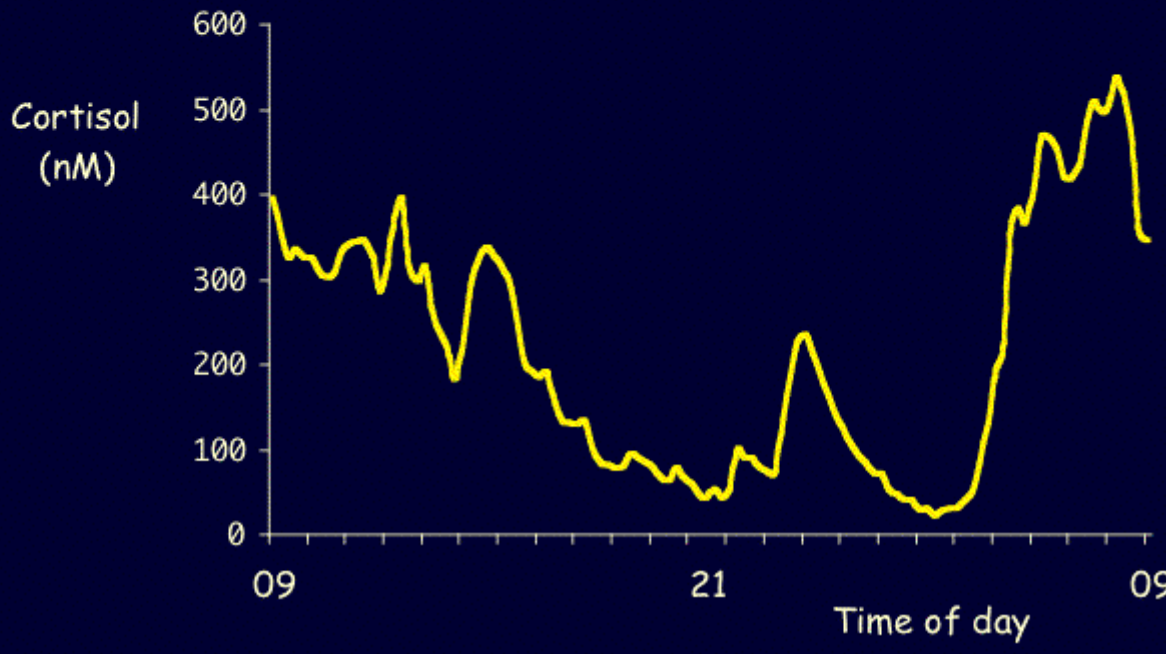
Regulation of hormone release

- Feedback
  - ✓ Negative
  - ✓ Positive (only narrow dose range)
- Nerve regulation
  - ✓ pain, emotions, sex, injury, stress,...
  - ✓ e.g. ↑ oxytocin with nipple stimulation


Combined feedback
Stress etc.
CRH secretion in hypothalamus
stimulation
ACTH secretion in pituitary
↑ plasma ACTH
inhibition
cortisol secretion in adrenals
↑ plasma cortisol

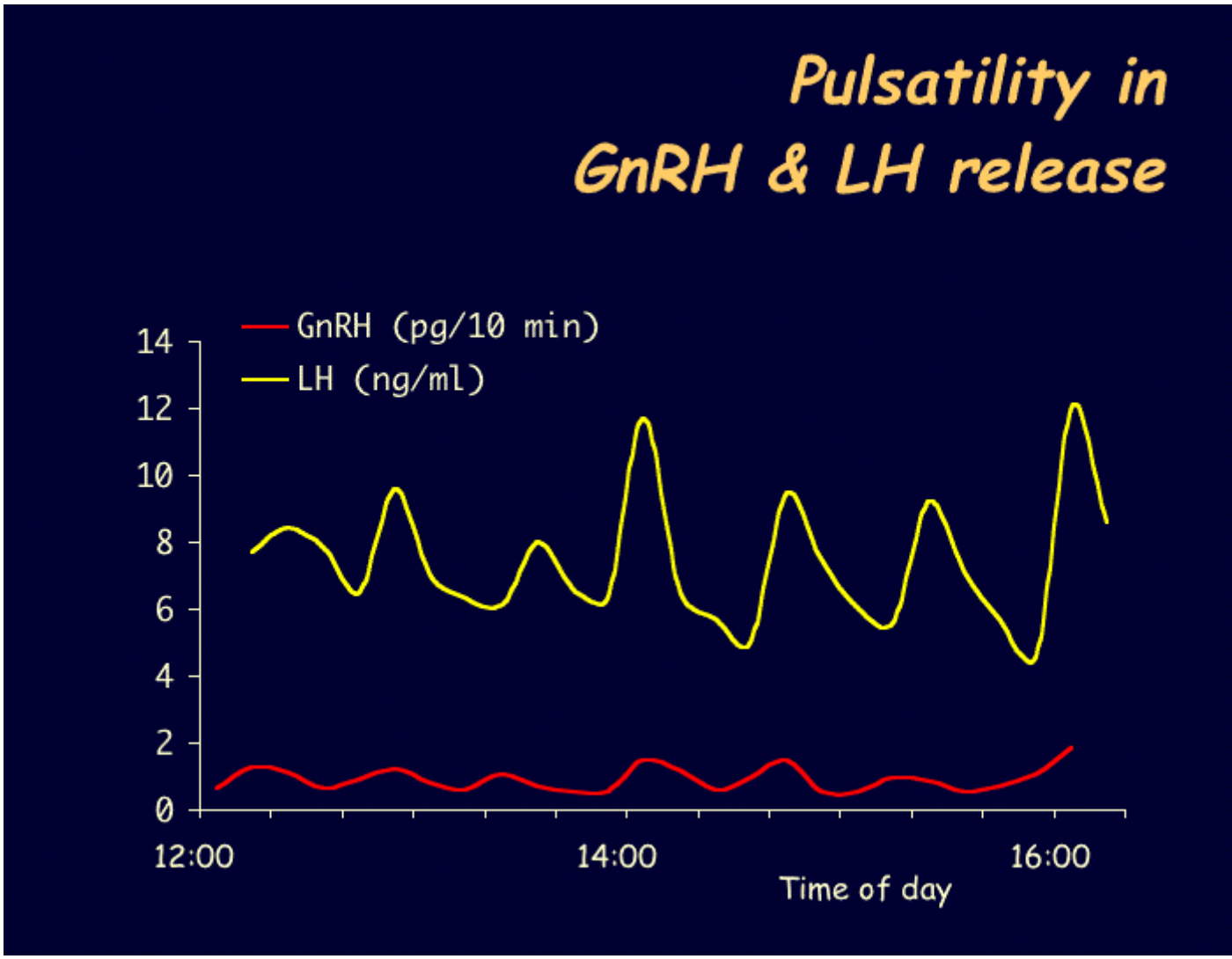
Regulation of hormone release

- Rhythms
  - ✓ circadian



Regulation of hormone release

- Rhythms
  - ✓ circadian
    - light/dark fine/tune endogenous rhythm of cells & suprachiasmatic nucleus of hypothalamus
    - melatonin, cortisol
  - ✓ monthly
  - ✓ seasonal (day length; atavistic)
  - ✓ developmental (puberty, menopause)
- Pulsations/oscillations
    - gonadotropins


Pulsatility in
GnRH & LH release
GnRH (pg/10 min)
LH (ng/ml)
14
12
10
8
6
4
2
0
12:00
14:00
16:00
Time of day

Hormone action

- Receptor
  - ✓ specificity of a response to a given hormone
- (Second messenger)
- Δ activity or concentration of enzymes, transcription factors, or structural proteins

Hormone action

Peptides/proteins Catecholamines	Steroid & thyroid hormones
Receptor in cell membrane	Receptor in cytosol or nucleus
Second messengers → Δ protein activity	Δ gene expression
Fast	Slower

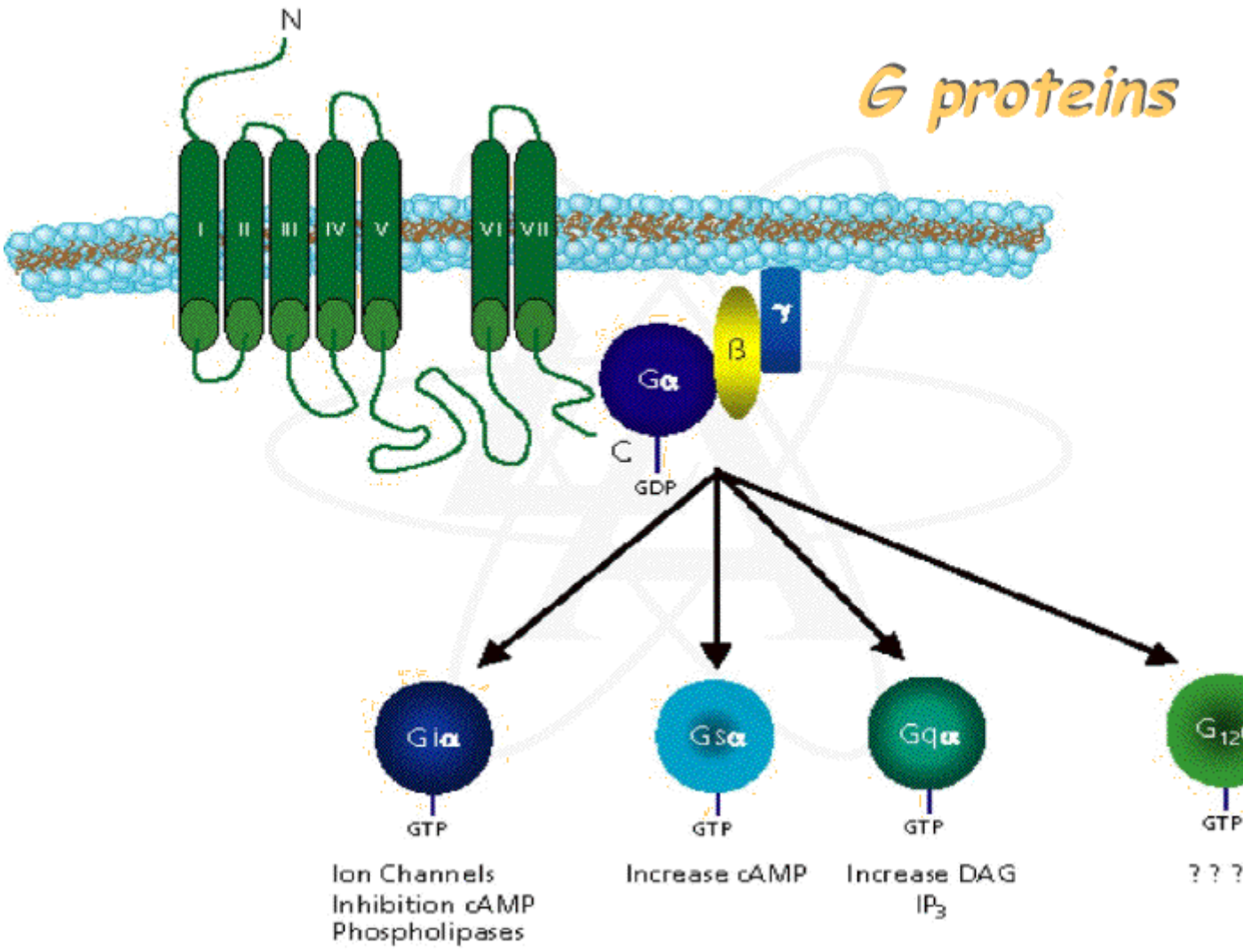
Receptors

- Δ affinity or expression modulates hormone action
  - e.g. phosphorylation, pH, osmolarity,...
- down-regulation
- up-regulation

Membrane receptors

- Large glycoproteins, often several subunits
- Typically 7x through membrane
- After activation:
  - ✓ dissociation from the hormone
  - ✓ or endocytosis of the complex, then degradation in lysozomes, recycling

G proteins

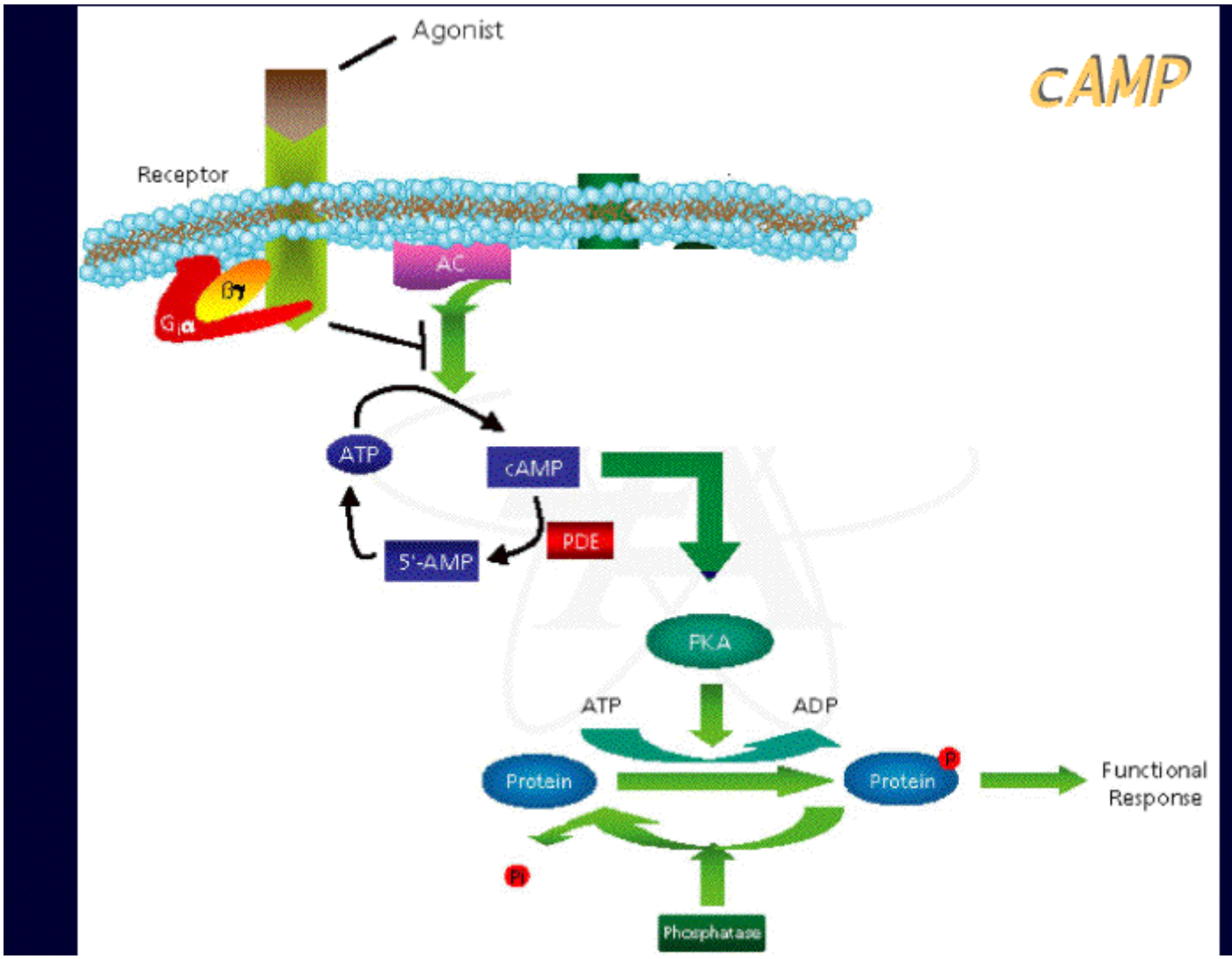

N
I
II
III
IV
V
VI
VII
Gα
β
γ
C
GDP
Giα
GTP
Gsα
GTP
Gqα
GTP
G12
GTP
Ion Channels
Inhibition cAMP
Phospholipases
Increase cAMP
Increase DAG
IP3
? ? ?

G proteins

- ✓ a subunit binds activated receptor
- ✓ releases GDP, binds GTP
- ✓ dissociates from its b subunit & the receptor
- ✓ binds & activates/inhibits effector (adenyl/guanylate cyclase, phospholipase C)
- ✓ hydrolyzes GTP to GDP
- ✓ re-associates with its b-g dimer

Intracellular signal transduction (second messengers)

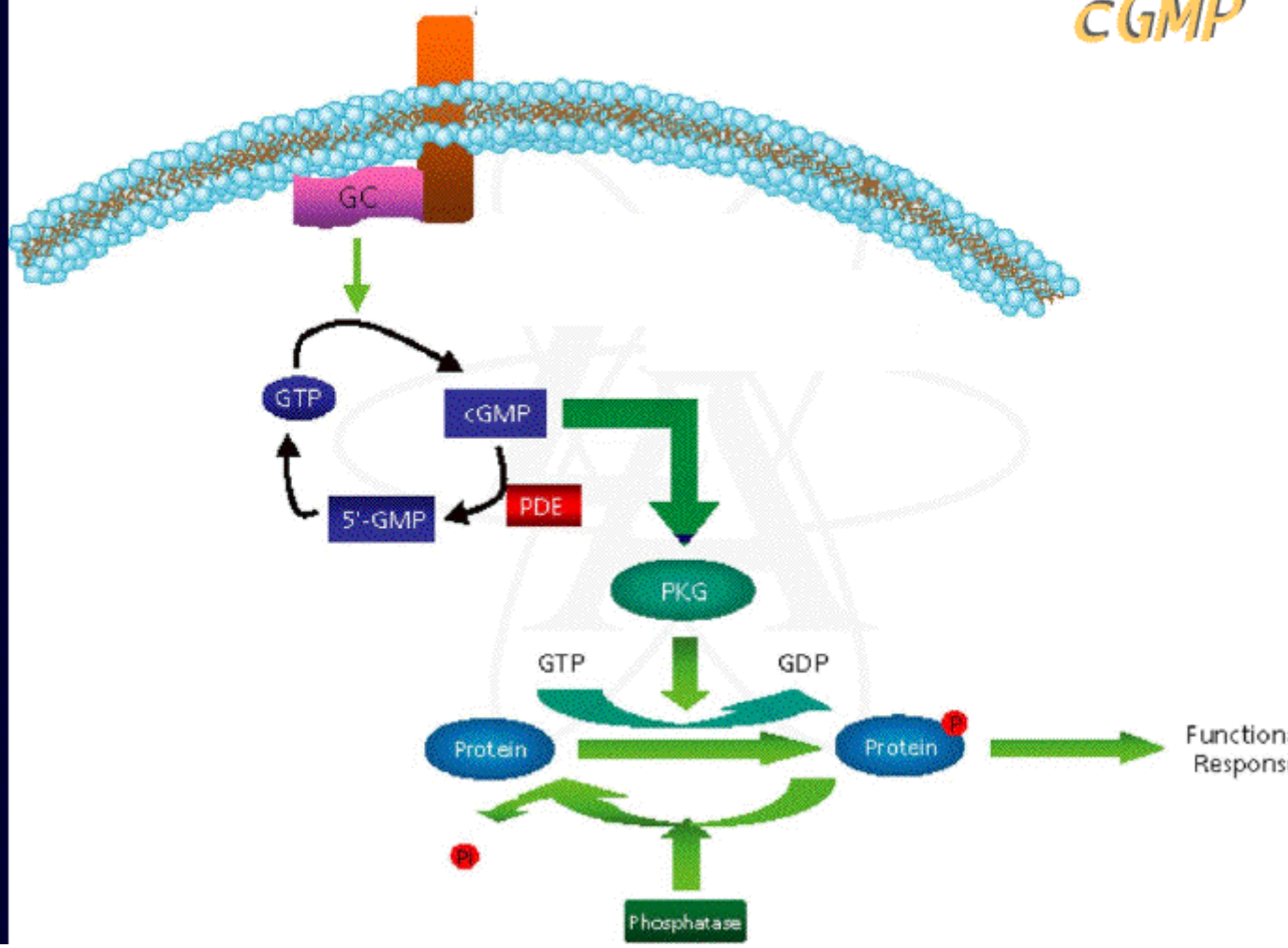
- ✓ cAMP
- ✓ cGMP
- ✓ IP_3
- ✓ Ca/calmodulin
- ✓ tyr kinases
- ✓ Smad
- ✓ MAP kinases
- ✓ One hormone can use several systems (in various cells or for different functions)


cAMP
Agonist
Receptor
AC
βγ
Gα
ATP
cAMP
PDE
5'-AMP
PKA
ATP
ADP
Protein
Protein
P
Functional Response
Pi
Phosphatase

Adenylate cyclase - cAMP - protein kinase A

- ✓ PKA phosphorylates target enzymes (in/activation)
- ✓ sometimes complementary (e.g. Ca channel activation + Ca pump inhibition)
- ✓ can affect gene expression
  - cAMP regulatory element (CRE) on DNA binds transcription factor, CRE binding protein (CREB)
- ✓ cAMP hydrolysis: phosphodiesterases

cGMP


GC
GTP
cGMP
5'-GMP
PDE
PKG
GTP
GDP
Protein
P
Protein
Pi
Phosphatase

Ca-calmodulin

- ✓ G proteins activate Ca channels (ROC)
- ✓ Ca influx stimulates Ca release from endoplasmic reticulum (CICR)
- ✓ Ca, mainly by binding calmodulin, modulates many enzymes, often via protein kinase C

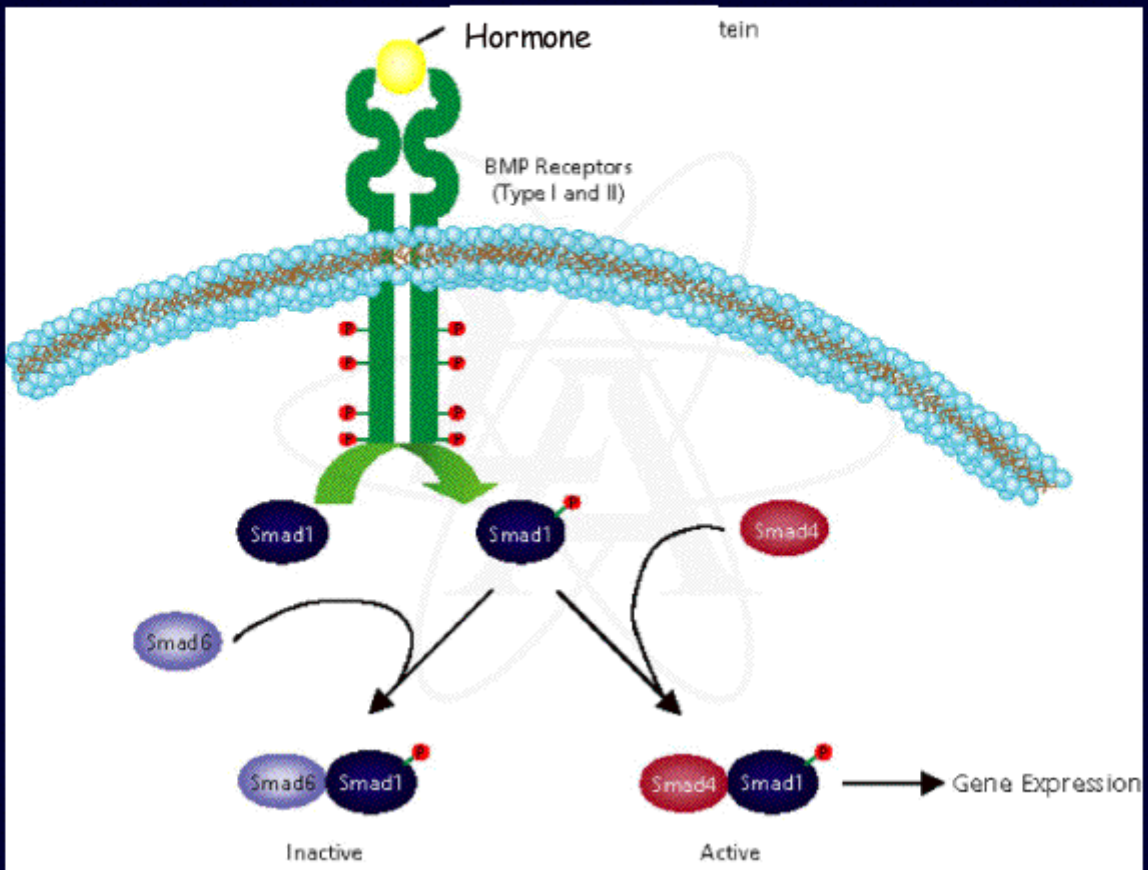
Phospholipase C - IP_3 & DAG

- ✓ from cell membrane phospholipids
- ✓ IP_3 activates Ca channel of the endoplasmic reticulum
- ✓ DAG: ↑↑ PKC affinity to Ca

Tyrosin kinases

- ✓ Receptor autophosphorylation upon hormone binding unmasks tyr-kinase activity
  - typically insulin (& growth factors)
- ✓ Or conformational change of the receptor upon hormone binding attracts & activates cytoplasmic tyr-kinases
  - e.g. growth hormone
- ✓ tyr-kinases phosphorylate cascades of tyr & ser kinases & phosphatases

Inhibins, activins & TGF system



Intracellular receptors

- Lipophilic hormones:
  - ✓ Thyroid
  - ✓ Steroid
  - ✓ Vitamin D
- Enter the cell or all the way to nucleus, where they bind the receptor (large oligomeric protein)

Intracellular receptors

- C-terminal domain binds hormone
  - ✓ hormone specificity
- Central domain binds DNA
  - ✓ (HRE, hormone regulatory unit, 8-15 bases)
  - ✓ gene specificity
- N-terminal domain activates RNA polymerase

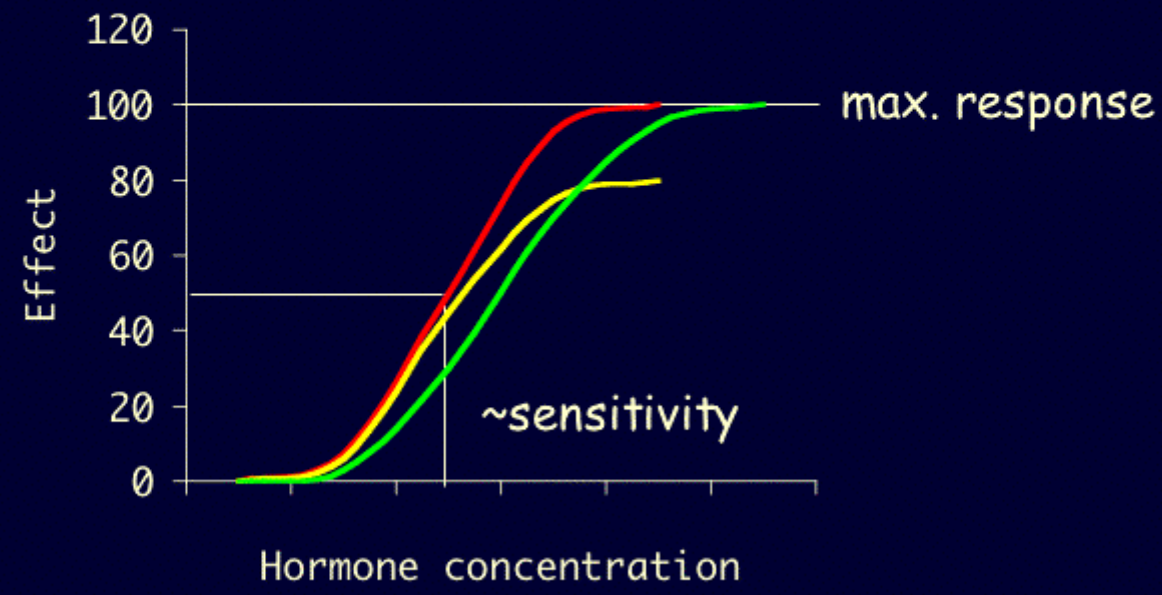
Function of intracellular receptors

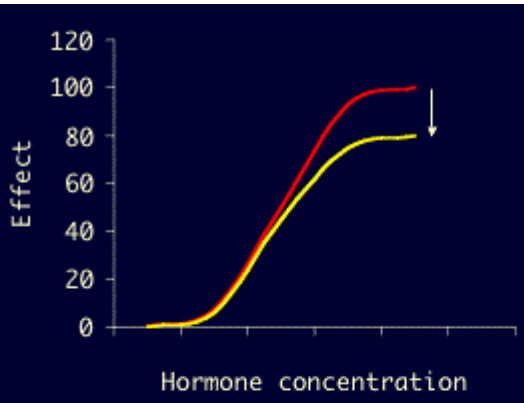
- Hormone displaces inhibitory protein (e.g. HSP) → translocation to nucleus, DNA binding
  - corticoids
- Or hormone binding displaces the receptor from resting, inhibitory association with DNA
  - thyroid hormones

Magnitude of response

- hormone concentration
- number of receptor molecules
- duration of exposure
- intracellular conditions (second messengers, kinases,...)
- synergistic or antagonistic influences

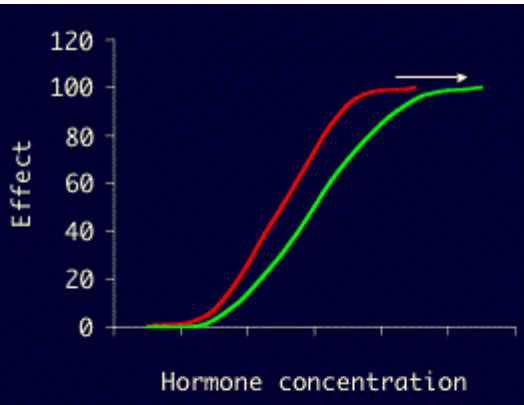
Dose/response





Decrease in max. response

- less target cells
- less receptors
- less/lower activity of enzymes activated by hormone
- less substrate for final product
- more non-competitive inhibitor



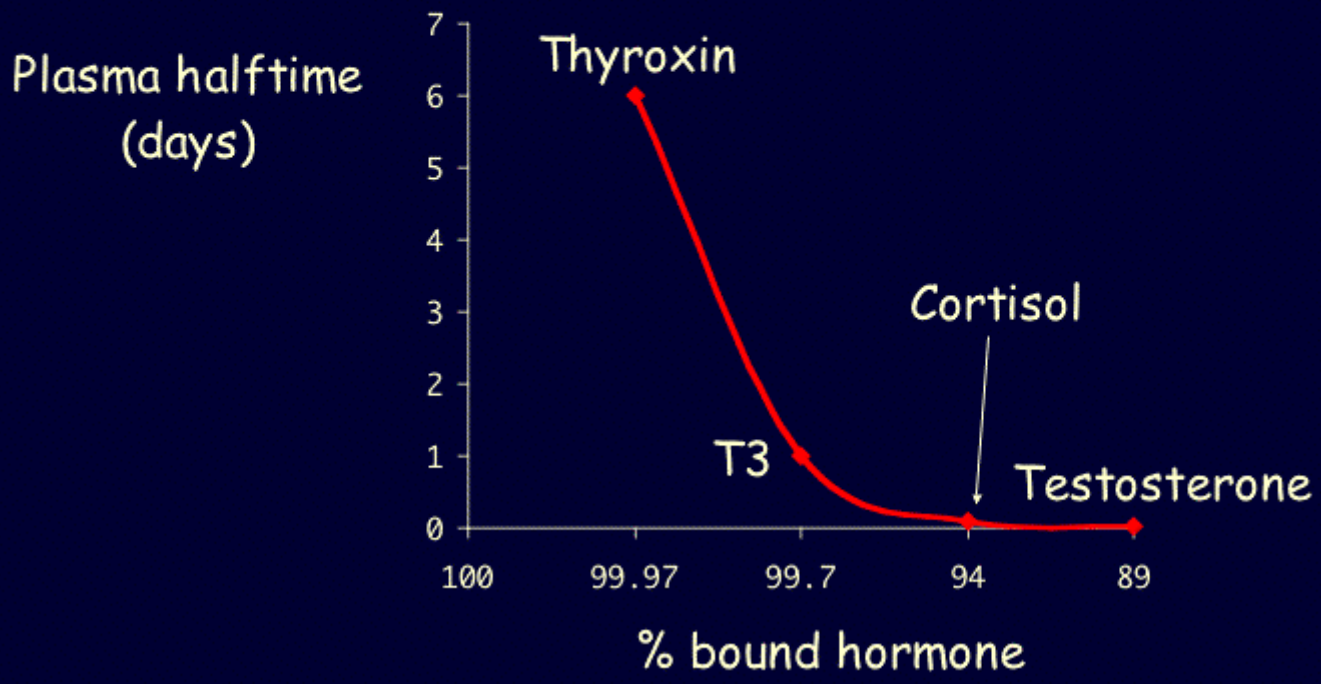
Drop in sensitivity

- less receptors
- lower receptor affinity
- modulating factors
- faster hormone degradation
- antagonistic hormones

Transport of hormones

- Freely in blood:
  - ✓ Catecholamines
  - ✓ Most peptides
- Specific transport globulins (from liver):
  - ✓ Steroids
  - ✓ Thyroid hormones

Transporter binding lengthens hormone halftime



Inactivation of hormones

- Target tissue uptake
- Metabolic degradation (plasma, liver, kidney)
- Excretion in urine
  (↓ by transporter binding; low for proteins - also re-absorbtion & degradation in kidneys)