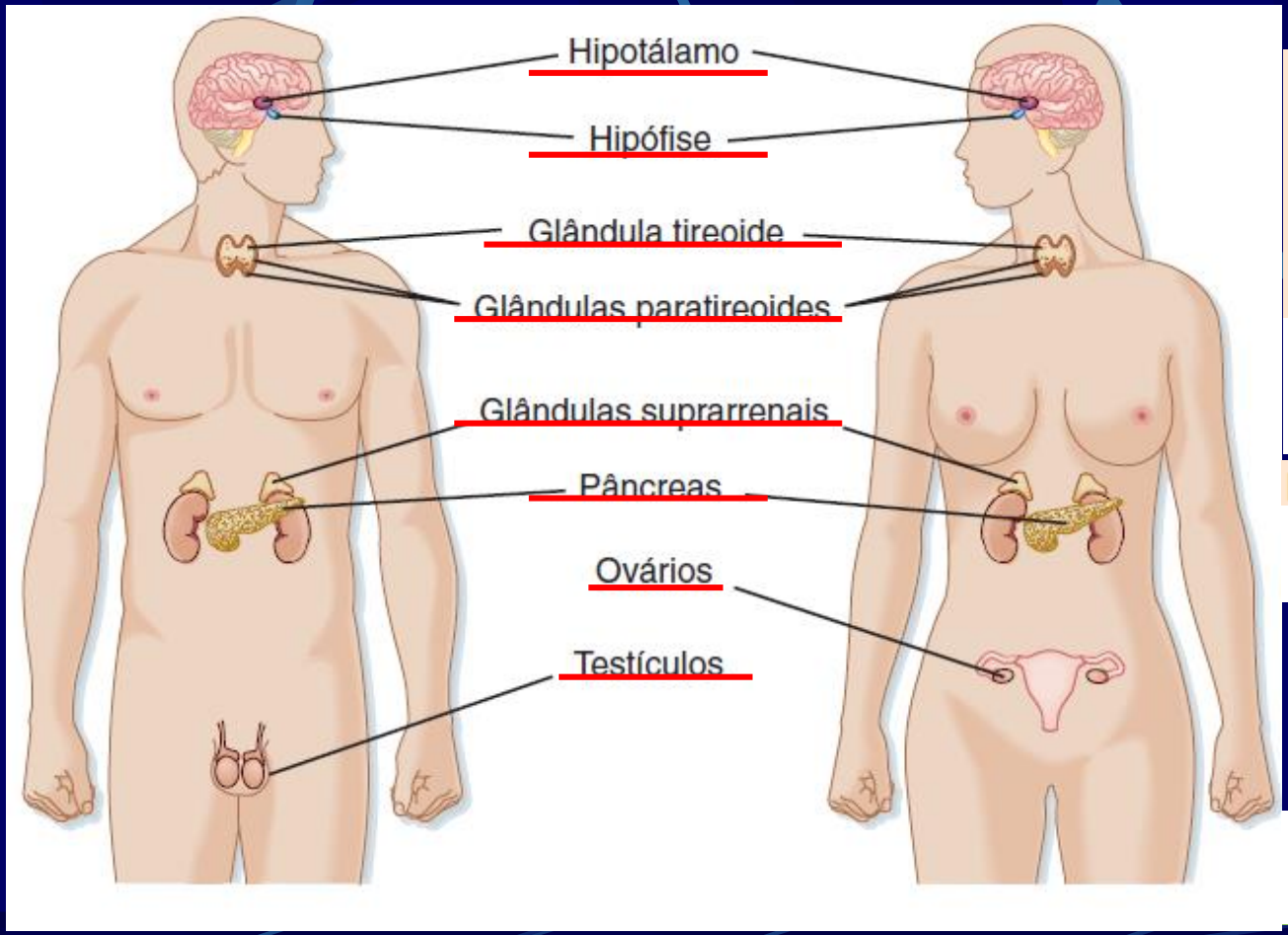
Localização anatômica dos principais órgãos endócrinos



Hormônio antidiurético (ADH; vasopressina)
Ocitocina
Hormônio liberador de corticotrofina (CRH)
Hormônio liberador de tirotrofina (TRH)
Hormônio liberador de gonadotrofina (GnRH)
Hormônio liberador de hormônio de crescimento (GHRH)
Somatostatina
Dopamina

Hormônio de crescimento (GH)
Prolactina
Hormônio adrenocorticotrófico (ACTH)
Hormônio estimulante da tireoide (TSH)
Hormônio folículo estimulante (FSH)
Hormônio luteinizante (LH)

Tetraiodotironina (T_4; tiroxina)
Triiodotironina (T_3)
Calcitonina

Hormônio paratireoide (PTH)

Insulina
Glucagon
Somatostatina

Epinefrina
Norepinefrina
Cortisol
Aldosterona
Desidroepiandrosterona sulfato (DHEAS)

Estradiol-17β
Progesterona
Inibina

Testosterona
Hormônio antimülleriano (AMH)
Inibina


Hormônios
Luz
Fator de crescimento
Odor
Feromônio
Tato
Antígeno
Gosto
Neurotransmissor
Nutrientes
Resposta Fisiológica

Classificação Sinais químicos

- Quanto à distância em que atuam:
  - endócrinos (hormônios)
  - parácrinos
  - autócrinos

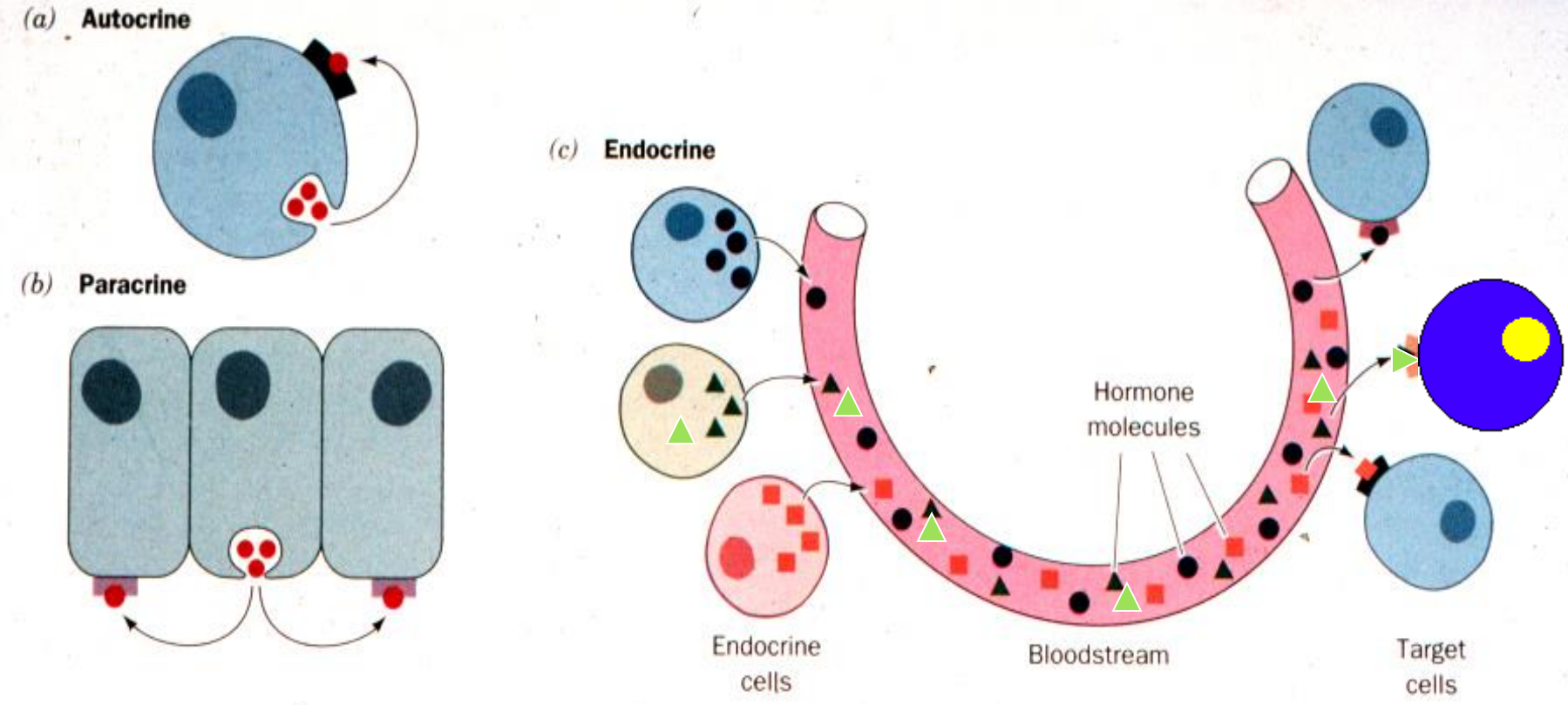


FIGURE 34-86. Hormonal communications are classified according to the distance over which the signal acts: (*a*) autocrine signals are directed at the cell that produced them, (*b*) paracrine signals are directed at nearby cells, and (*c*) endocrine signals are directed at distant cells through the intermediacy of the bloodstream.

Classificação dos sinais químicos (hormônios)

- Quanto à sua natureza química:
  - Proteínas e peptídeos
  - Esteróides
  - **Derivados de aminoácidos (aminas)**

Natureza química de outros sinais

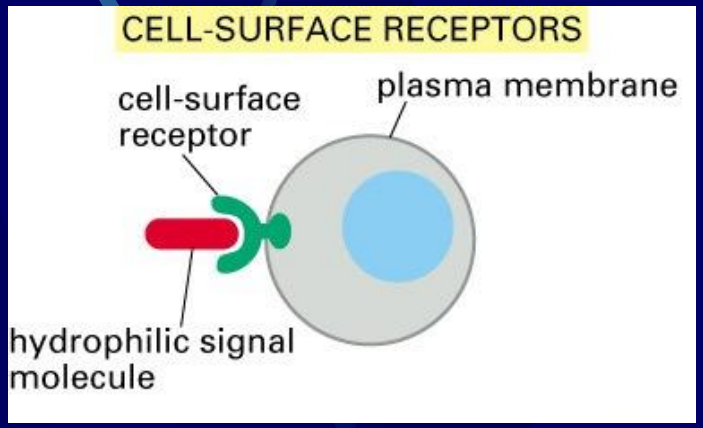
- derivados de ácidos graxos(*ácido araquidônico*): prostaglandinas , leucotrienos
- gases: NO (óxido nítrico); CO (monóxido de carbono); H_2S (ácido sulfídrico)
- nucleotídeos
- aminoácidos (ex: glutamato, glicina) e derivados de AA (ex: GABA, serotonina)

Características comuns de todos os hormônios

- Receptores específicos nas células - alvo
- Concentrações muito baixas (10^{-9} a 10^{-12} M)
- Não criam reações novas
- Não são secretados sempre com a mesma velocidade

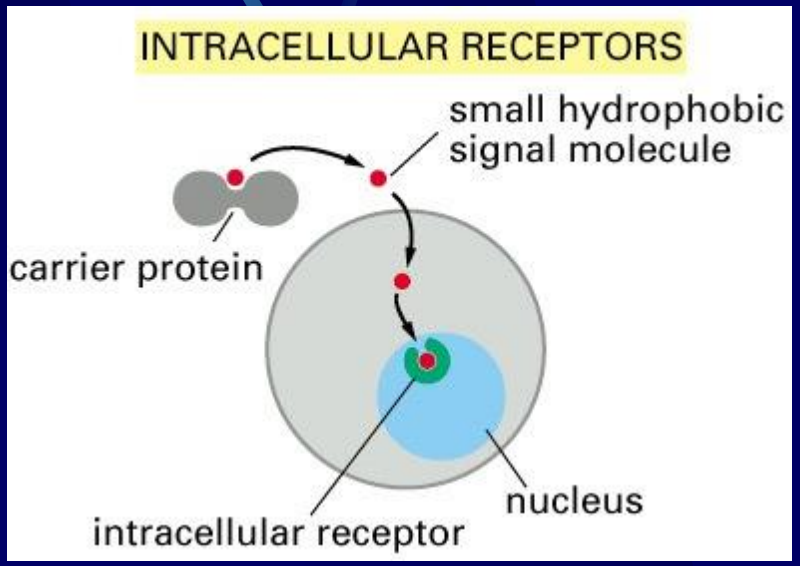
Hormônios proteicos e catecolaminas

- Meia-vida curta
- Induzem respostas rápidas
- Não são ligados a proteínas plasmáticas específicas
- Receptores localizados na membrana plasmática
- Atuam através de segundos mensageiros



Hormônios esteróides e tiroideanos

- Meia-vida longa
- Induzem respostas mais prolongadas
- São ligados a proteínas plasmáticas específicas
- Receptores intracelulares e nucleares
- Atuam através do controle da transçrição gênica e/ou estabilidade do mRNA

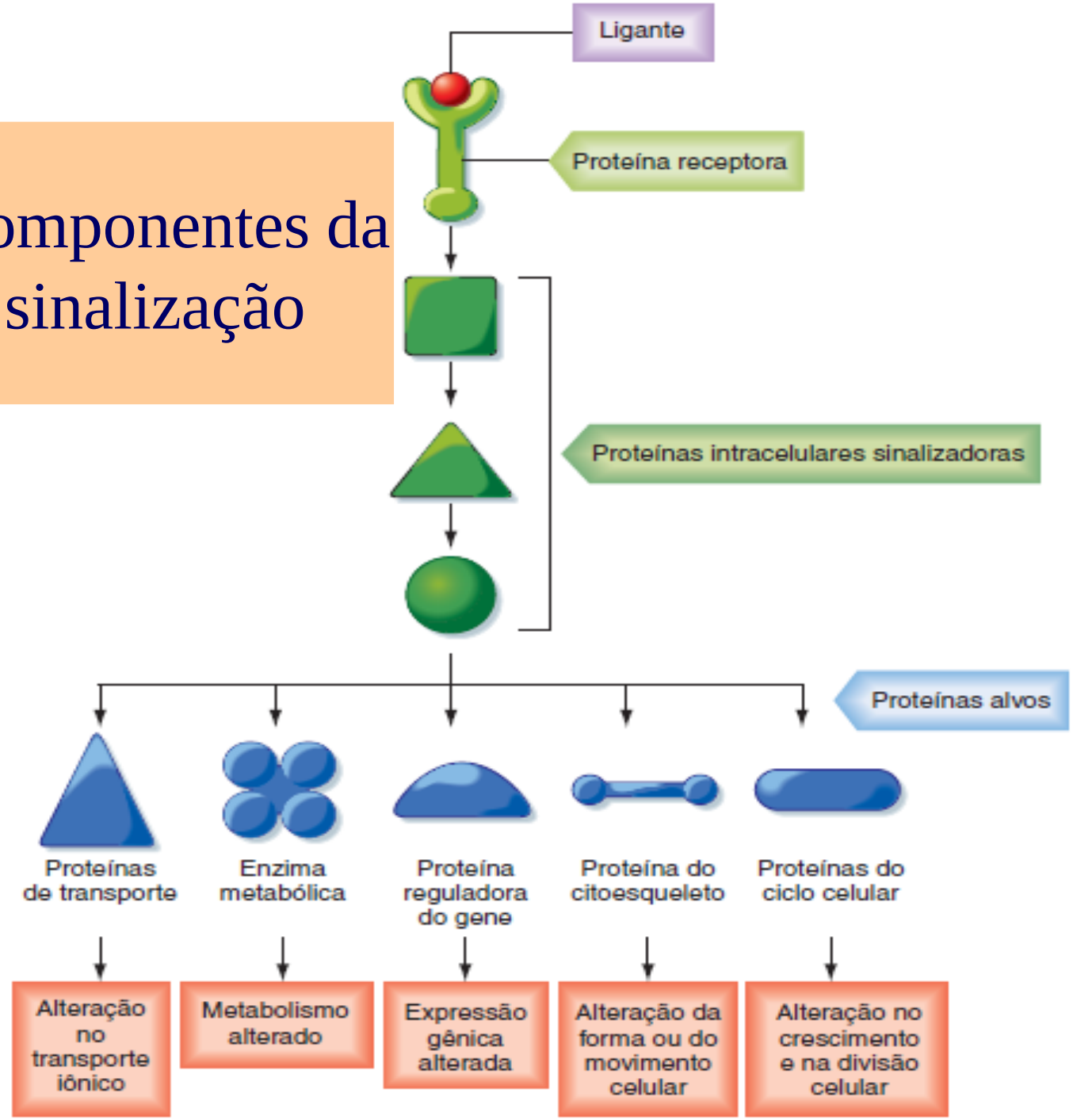


Comunicação entre as células pelos sinais químicos

1. Síntese
2. Liberação
3. Transporte
4. Detecção do sinal (receptores):reconhecimento
5. Mudanças na célula-alvo (resposta fisiológica)
6. Remoção do sinal (término da resposta)

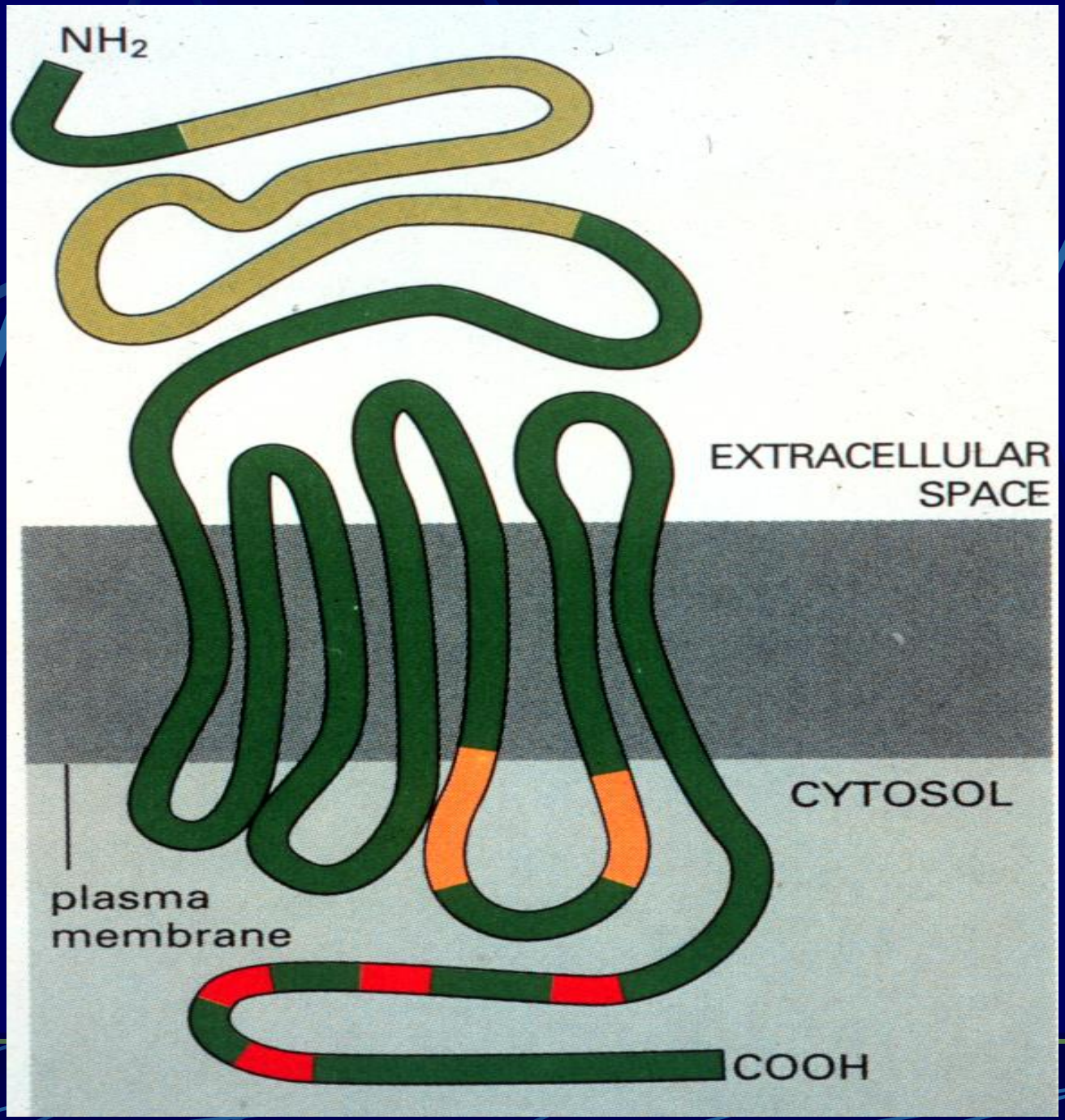

Hormônios
Luz
Fator de crescimento
Odor
Feromônio
Tato
Antígeno
Gosto
Neurotransmissor
Nutrientes
?
Resposta Fisiológica

Componentes da sinalização



Mecanismos de transdução de sinais

- 1 – **Receptores** – **acoplados a proteínas G (GPCRs) -** alteram a atividade de enzimas na membrana plasmática


NH_2
EXTRACELLULAR SPACE
CYTOSOL
plasma membrane
COOH

Receptores GPCR

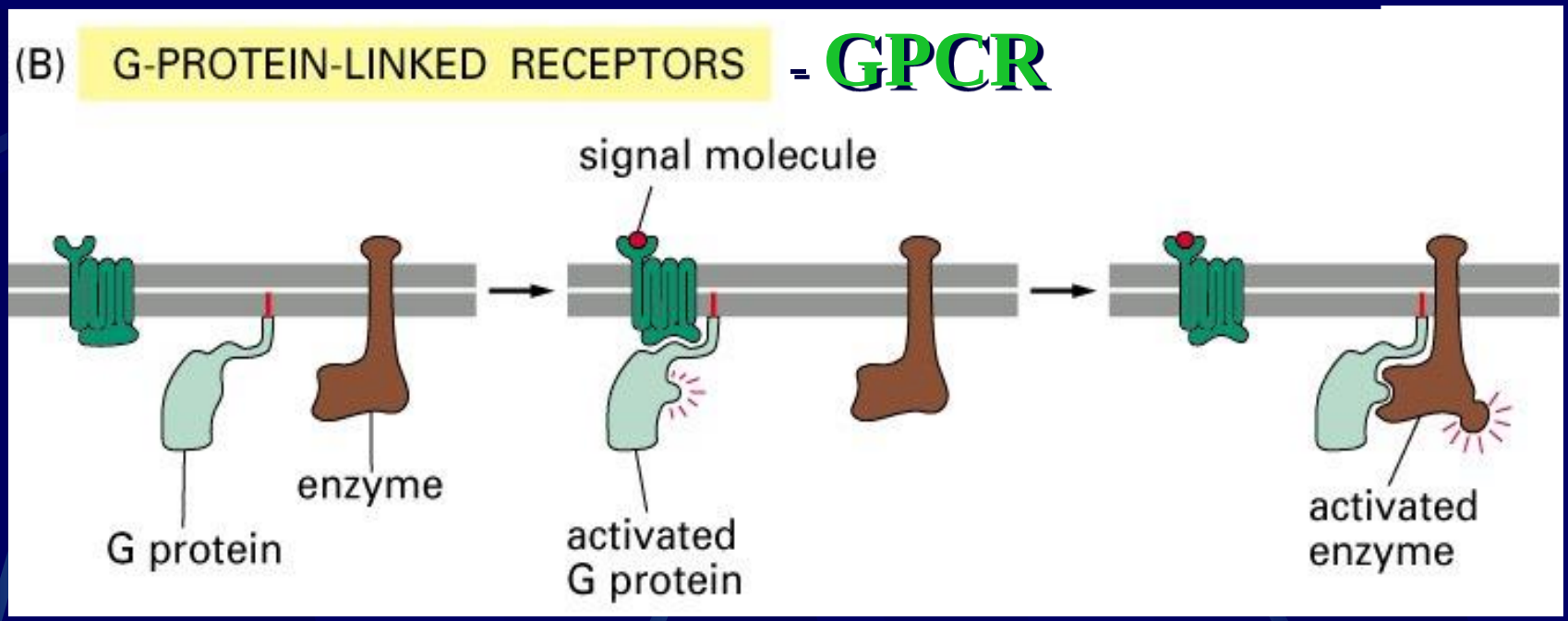
- Genoma humano codifica mais de 1000 membros desta família!!!

~ 350 receptores para detecção de hormônios, fatores de crescimento, e outras moléculas;

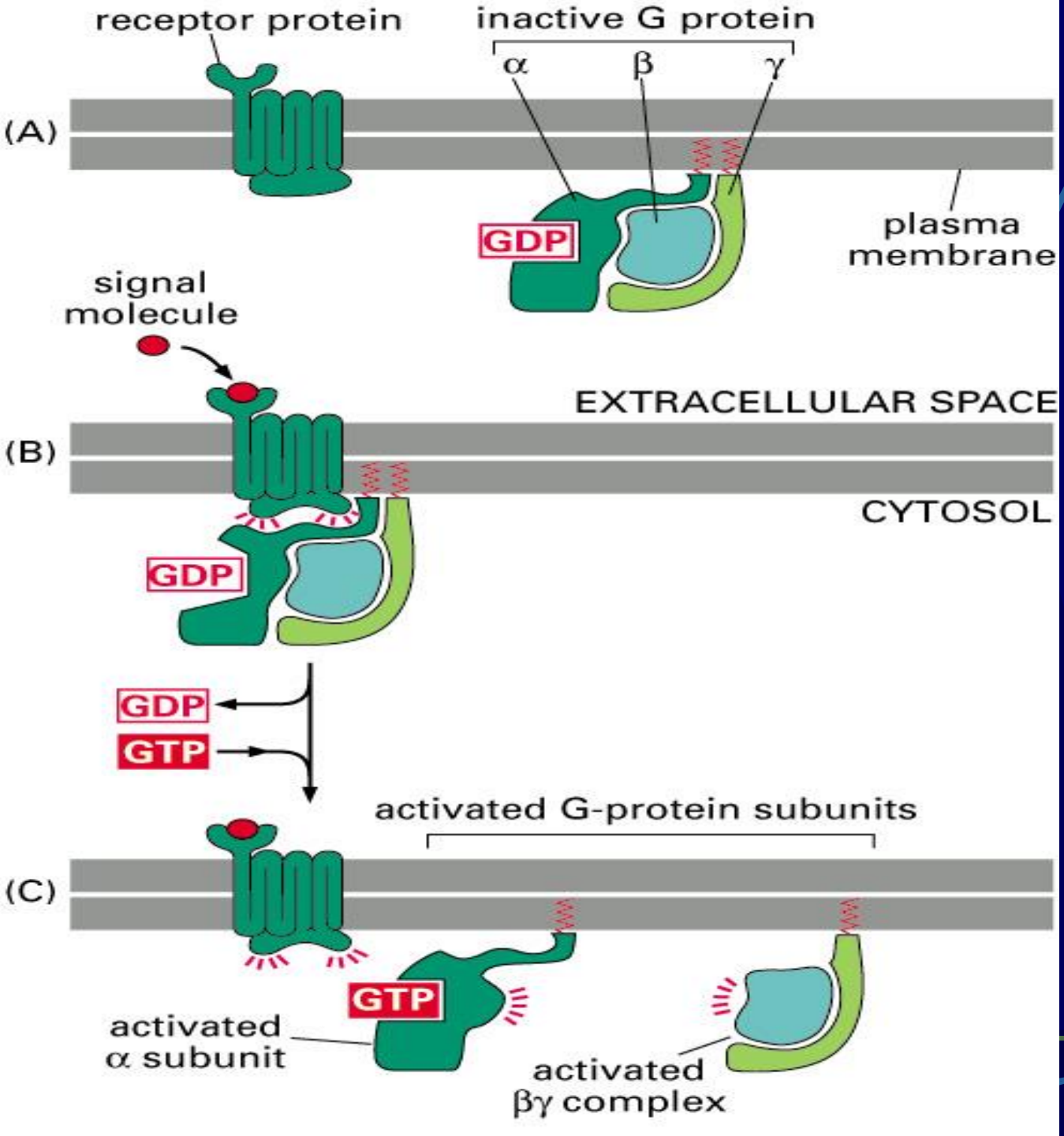
~500 receptores -moléculas olfatórias, de gosto, luz

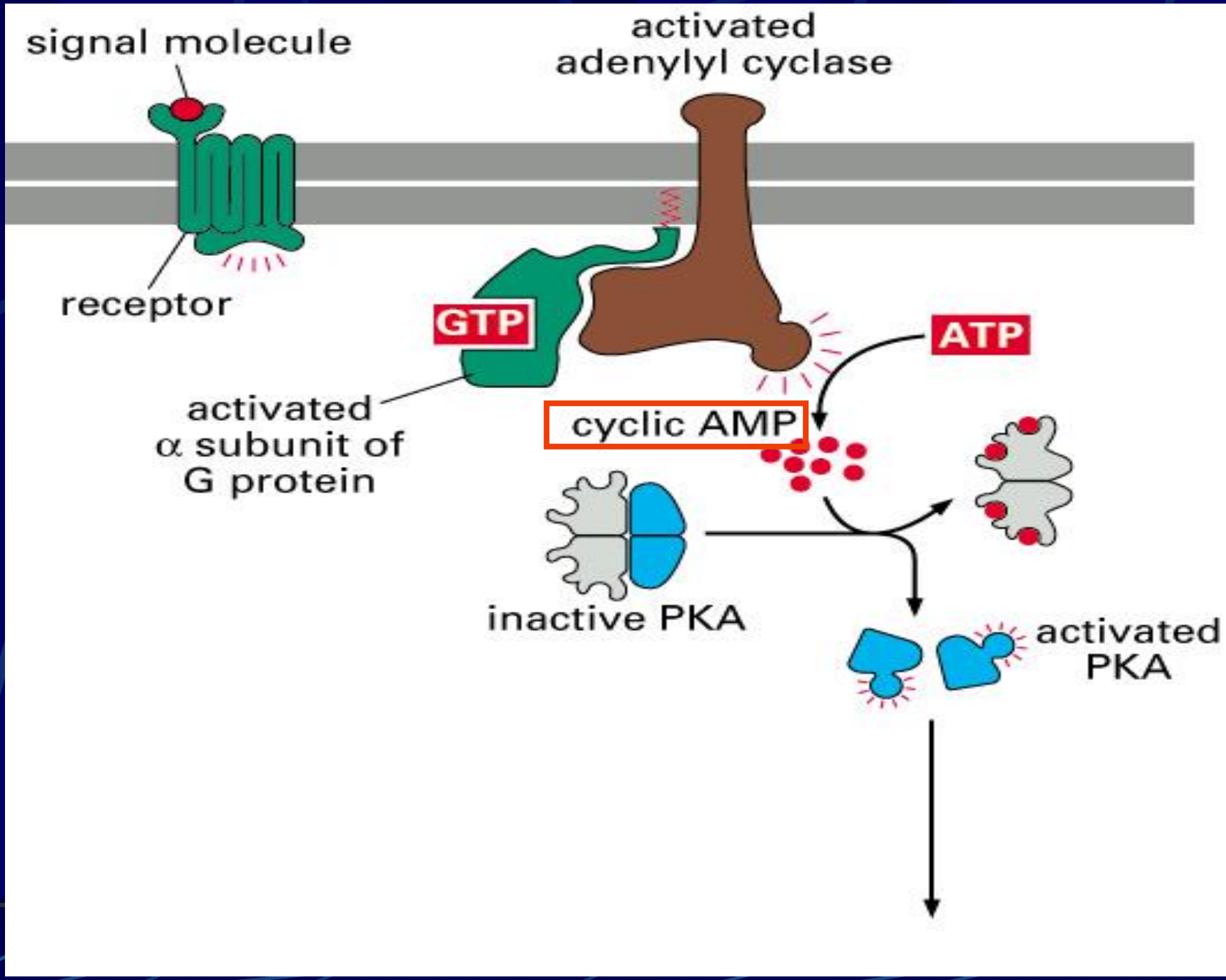
~150 receptores “ órfãos “

HORMÔNIOS HIDROSSOLÚVEIS
RECEPTORES



⇨ **receptores com 7 domínios transmembrana**
⇨ **geração de segundo mensageiro**


receptor protein
inactive G protein
α
β
γ
(A)
GDP
plasma membrane
signal molecule
EXTRACELLULAR SPACE
(B)
CYTOSOL
GDP
GDP
GTP
activated G-protein subunits
(C)
GTP
activated α subunit
activated βγ complex


signal molecule
activated
adenylyl cyclase
receptor
GTP
ATP
activated
α subunit of
G protein
cyclic AMP
inactive PKA
activated
PKA

Adrenalina

Noradrenalina

Intracelular

Gβ

Gαs

Gγ

GTP

Adenilil Ciclase

ATP

AMPc

AMPc

P

CREB

Núcleo

RNAm

Proteínas

R

C

R

C

PKA

P

Proteínas

Efeito Biológico

Table 15–1 Some Hormone-induced Cell Responses Mediated by Cyclic AMP

TARGET TISSUE	HORMONE	MAJOR RESPONSE
Thyroid gland	thyroid-stimulating hormone (TSH)	thyroid hormone synthesis and secretion
Adrenal cortex	adrenocorticotrophic hormone (ACTH)	cortisol secretion
Ovary	luteinizing hormone (LH)	progesterone secretion
Muscle	adrenaline	glycogen breakdown
Bone	parathormone	bone resorption
Heart	adrenaline	increase in heart rate and force of contraction
Liver	glucagon	glycogen breakdown
Kidney	vasopressin	water resorption
Fat	adrenaline, ACTH, glucagon, TSH	triglyceride breakdown

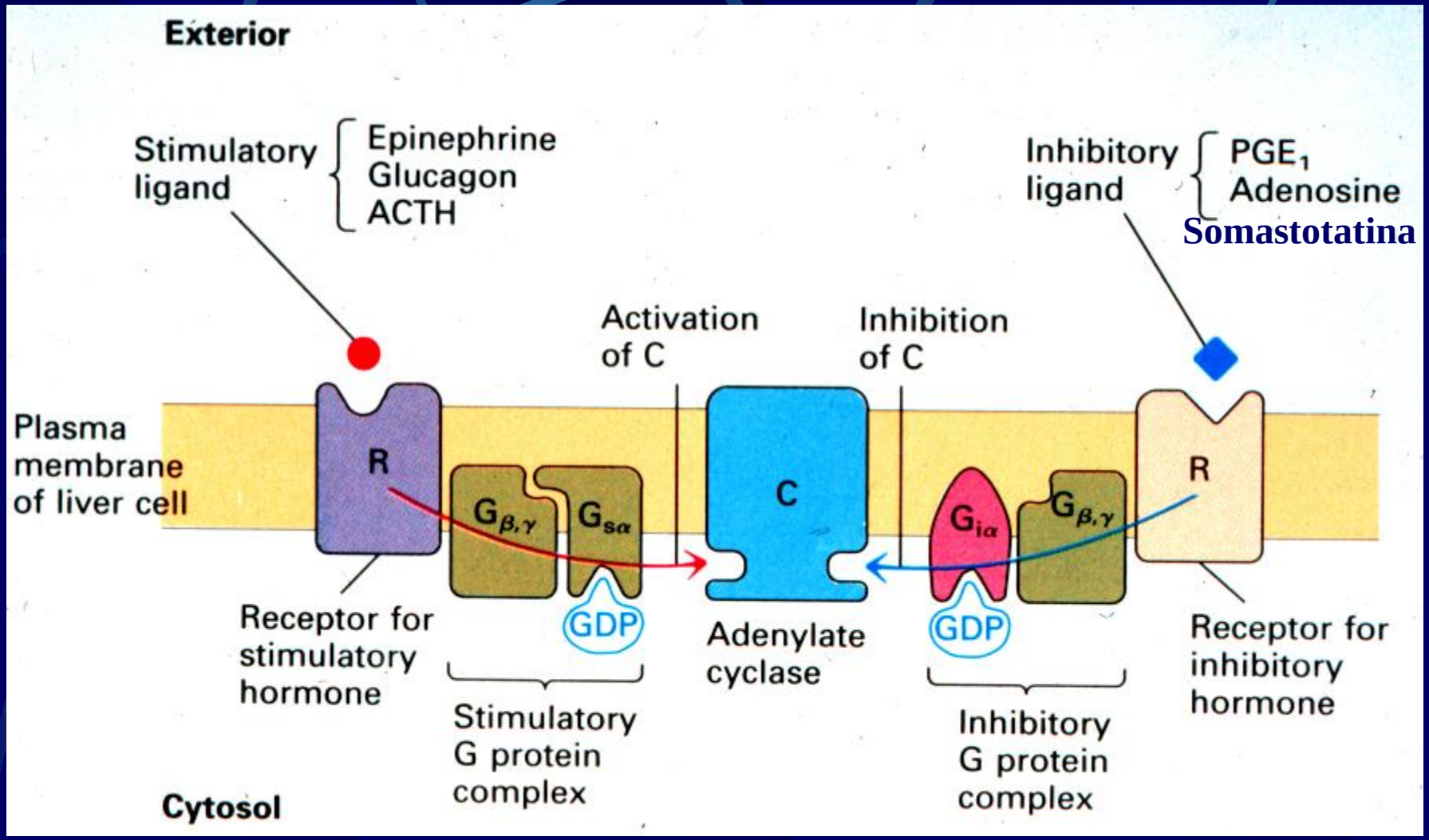
Mecanismos de transdução de sinais

- 1 – Receptores – acoplados a proteínas G alteram a atividade de enzimas na membrana plasmática .

  Ex:

Gs $\rightarrow \uparrow$ adenil ciclase $\rightarrow \uparrow$ cAMP $\rightarrow \uparrow$ PKA

Gi $\rightarrow \downarrow$ adenil ciclase $\rightarrow \downarrow$ cAMP $\rightarrow \downarrow$ PKA


Exterior
Stimulatory ligand
Epinephrine
Glucagon
ACTH
Inhibitory ligand
PGE1
Adenosine
Somastotatina
Activation of C
Inhibition of C
Plasma membrane of liver cell
R
Gβ,γ
Gsα
C
Giα
Gβ,γ
R
GDP
GDP
Receptor for stimulatory hormone
Adenylate cyclase
Receptor for inhibitory hormone
Stimulatory G protein complex
Inhibitory G protein complex
Cytosol

Mecanismos de transdução de sinais

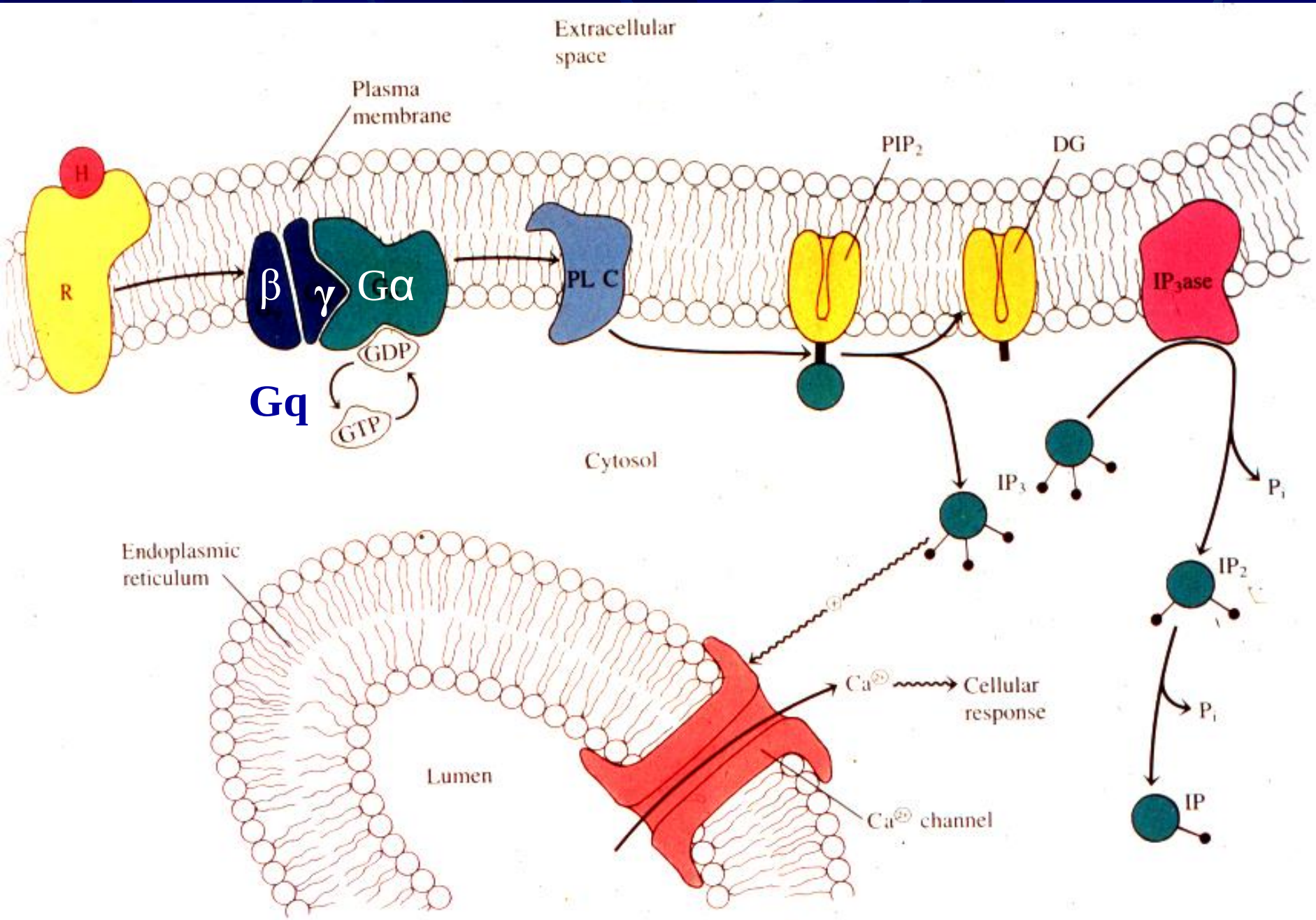
- 1 – Receptores – acoplados a proteínas G alteram a atividade de enzimas na membrana plasmática .

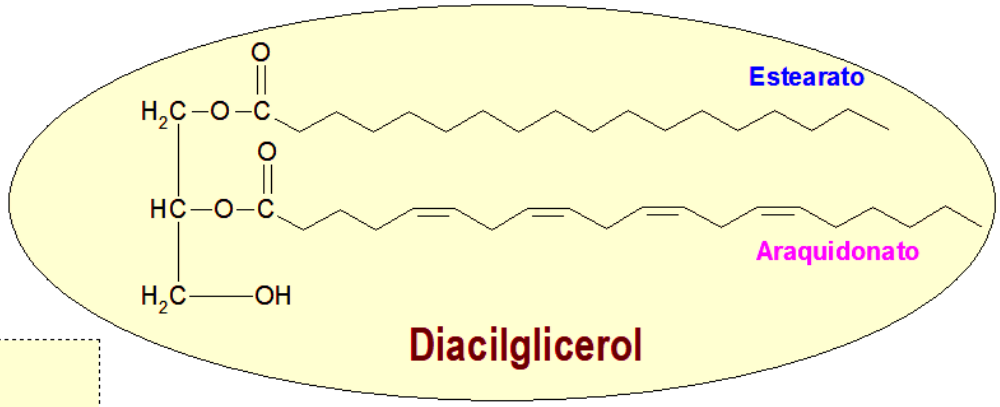
  Ex:

Gs $\rightarrow \uparrow$ adenil ciclase $\rightarrow \uparrow$ cAMP $\rightarrow \uparrow$ PKA

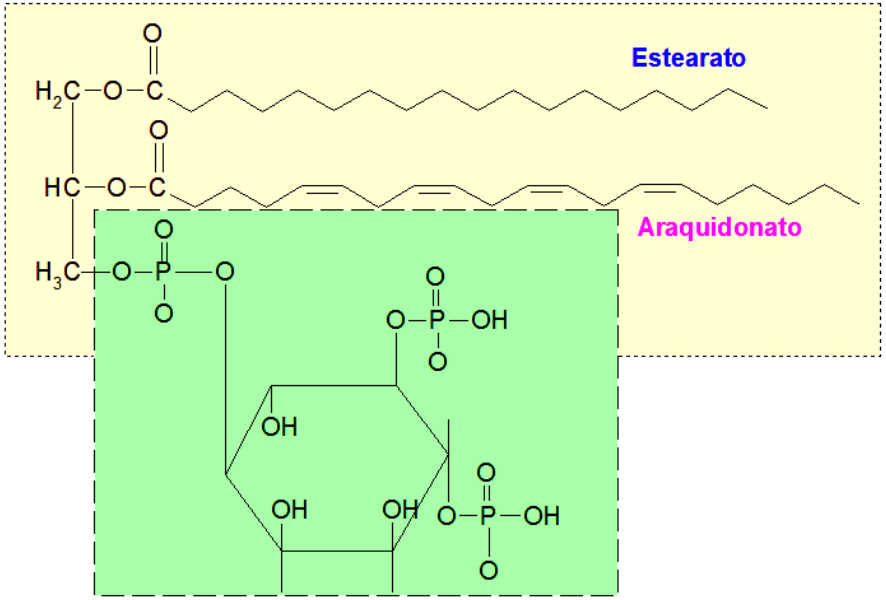
Gi $\rightarrow \downarrow$ adenil ciclase $\rightarrow \downarrow$ cAMP $\rightarrow \downarrow$ PKA

Gq $\rightarrow \uparrow$ fosfolipase C $\rightarrow \uparrow$ IP_3 (Ca^{++}) e DAG $\rightarrow \uparrow$ PKC

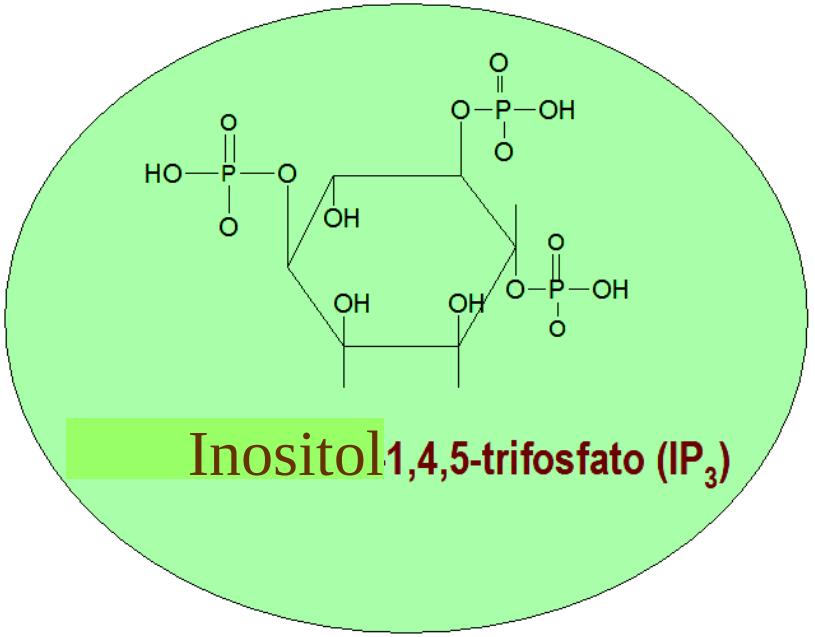

Extracellular space
Plasma membrane
H
R
β
γ
Gα
GDP
GTP
Gq
PL C
PIP2
DG
IP3ase
Cytosol
IP3
Pi
IP2
Pi
IP
Endoplasmic reticulum
Lumen
Ca2+
Cellular response
Ca2+ channel



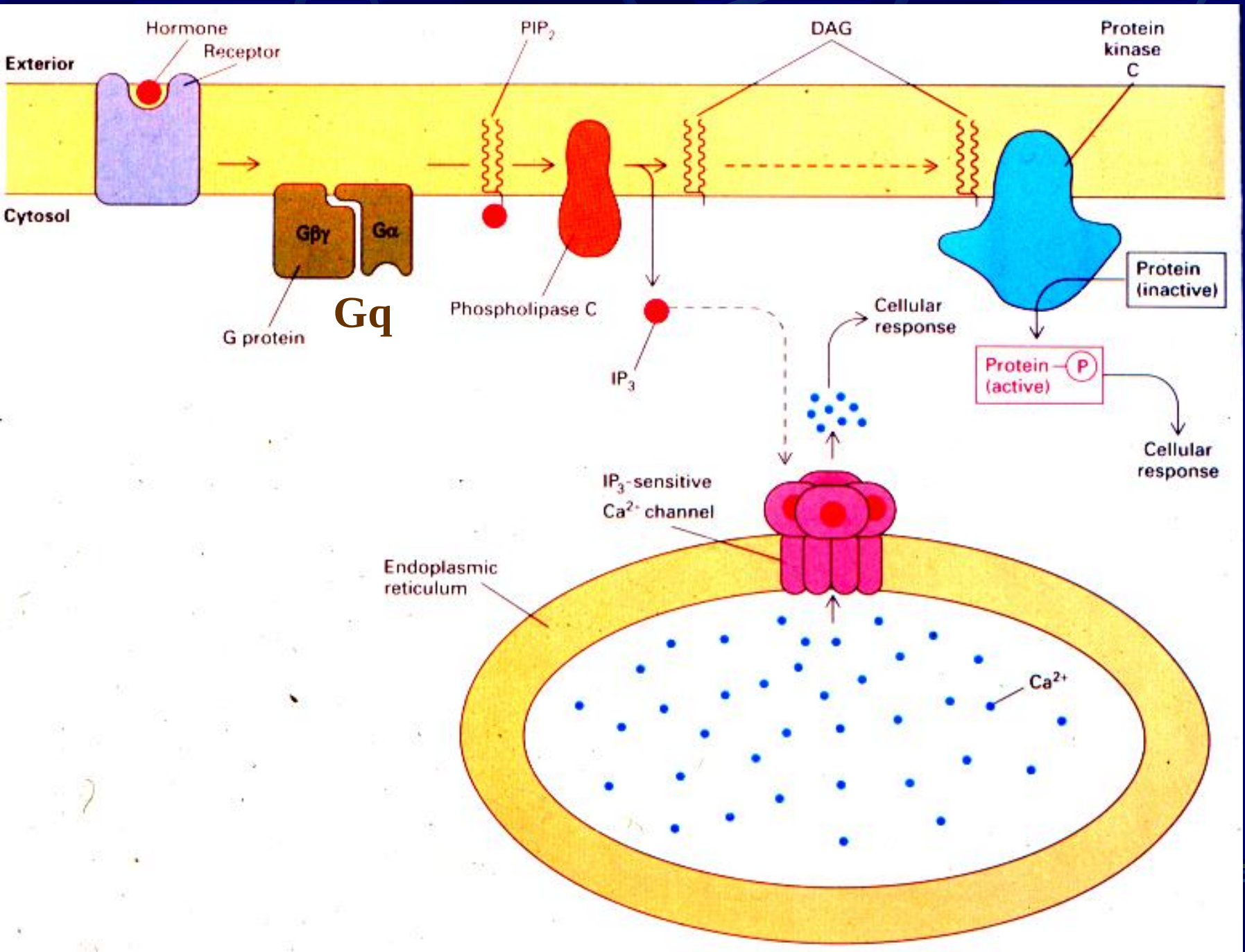
Diacilglicerol



Fosfatidilinositol-4,5-bisfosfato (PIP_2)

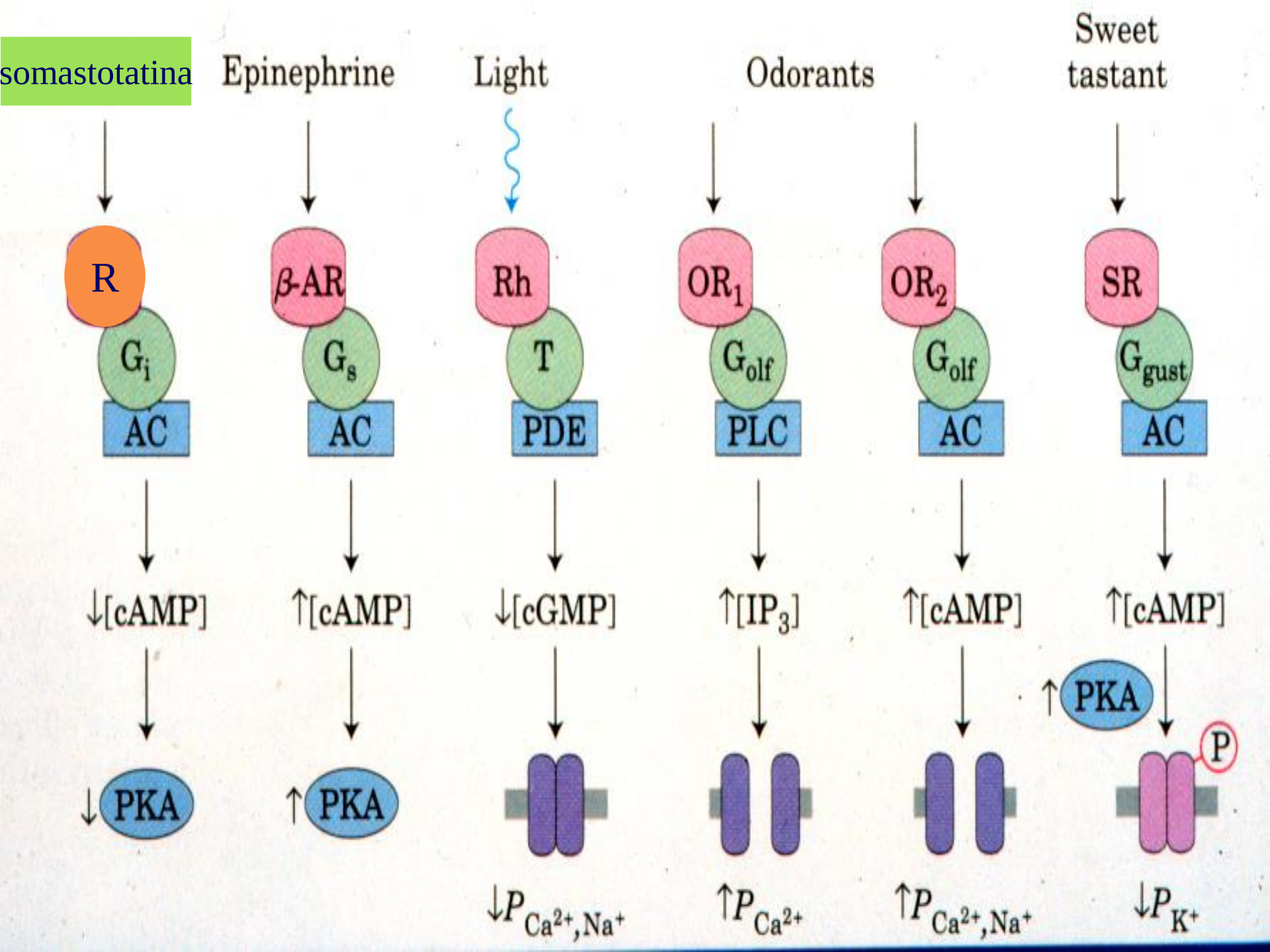


Inositol 1,4,5-trifosfato (IP_3)


Hormone
Receptor
Exterior
Cytosol
PIP2
DAG
Protein kinase C
Gβγ
Gα
G protein
Gq
Phospholipase C
IP3
Protein (inactive)
Cellular response
Protein (active)
P
Cellular response
IP3-sensitive Ca2+ channel
Endoplasmic reticulum
Ca2+

Algumas respostas celulares conhecidas serem mediadas pela via fosfatidil inositol

Sinal externo	*Tecido*	*Resposta celular*
Vasopressina	Fígado	Glicogenólise
ACH	Pâncreas	Secreção de amilase
ACH	Músculo liso	Contração
ACH	Cél. β pâncreas	Secreção de insulina
		Secreção de prolactina
TRH	Hipófice anterior	Secreção de TSH
Serotonina	Gland. salivar (inseto)	Secreção de histamina
Fatores de crescimento	Fibroblastos	Síntese de DNA
GnRH	Hipófise	Liberação de FSH e LH


somastotatina
Epinephrine
Light
Odorants
Sweet tastant
R
G_i
AC
β-AR
G_s
AC
Rh
T
PDE
OR_1
G_{olf}
PLC
OR_2
G_{olf}
AC
SR
G_{gust}
AC
$\downarrow$[cAMP]
$\uparrow$[cAMP]
$\downarrow$[cGMP]
$\uparrow$[IP_3]
$\uparrow$[cAMP]
$\uparrow$[cAMP]
$\downarrow$ PKA
$\uparrow$ PKA
$\uparrow$ PKA
P
$\downarrow P_{Ca^{2+},Na^+}$
$\uparrow P_{Ca^{2+}}$
$\uparrow P_{Ca^{2+},Na^+}$
$\downarrow P_{K^+}$

Mecanismos de transdução de sinais

- 1 – Receptores – acoplados a proteínas G **(GPCR)** alteram a atividade de enzimas na membrana plasmática ou canais iônicos.

  Ex:

Gs → ↑ adenil ciclase → ↑ cAMP → ↑ PKA

Gi → ↓ adenil ciclase → ↓ cAMP → ↓ PKA

Gq → ↑ fosfolipase C → ↑ IP_3 (Ca^{++}) e DAG → ↑ PKC

G_{gust} → ↑ adenil ciclase → ↑cAMP, ↑ PKA → ↓P K

G_{olf} → ↑ adenil ciclase → ↑cAMP → ↑P Ca^{++} e Na^{+} → ↑P Cl

G_{olf} → ↑ fosfolipase C → ↑ IP_3 → ↑ P Ca^{++}

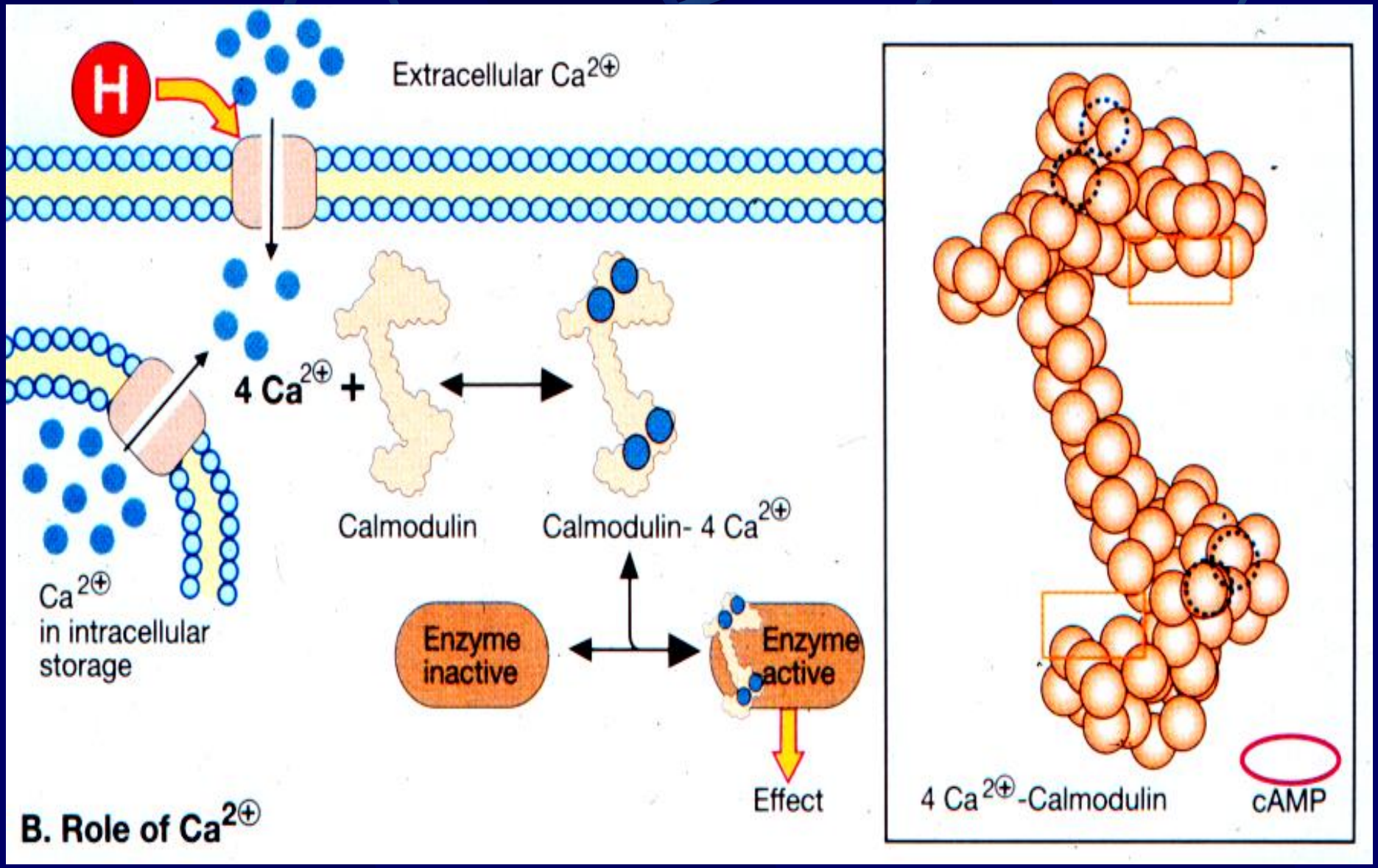

H
Extracellular Ca2⊕
4 Ca2⊕ +
Calmodulin
Calmodulin- 4 Ca2⊕
Ca2⊕
in intracellular
storage
Enzyme
inactive
Enzyme
active
Effect
B. Role of Ca2⊕
4 Ca2⊕-Calmodulin
cAMP

TABLE 12–5 Some Proteins Regulated by Ca^{2+} and Calmodulin

Adenylyl cyclase (brain)

Ca^{2+}/calmodulin-dependent protein kinases (CaM kinases I to IV)

Ca^{2+}-dependent Na^{+} channel (*Paramecium*)

Ca^{2+}-release channel of sarcoplasmic reticulum

Calcineurin (phosphoprotein phosphatase 2B)

cAMP phosphodiesterase

cAMP-gated olfactory channel

cGMP-gated Na^{+}, Ca^{2+} channels (rod and cone cells)

Glutamate decarboxylase

Myosin light chain kinases

NAD^{+} kinase

Nitric oxide synthase

Phosphoinositide 3-kinase

Plasma membrane Ca^{2+} ATPase (Ca^{2+} pump)

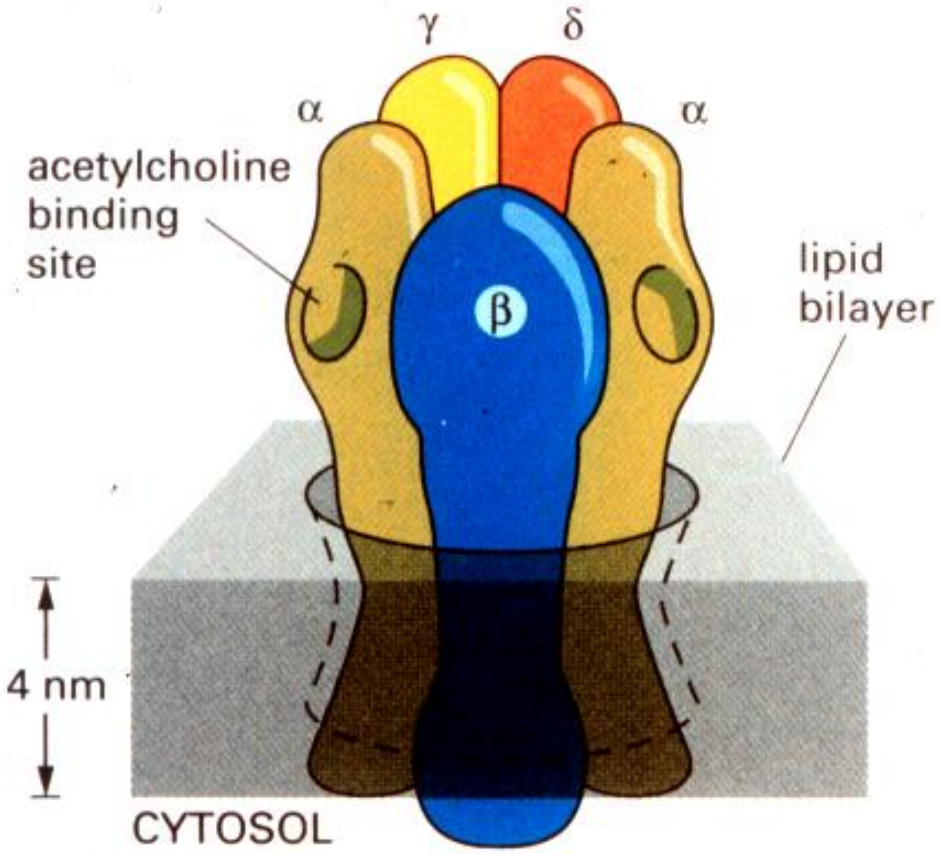
RNA helicase (p68)

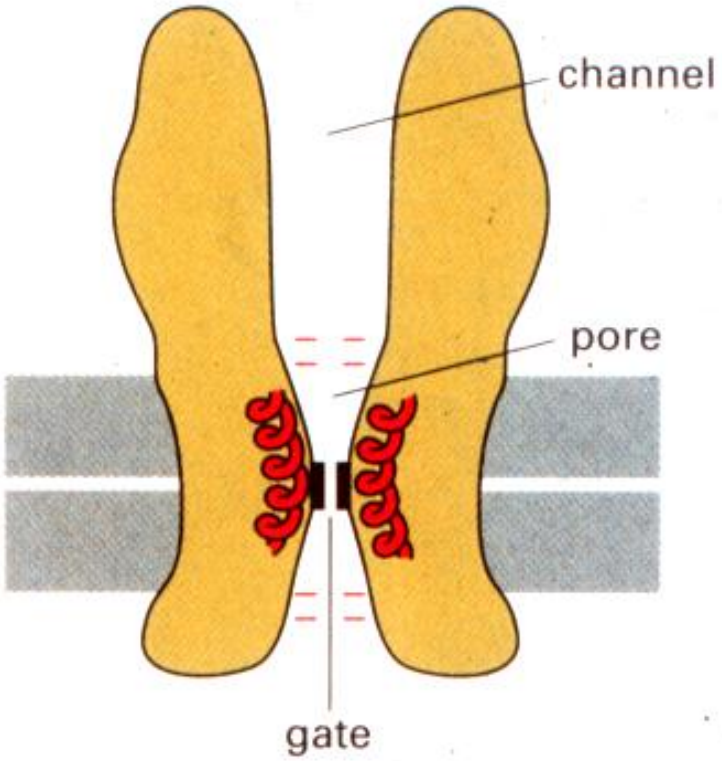
Glicogênio fosforilase quinase

Mecanismos de transdução de sinais

- 2 – Receptores – que são Canais iônicos

EX: Receptor nicotínico da ACH


γ
δ
α
α
acetylcholine
binding
site
β
lipid
bilayer
4 nm
CYTOSOL


channel
pore
gate

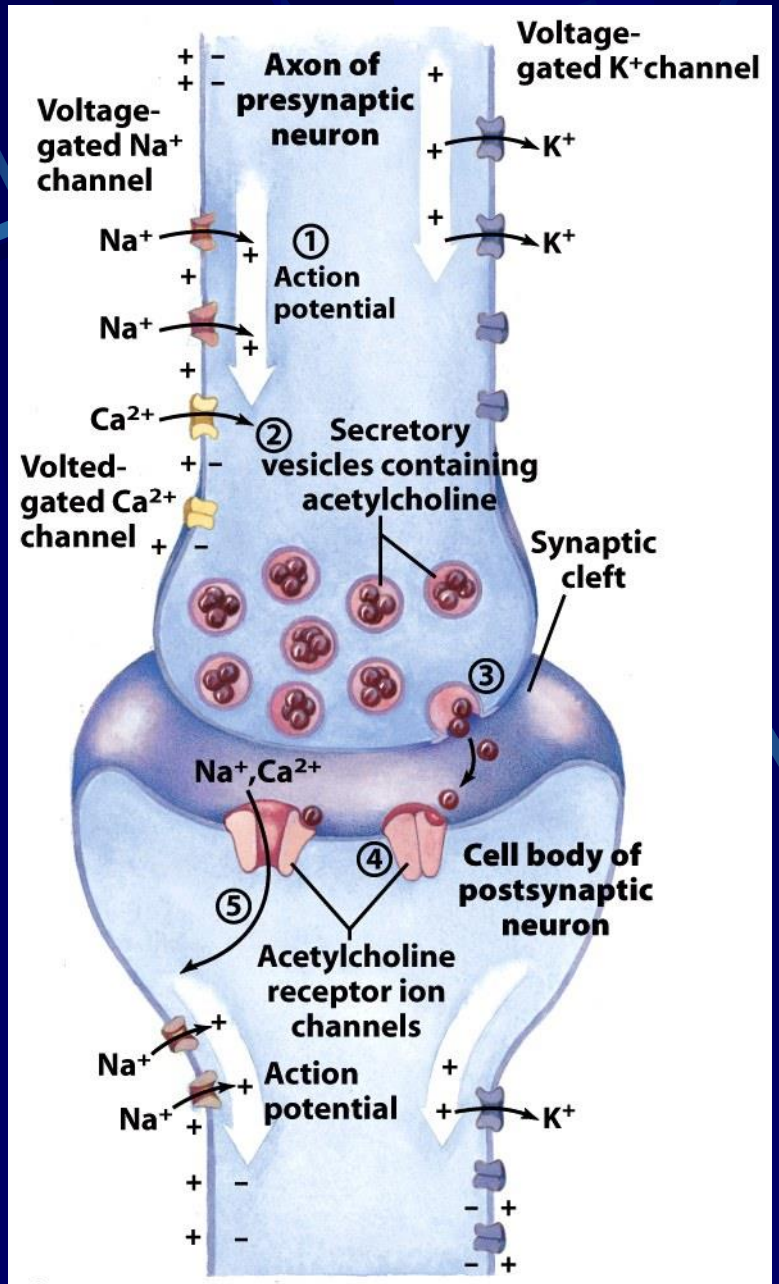


Figure 12-25

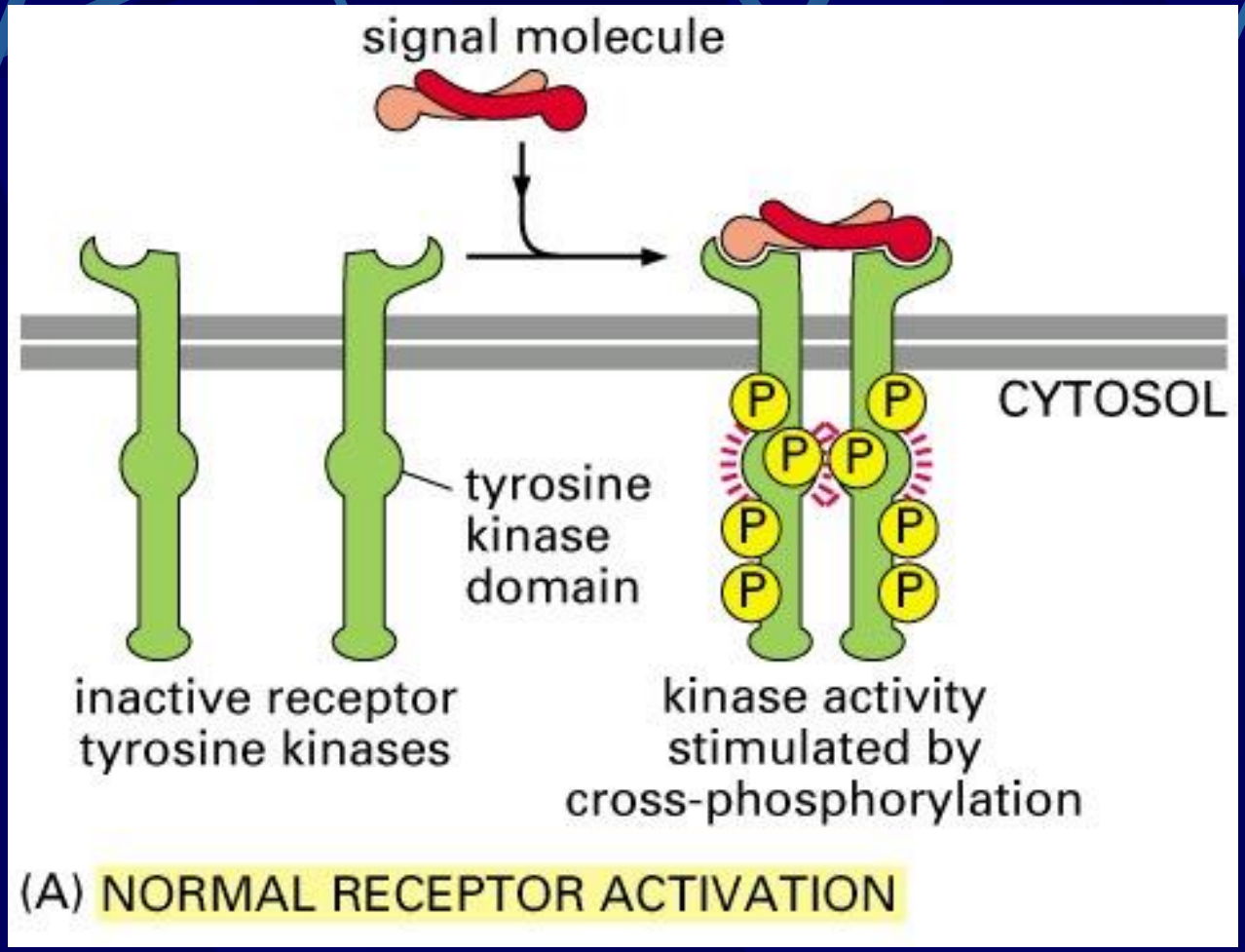
Lehninger Principles of Biochemistry, Fifth Edition

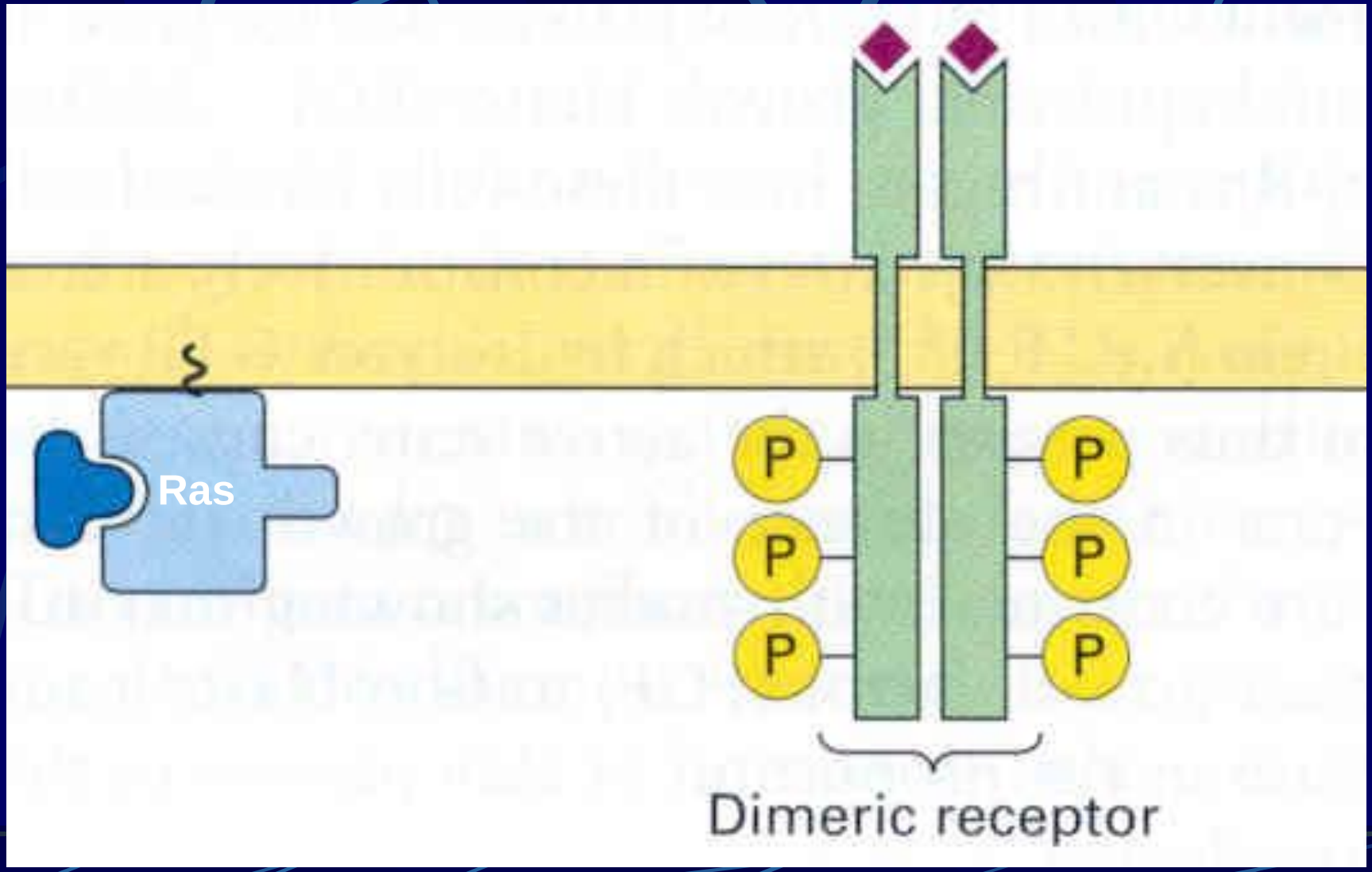
Mecanismos de transdução de sinais

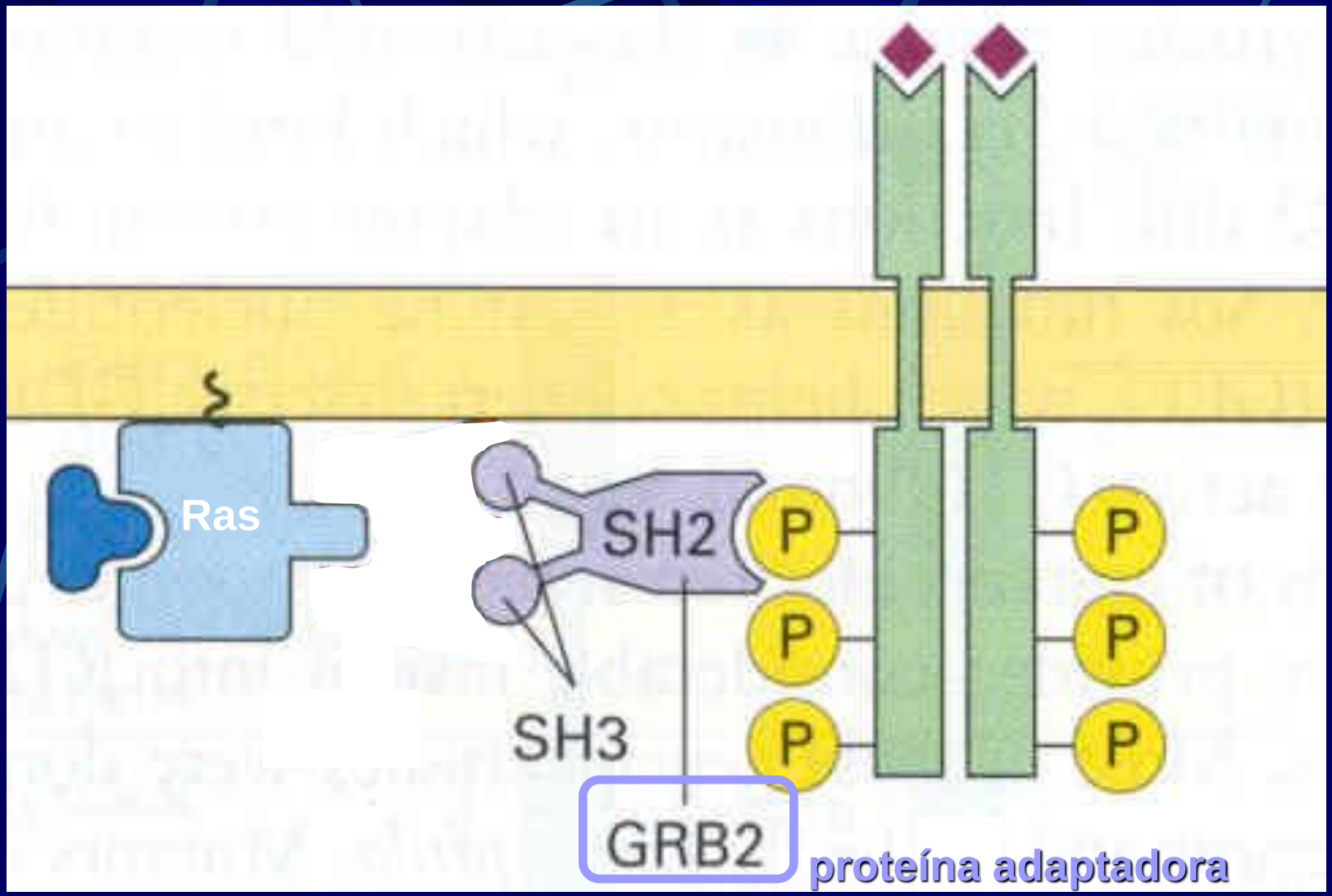
3 – Receptores – que são Enzimas

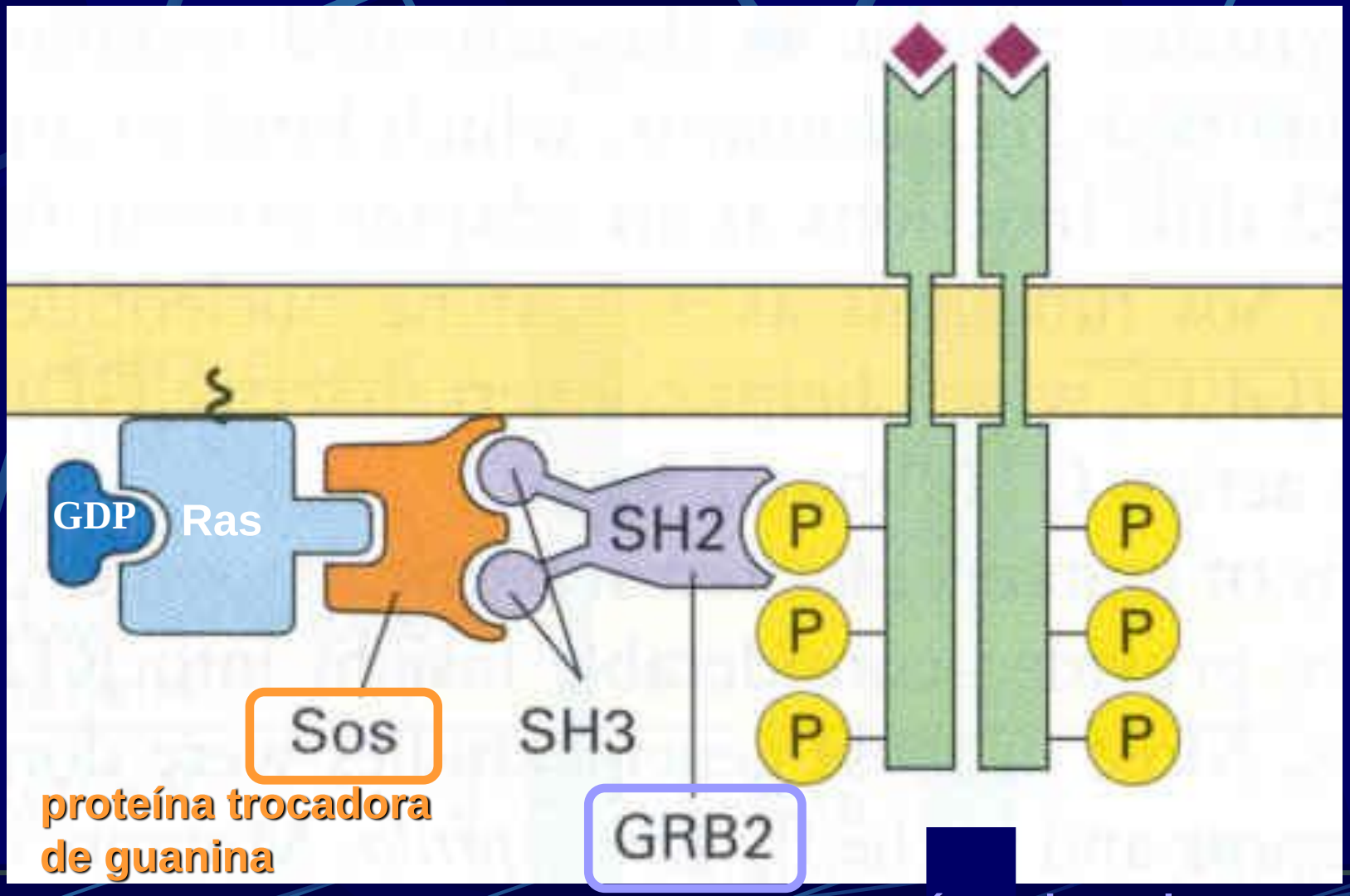
- Tirosina quinase Ex: insulina; EGF
- Guanilato ciclase Ex: ANP
- Ser/Thr quinase Ex: TGF - β
- Tirosina- fosfatase

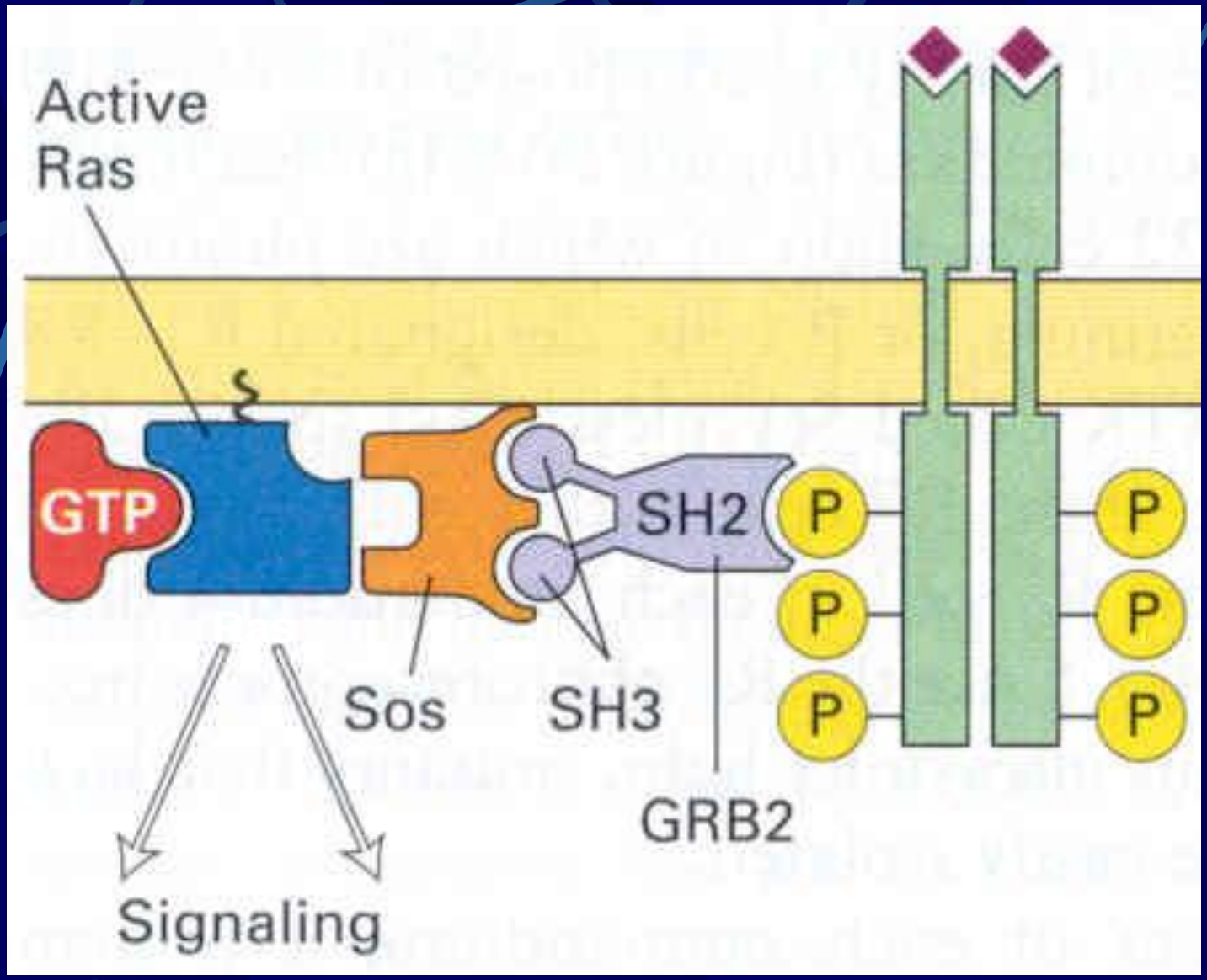
RECEPTORES TIROSINA KINASE
autofosforilação

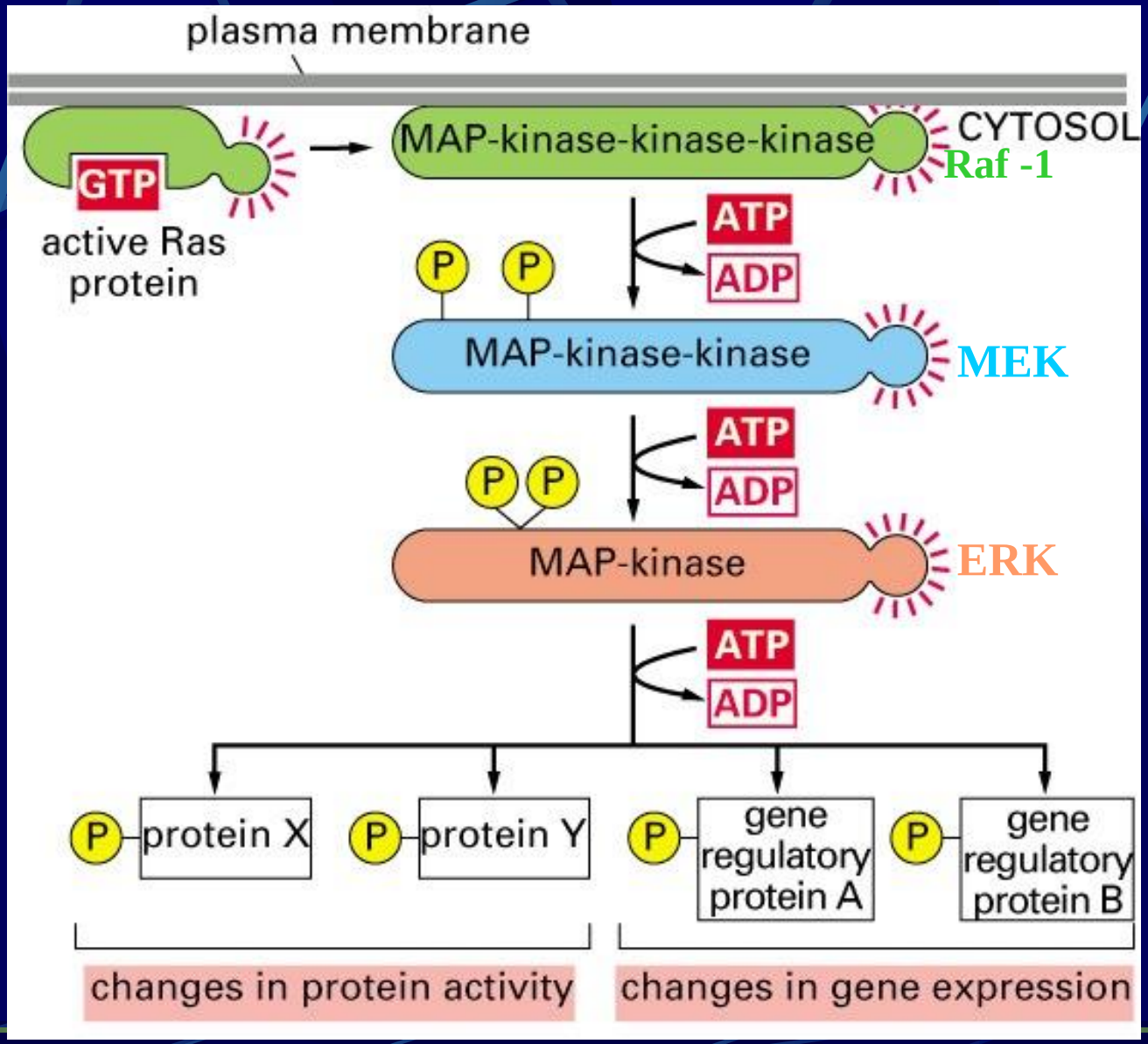


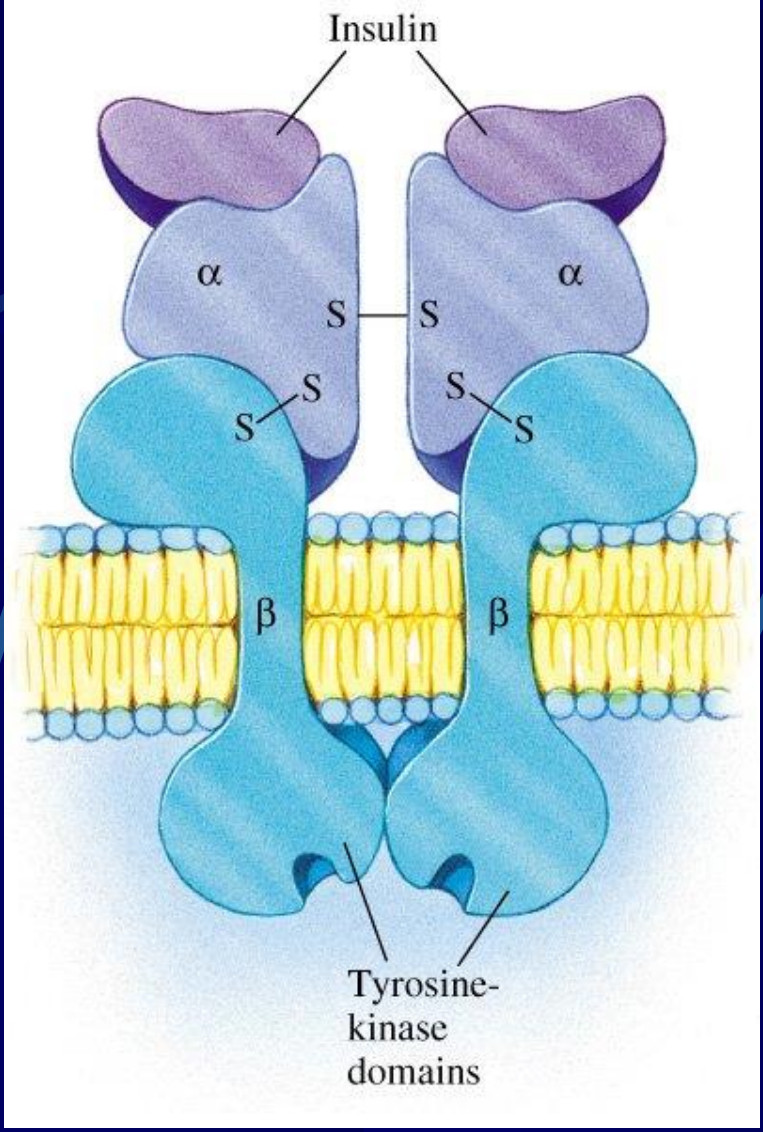

Ras
P
P
P
P
P
P
Dimeric receptor


Ras
SH2
SH3
GRB2
P
P
P
P
P
P
proteína adaptadora

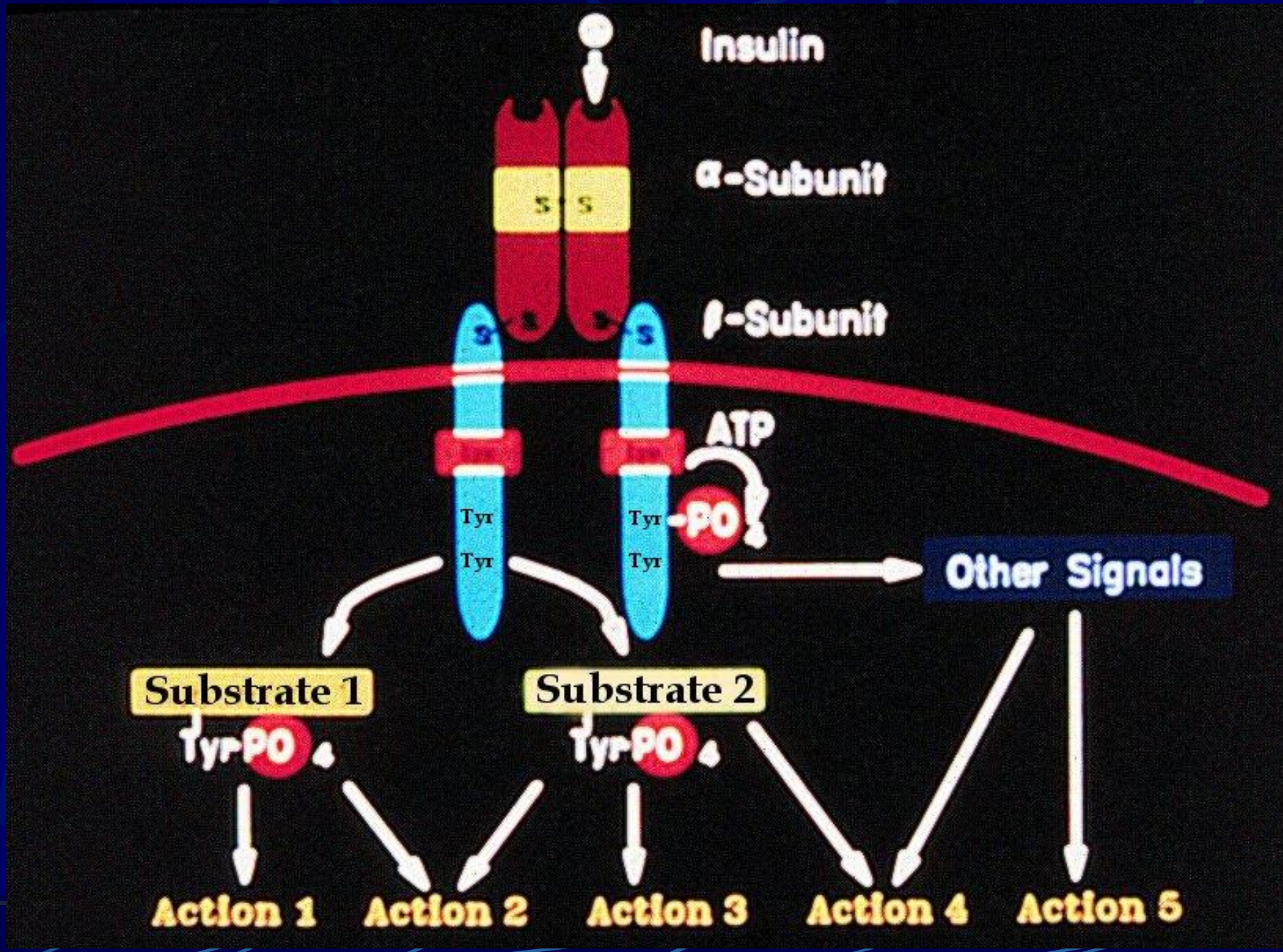

GDP
Ras
SH2
P
P
P
P
P
P
Sos
SH3
GRB2
proteína trocadora
de guanina
proteína adaptadora

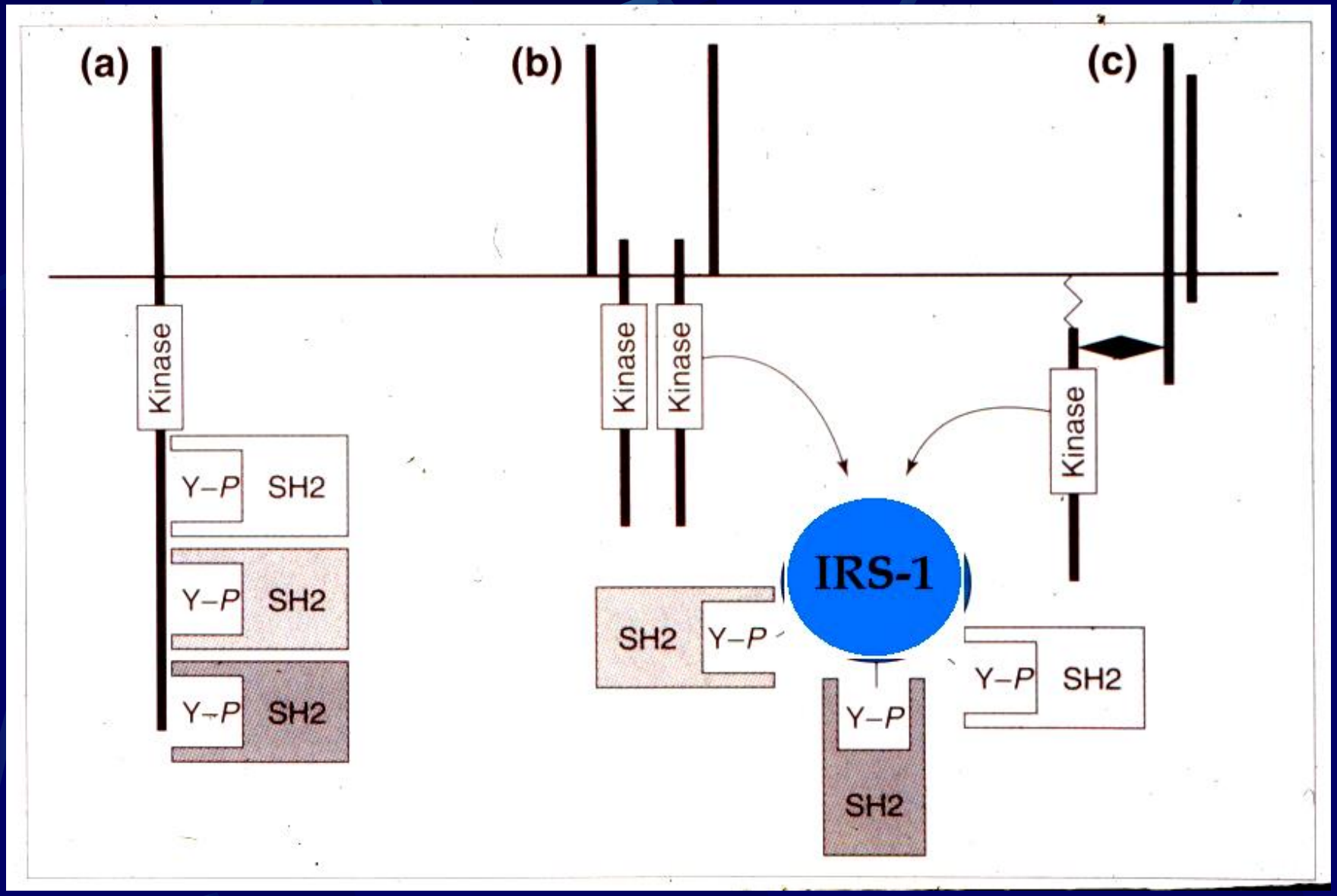

Active
Ras
GTP
SH2
P
P
P
P
P
P
Sos
SH3
GRB2
Signaling

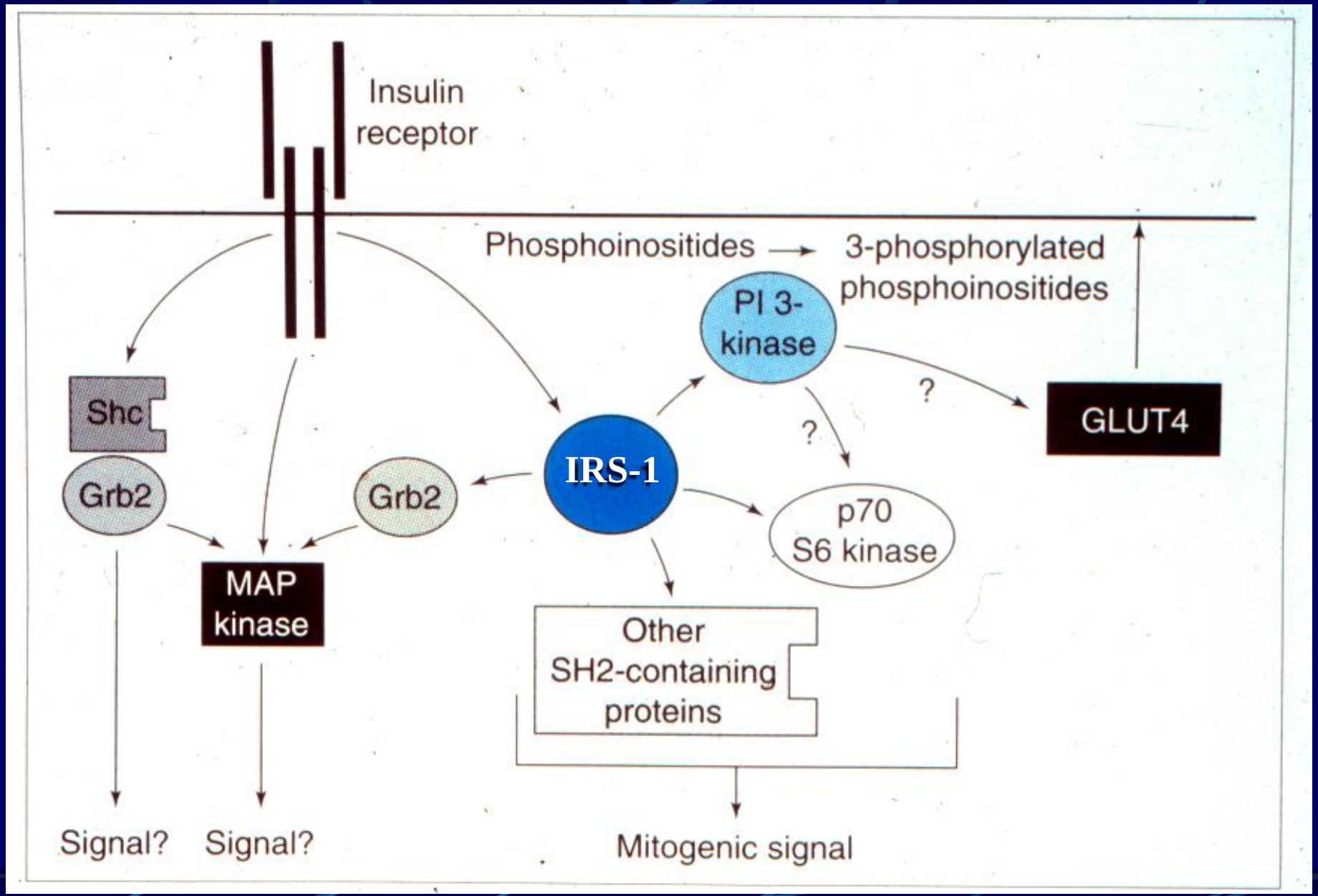

plasma membrane
GTP
active Ras protein
MAP-kinase-kinase-kinase
CYTOSOL
Raf -1
ATP
ADP
P
P
MAP-kinase-kinase
MEK
ATP
ADP
P
P
MAP-kinase
ERK
ATP
ADP
P
protein X
P
protein Y
P
gene regulatory protein A
P
gene regulatory protein B
changes in protein activity
changes in gene expression

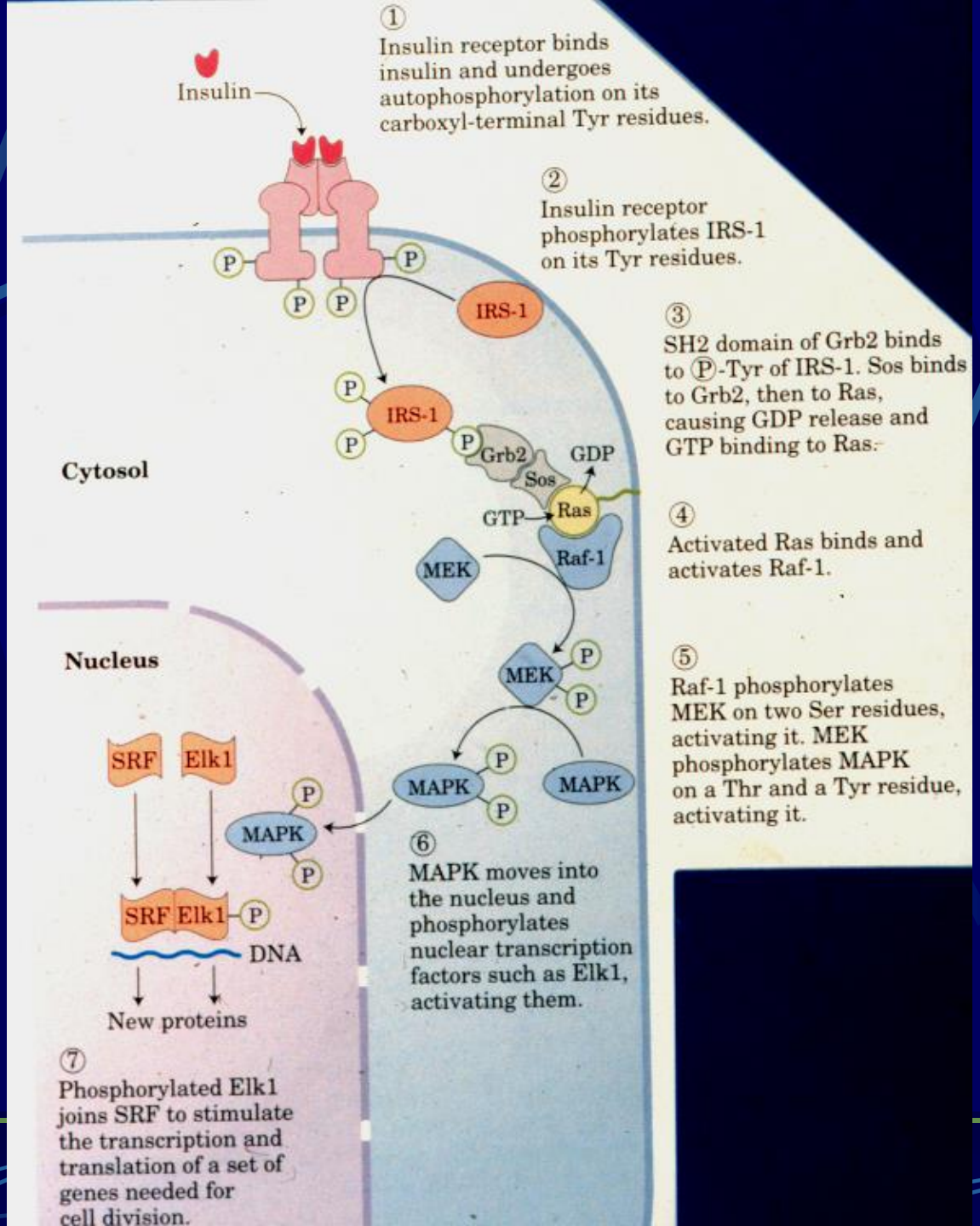


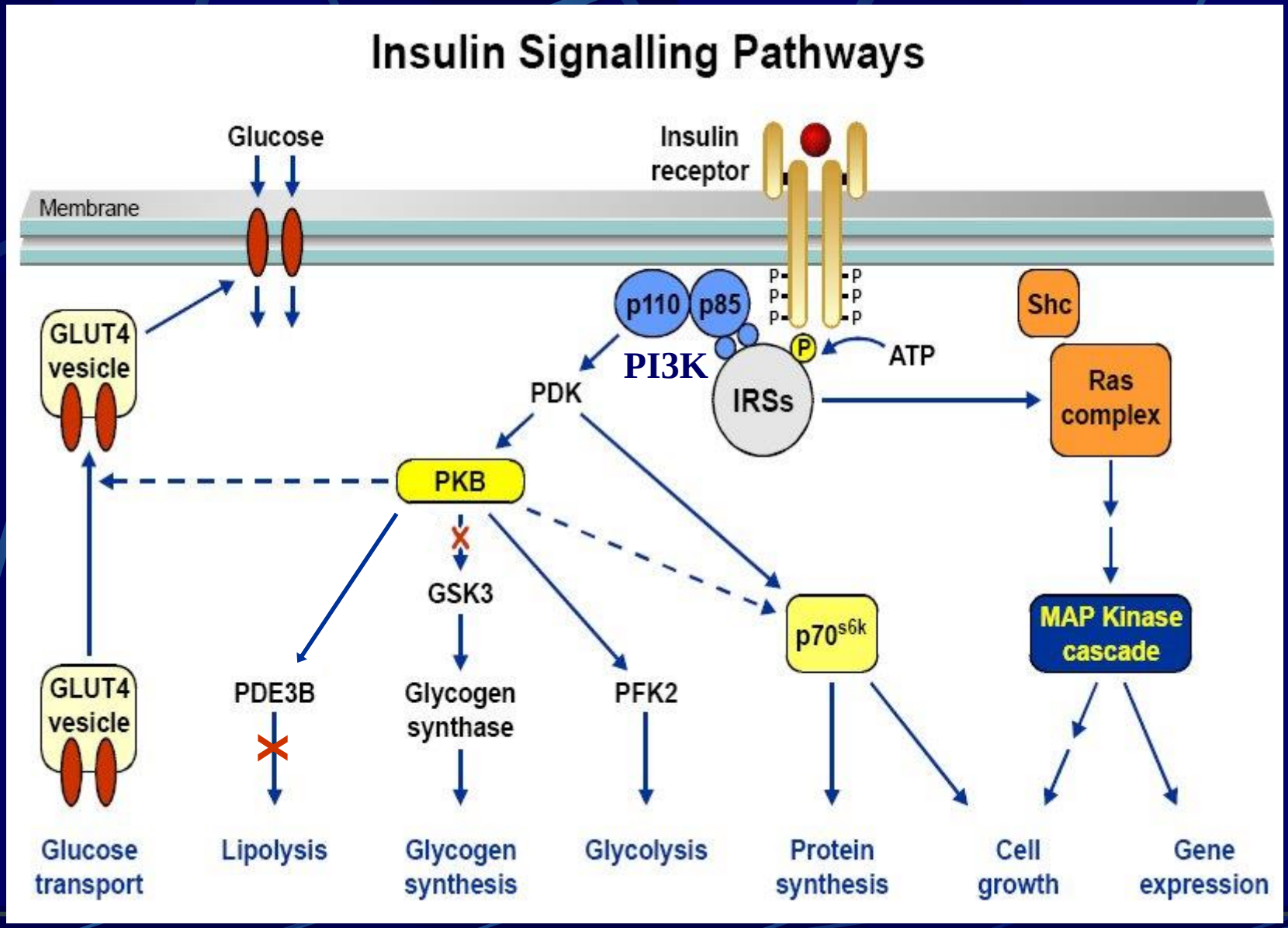
RECEPTORES TIROSINA KINASE

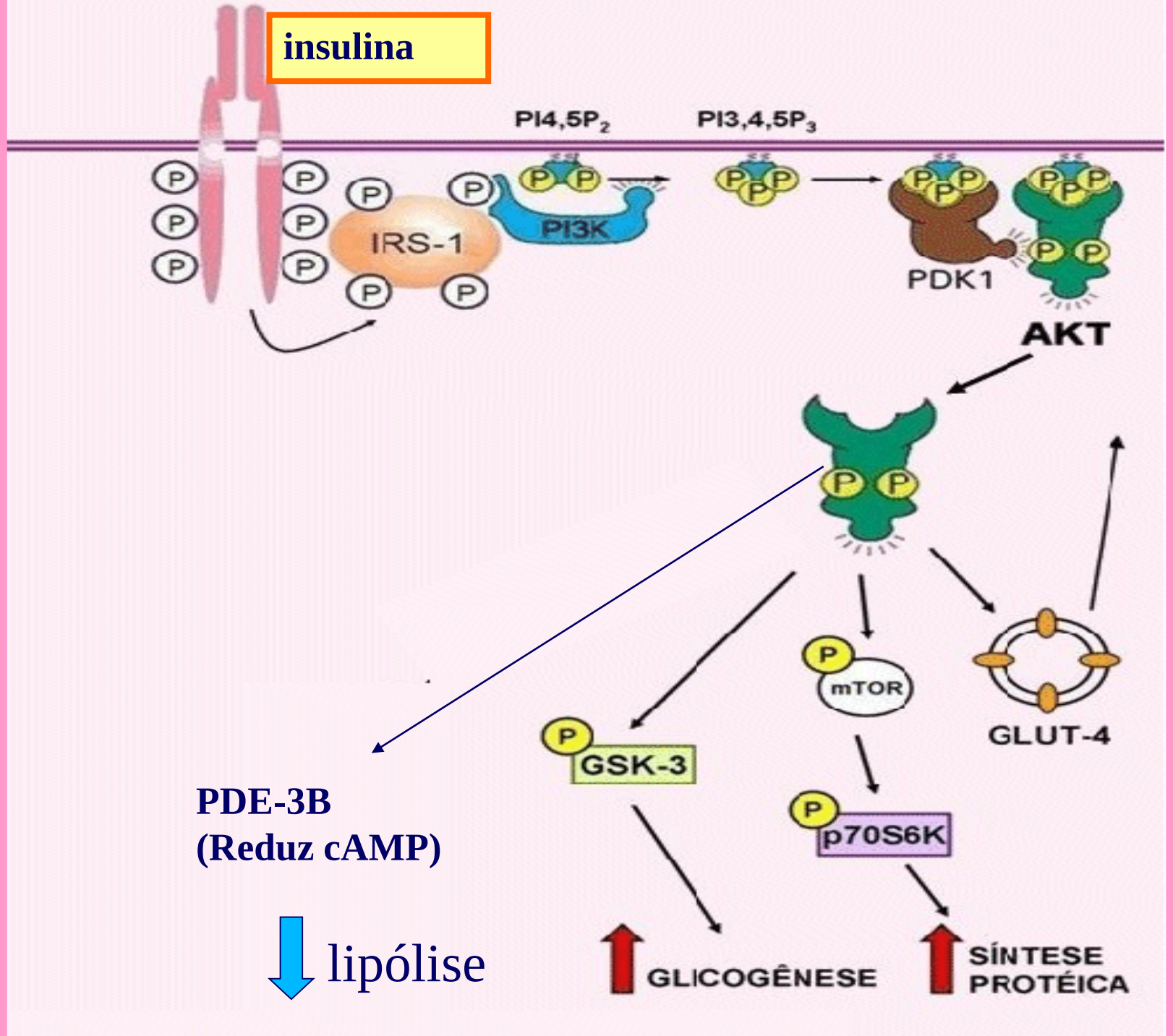

Insulin
α-Subunit
S S
β-Subunit
S S
ATP
Tyr
Tyr
Tyr
Tyr
PO
Other Signals
Substrate 1
Tyr-PO4
Substrate 2
Tyr-PO4
Action 1
Action 2
Action 3
Action 4
Action 5


(a)
(b)
(c)
Kinase
Kinase
Kinase
Kinase
Y–P
SH2
Y–P
SH2
Y–P
SH2
IRS-1
SH2
Y–P
Y–P
SH2
Y–P
SH2


Insulin receptor
Phosphoinositides
3-phosphorylated phosphoinositides
PI 3-kinase
?
GLUT4
Shc
Grb2
Grb2
IRS-1
?
p70 S6 kinase
MAP kinase
Other SH2-containing proteins
Signal?
Signal?
Mitogenic signal

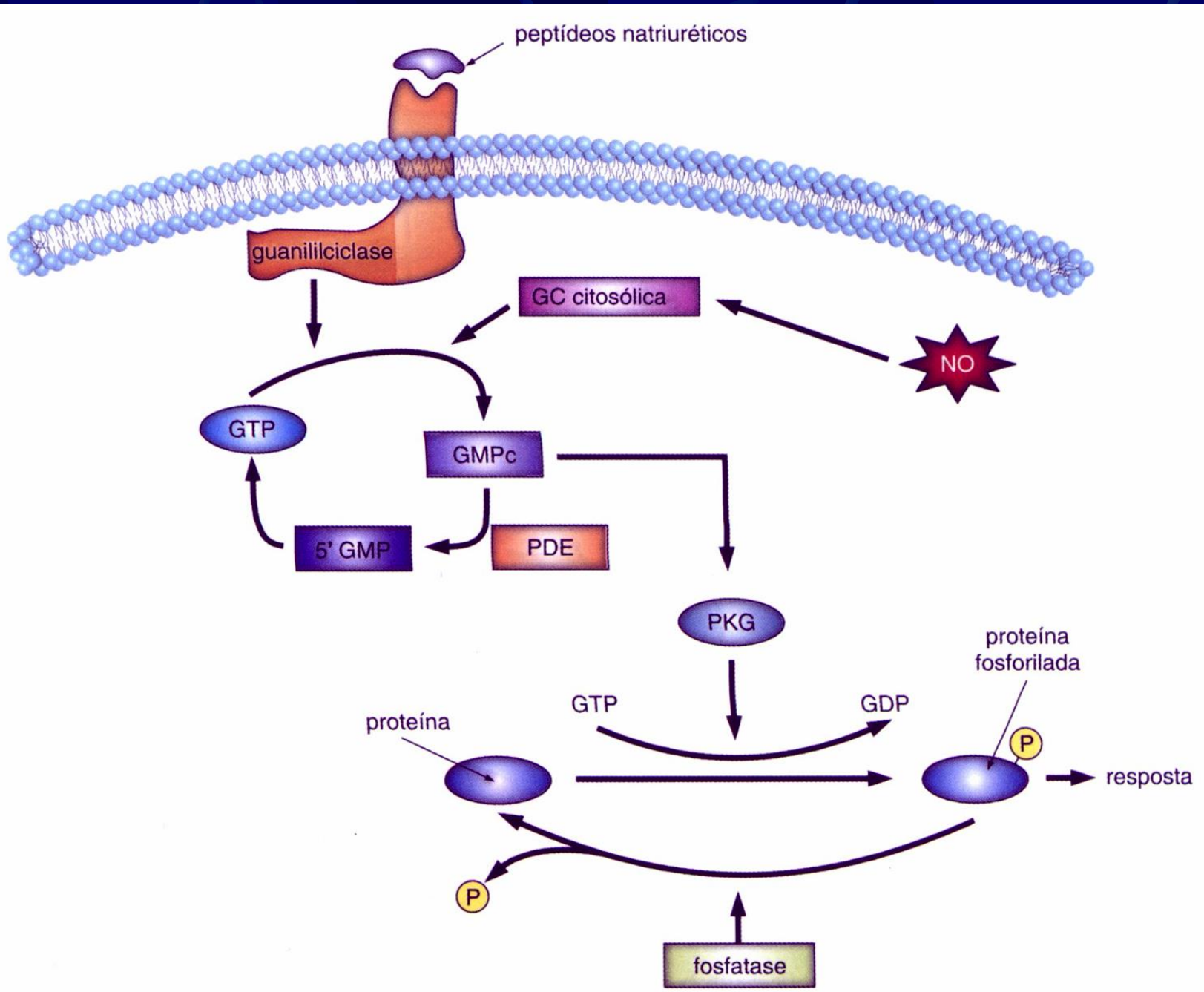

Insulin
① Insulin receptor binds insulin and undergoes autophosphorylation on its carboxyl-terminal Tyr residues.
② Insulin receptor phosphorylates IRS-1 on its Tyr residues.
③ SH2 domain of Grb2 binds to Ⓟ-Tyr of IRS-1. Sos binds to Grb2, then to Ras, causing GDP release and GTP binding to Ras.
④ Activated Ras binds and activates Raf-1.
⑤ Raf-1 phosphorylates MEK on two Ser residues, activating it. MEK phosphorylates MAPK on a Thr and a Tyr residue, activating it.
⑥ MAPK moves into the nucleus and phosphorylates nuclear transcription factors such as Elk1, activating them.
⑦ Phosphorylated Elk1 joins SRF to stimulate the transcription and translation of a set of genes needed for cell division.
Cytosol
Nucleus
IRS-1
Grb2
Sos
GDP
GTP
Ras
Raf-1
MEK
MAPK
SRF
Elk1
DNA
New proteins

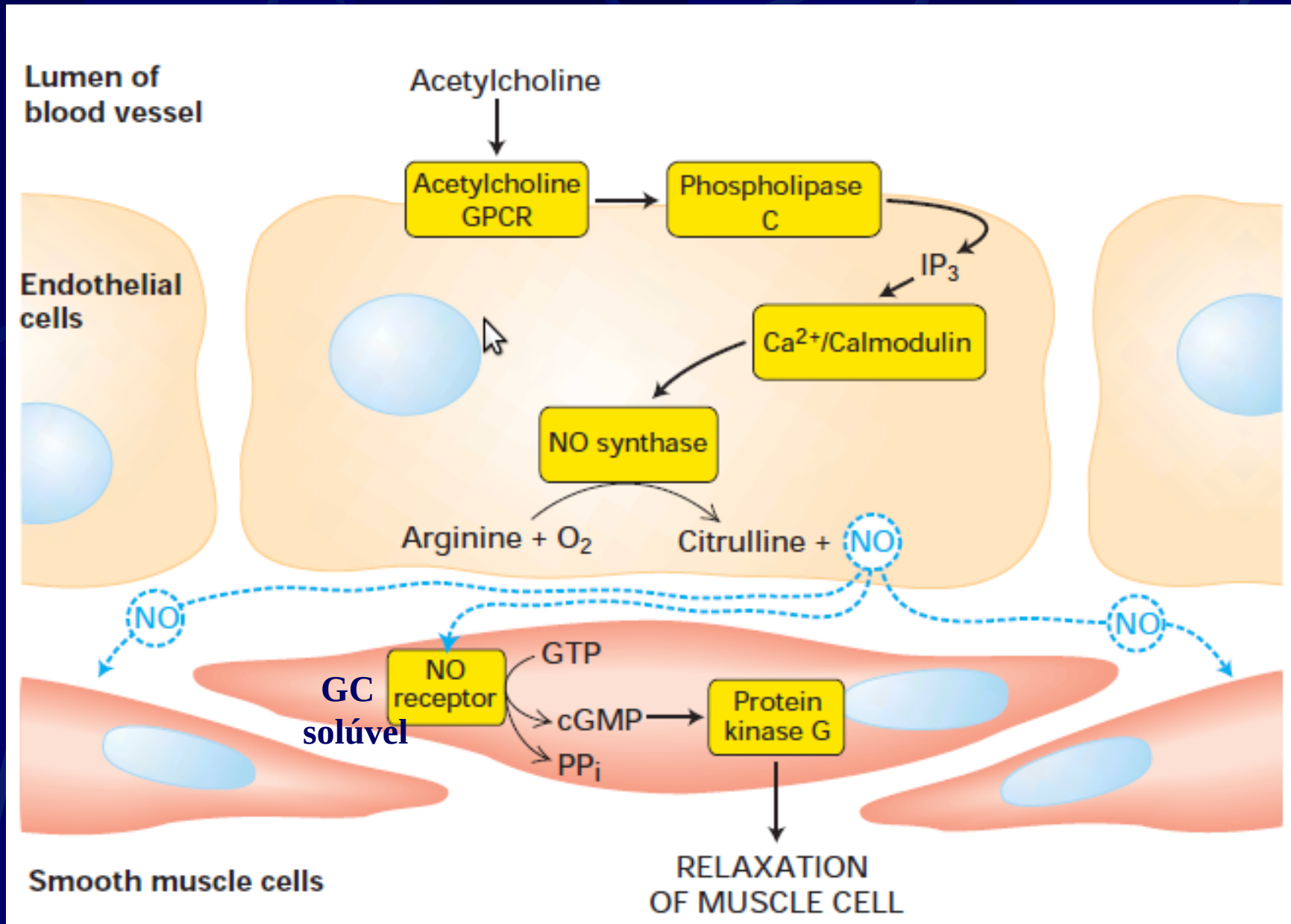

Insulin Signalling Pathways
Glucose
Insulin receptor
Membrane
GLUT4 vesicle
p110
p85
PI3K
P
ATP
Shc
PDK
IRSs
Ras complex
PKB
GSK3
p70s6k
MAP Kinase cascade
GLUT4 vesicle
PDE3B
Glycogen synthase
PFK2
Glucose transport
Lipolysis
Glycogen synthesis
Glycolysis
Protein synthesis
Cell growth
Gene expression


insulina
PI4,5P2
PI3,4,5P3
IRS-1
PI3K
PDK1
AKT
mTOR
GLUT-4
GSK-3
p70S6K
PDE-3B
(Reduz cAMP)
lipólise
GLICOGÊNESE
SÍNTESE
PROTÉICA

Mecanismos de transdução de sinais

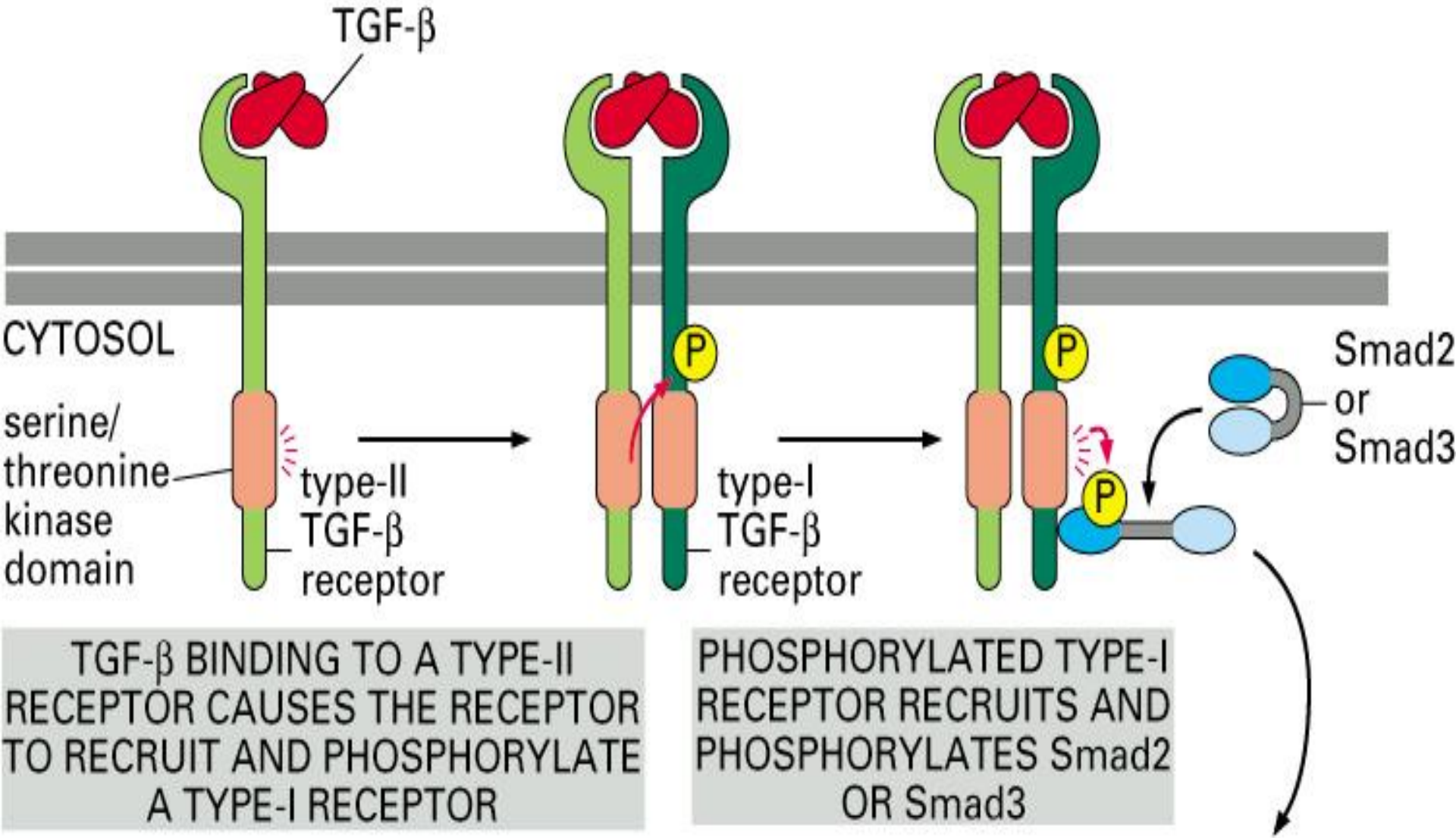
- 3 – Receptores – que são Enzimas
  - Tirosina quinase Ex: insulina; EGF
  - Guanilato ciclase Ex: ANP
  - Ser/Thr quinase Ex: TGF - β
  - Tirosina- fosfatase

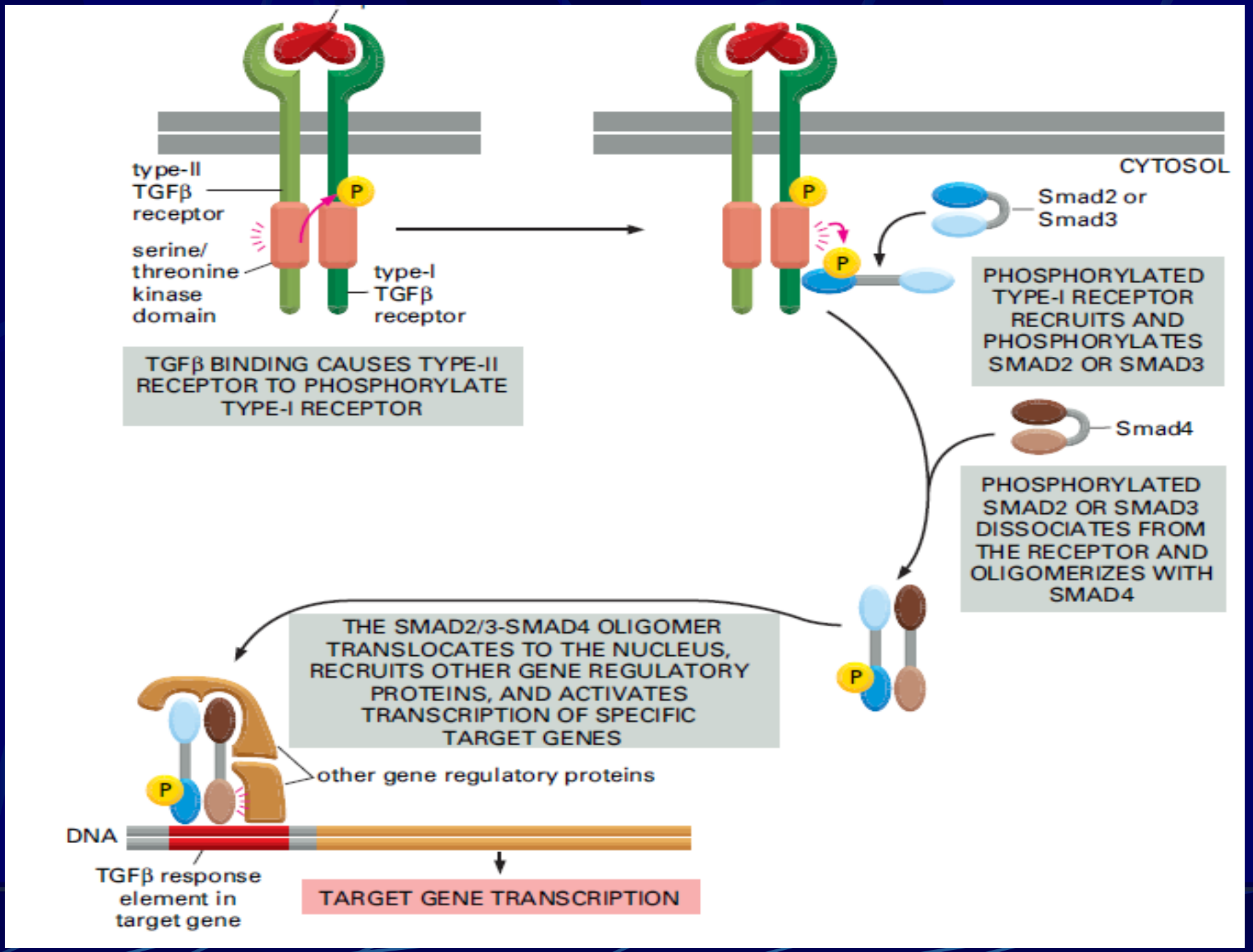

peptídeos natriuréticos
guanililciclase
GC citosólica
NO
GTP
GMPc
5' GMP
PDE
PKG
proteína fosforilada
GTP
GDP
proteína
P
resposta
P
fosfatase


Lumen of blood vessel
Acetylcholine
Acetylcholine GPCR
Phospholipase C
IP_3
Endothelial cells
Ca^{2+}/Calmodulin
NO synthase
Arginine + O_2
Citrulline + NO
NO
NO
GC solúvel
NO receptor
GTP
cGMP
PP_i
Protein kinase G
Smooth muscle cells
RELAXATION OF MUSCLE CELL

Mecanismos de transdução de sinais

- 3 – Receptores – que são Enzimas
  - Tirosina quinase Ex: insulina; EGF
  - Guanilato ciclase Ex: ANP
  - Ser/Thr quinase ex:
    TGF- β; activina; miostatina; BMPs
  - Tirosina- fosfatase


TGF-β
CYTOSOL
serine/
threonine
kinase
domain
type-II
TGF-β
receptor
P
type-I
TGF-β
receptor
P
P
Smad2
or
Smad3
TGF-β BINDING TO A TYPE-II RECEPTOR CAUSES THE RECEPTOR TO RECRUIT AND PHOSPHORYLATE A TYPE-I RECEPTOR
PHOSPHORYLATED TYPE-I RECEPTOR RECRUITS AND PHOSPHORYLATES Smad2 OR Smad3


type-II TGFβ receptor
serine/ threonine kinase domain
type-I TGFβ receptor
P
TGFβ BINDING CAUSES TYPE-II RECEPTOR TO PHOSPHORYLATE TYPE-I RECEPTOR
CYTOSOL
Smad2 or Smad3
PHOSPHORYLATED TYPE-I RECEPTOR RECRUITS AND PHOSPHORYLATES SMAD2 OR SMAD3
Smad4
PHOSPHORYLATED SMAD2 OR SMAD3 DISSOCIATES FROM THE RECEPTOR AND OLIGOMERIZES WITH SMAD4
THE SMAD2/3-SMAD4 OLIGOMER TRANSLOCATES TO THE NUCLEUS, RECRUITS OTHER GENE REGULATORY PROTEINS, AND ACTIVATES TRANSCRIPTION OF SPECIFIC TARGET GENES
other gene regulatory proteins
DNA
TGFβ response element in target gene
TARGET GENE TRANSCRIPTION

Mecanismos de transdução de sinais

- 3 – Receptores – que são Enzimas
  - Tirosina quinase Ex: insulina; EGF
  - Guanilato ciclase Ex: ANP
  - Ser/Thr quinase Ex: TGF - β
  - Tirosina- fosfatase

Mecanismos de transdução de sinais

- 4- Receptores – que não são enzimas mas se associam a enzimas (tirosina-quinases) citosólicas

EX: GH, eritropoetina, leptina, prolactina, citocinas (interferons), etc.

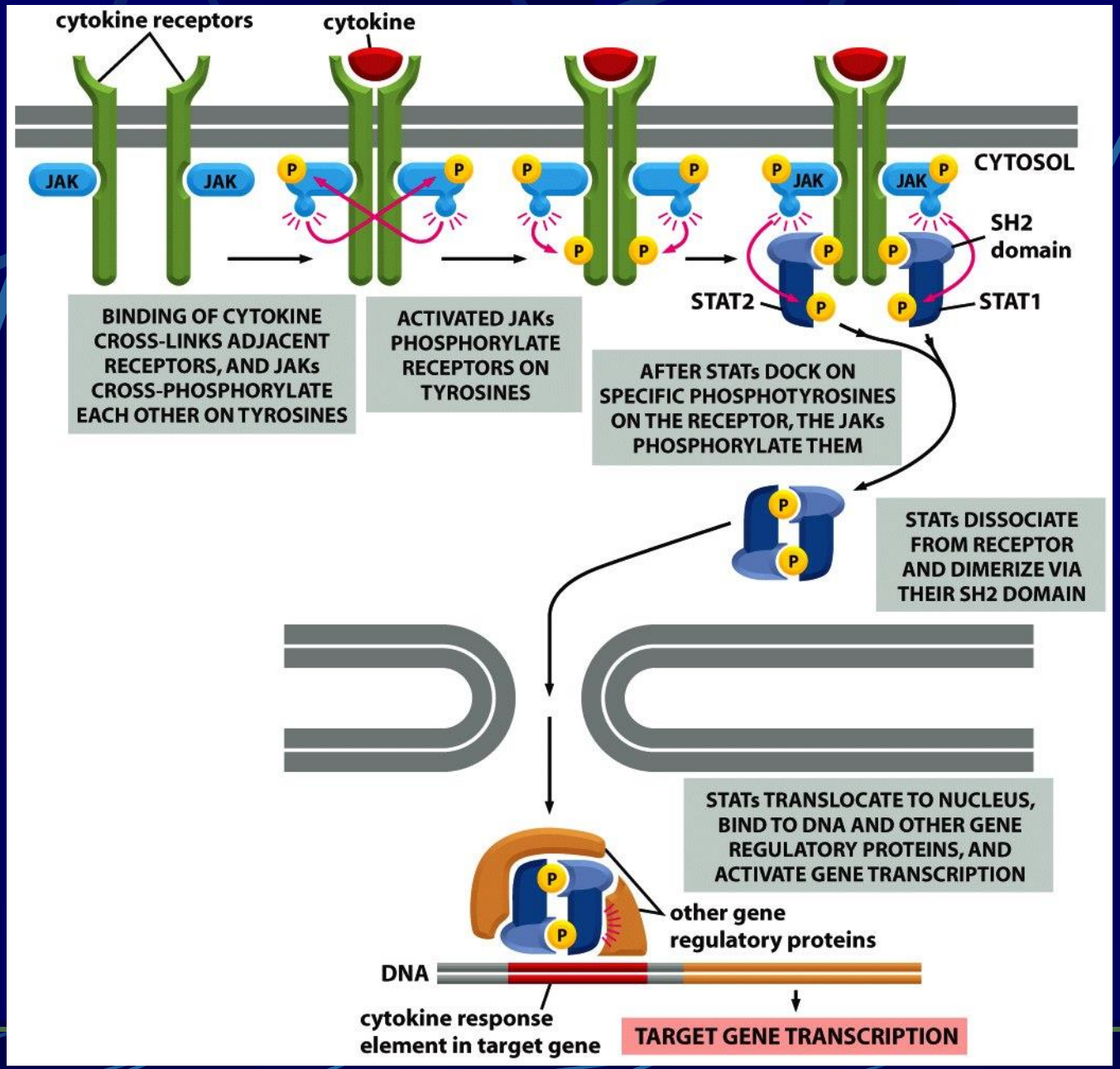
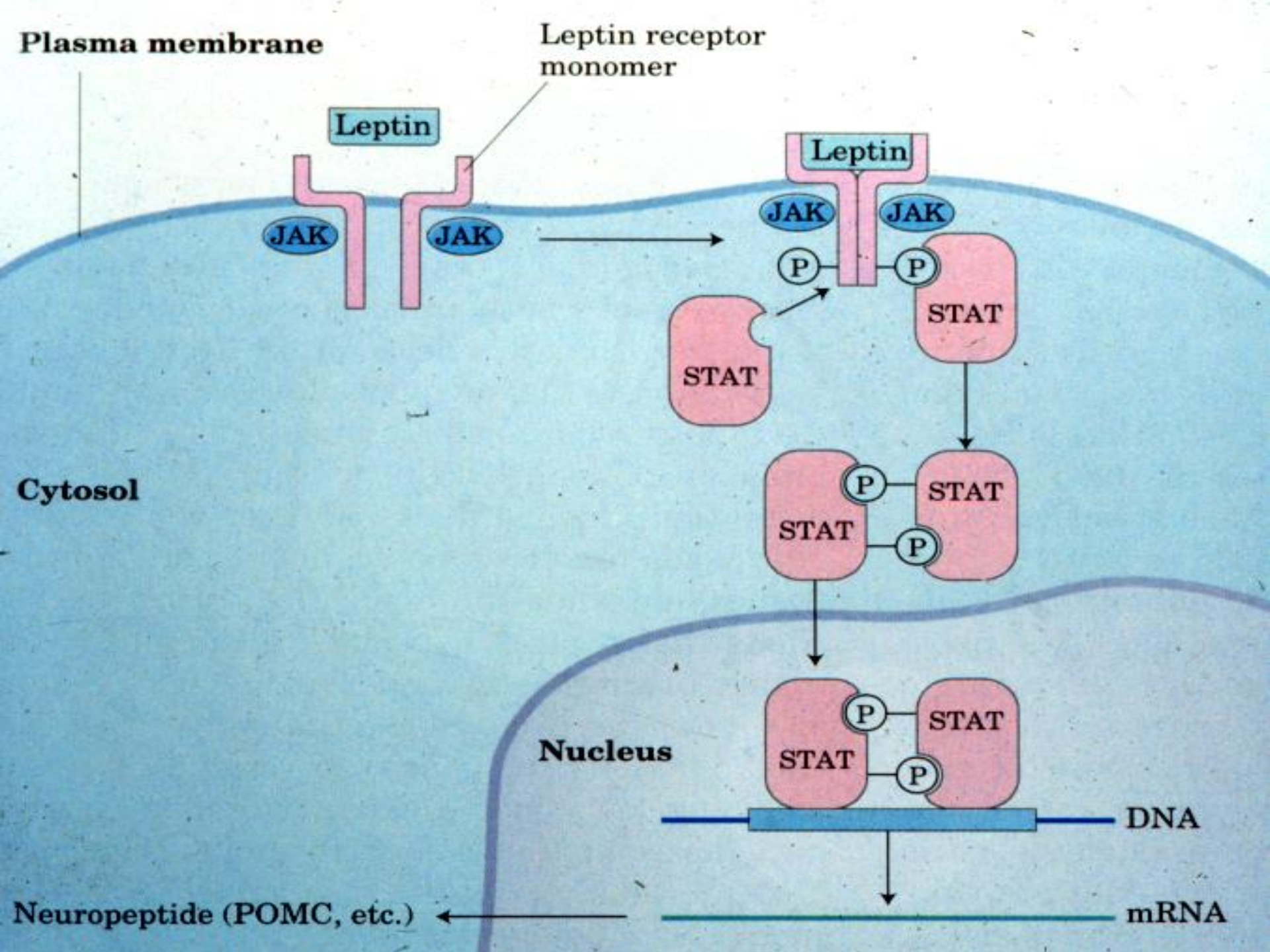


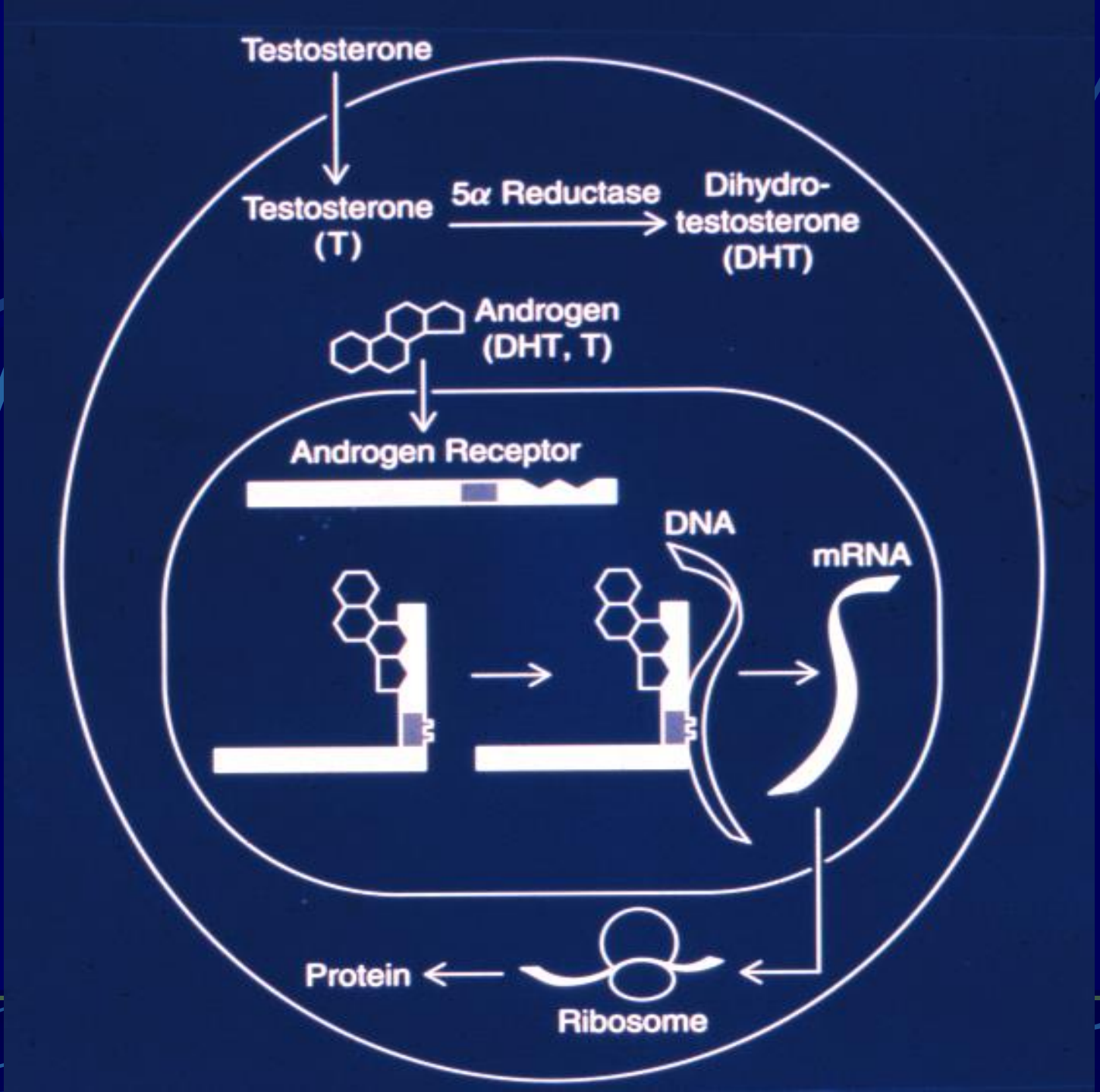
Figure 15-68 *Molecular Biology of the Cell* (© Garland Science 2008)

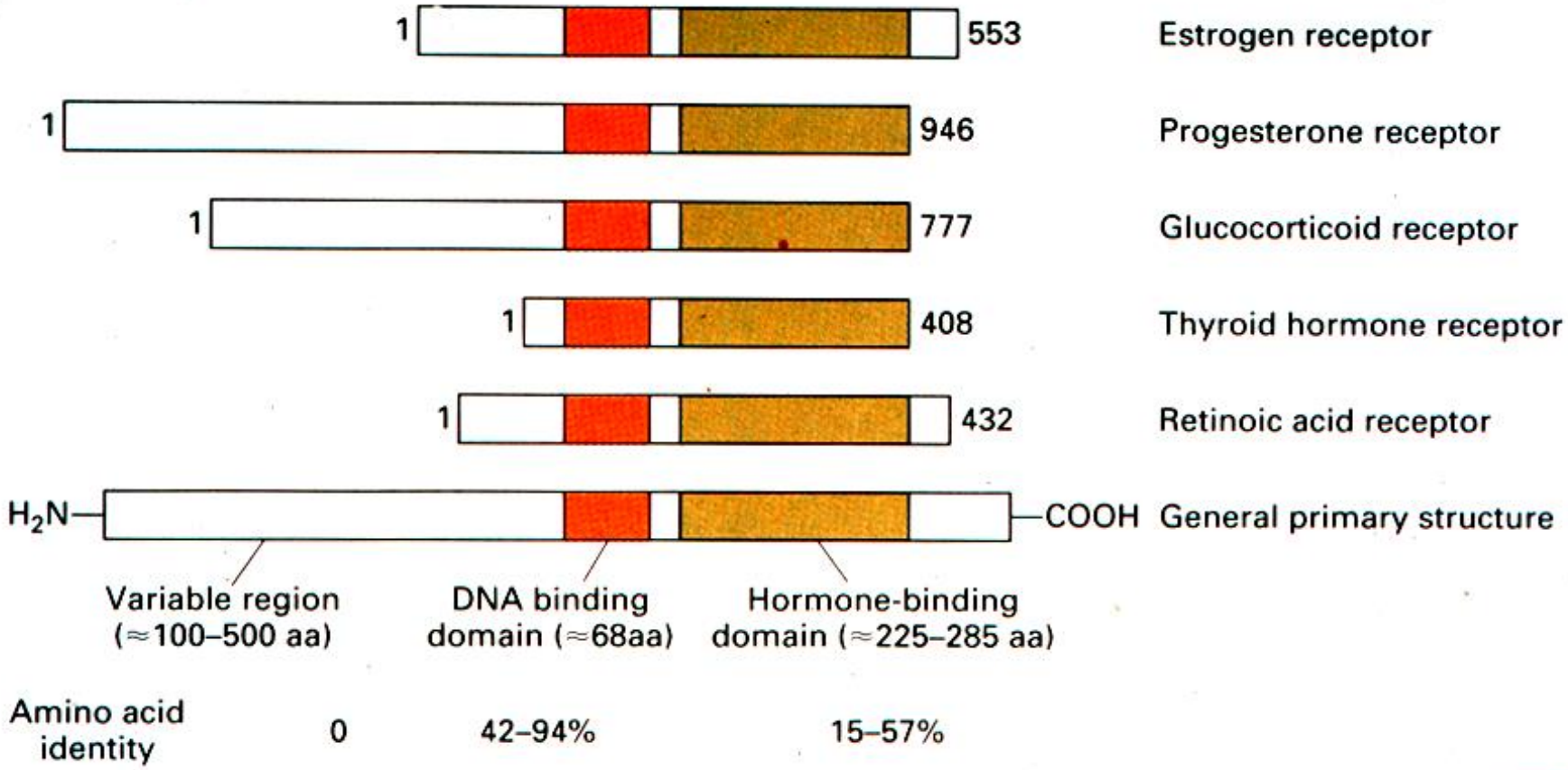

Plasma membrane
Leptin receptor monomer
Leptin
JAK
JAK
Leptin
JAK
JAK
P
P
STAT
STAT
Cytosol
P
STAT
STAT
P
Nucleus
P
STAT
STAT
P
DNA
Neuropeptide (POMC, etc.)
mRNA

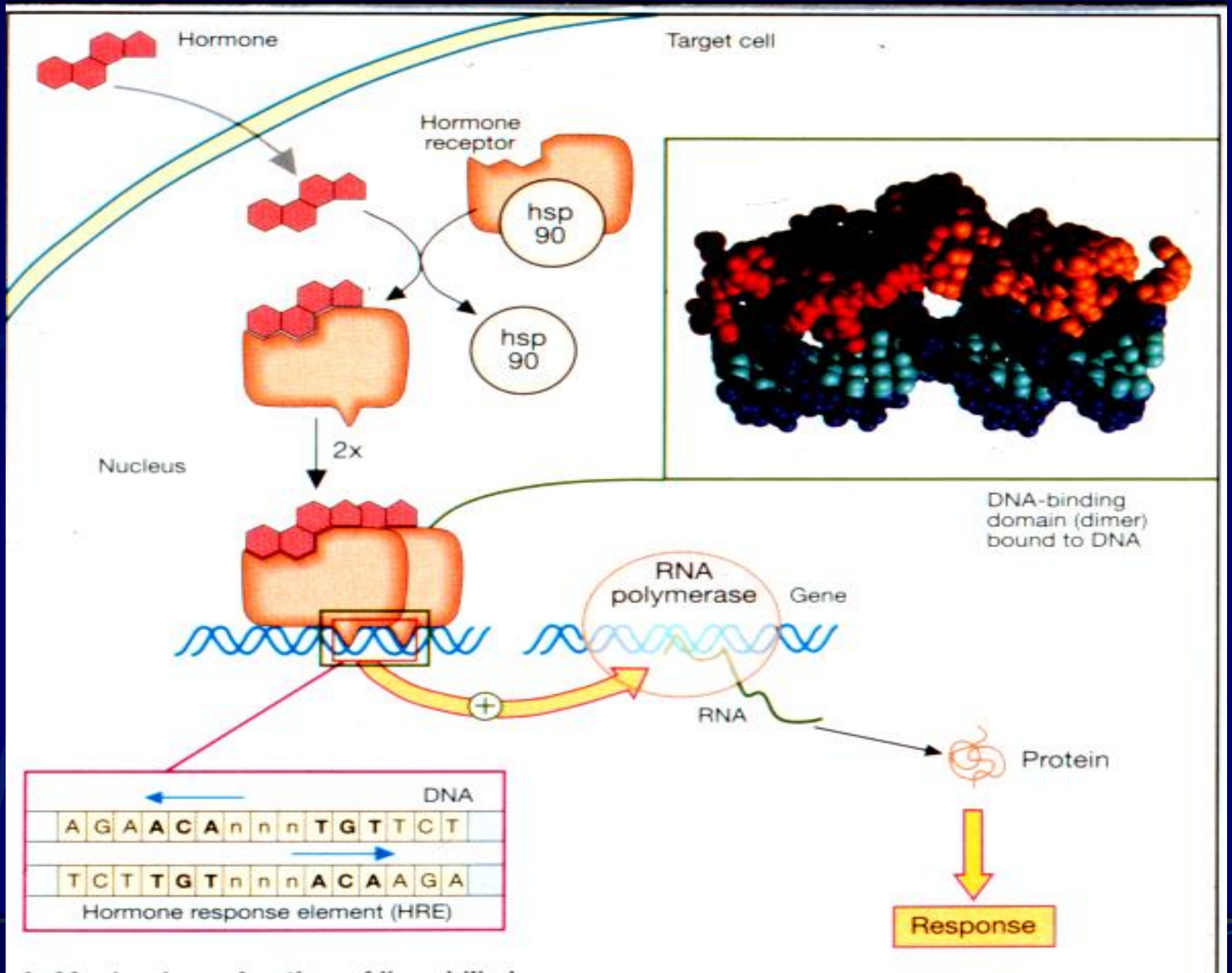
Mecanismos de transdução de sinais

- 5-Receptores – intracelulares (nucleares) → alteram a transcrição gênica e a síntese de proteínas. Ex:

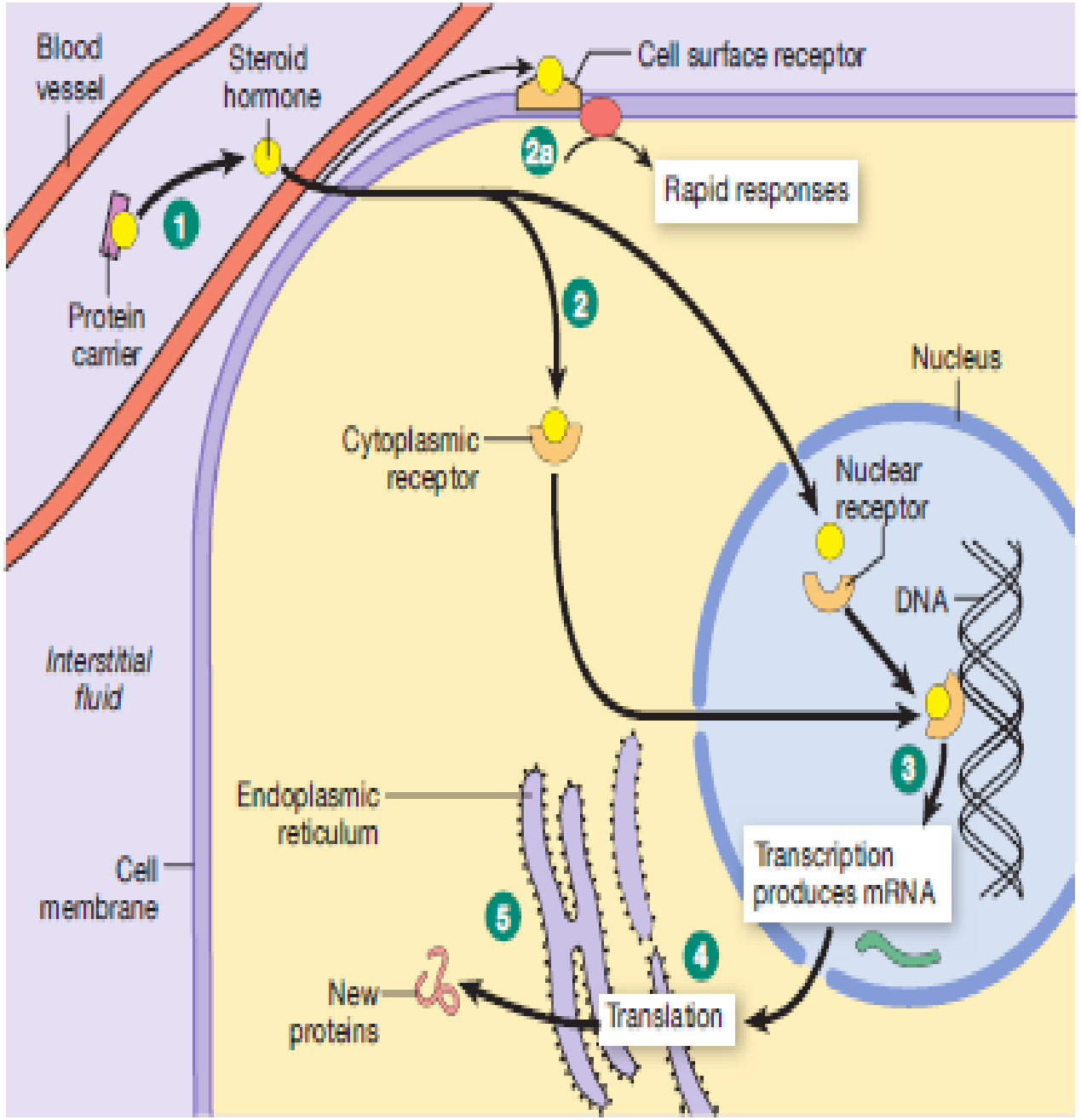
  Hormônios esteróides: testosterona, estrógeno, glicocorticóides, etc.


Testosterone
Testosterone (T)
5α Reductase
Dihydro-testosterone (DHT)
Androgen (DHT, T)
Androgen Receptor
DNA
mRNA
Protein
Ribosome


1
553
Estrogen receptor
1
946
Progesterone receptor
1
777
Glucocorticoid receptor
1
408
Thyroid hormone receptor
1
432
Retinoic acid receptor
H2N
COOH
General primary structure
Variable region (≈100–500 aa)
DNA binding domain (≈68aa)
Hormone-binding domain (≈225–285 aa)
Amino acid identity
0
42–94%
15–57%



A. Mechanism of action of lipophilic hormones



1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.

2. Steroid hormone receptors are in the cytoplasm or nucleus.

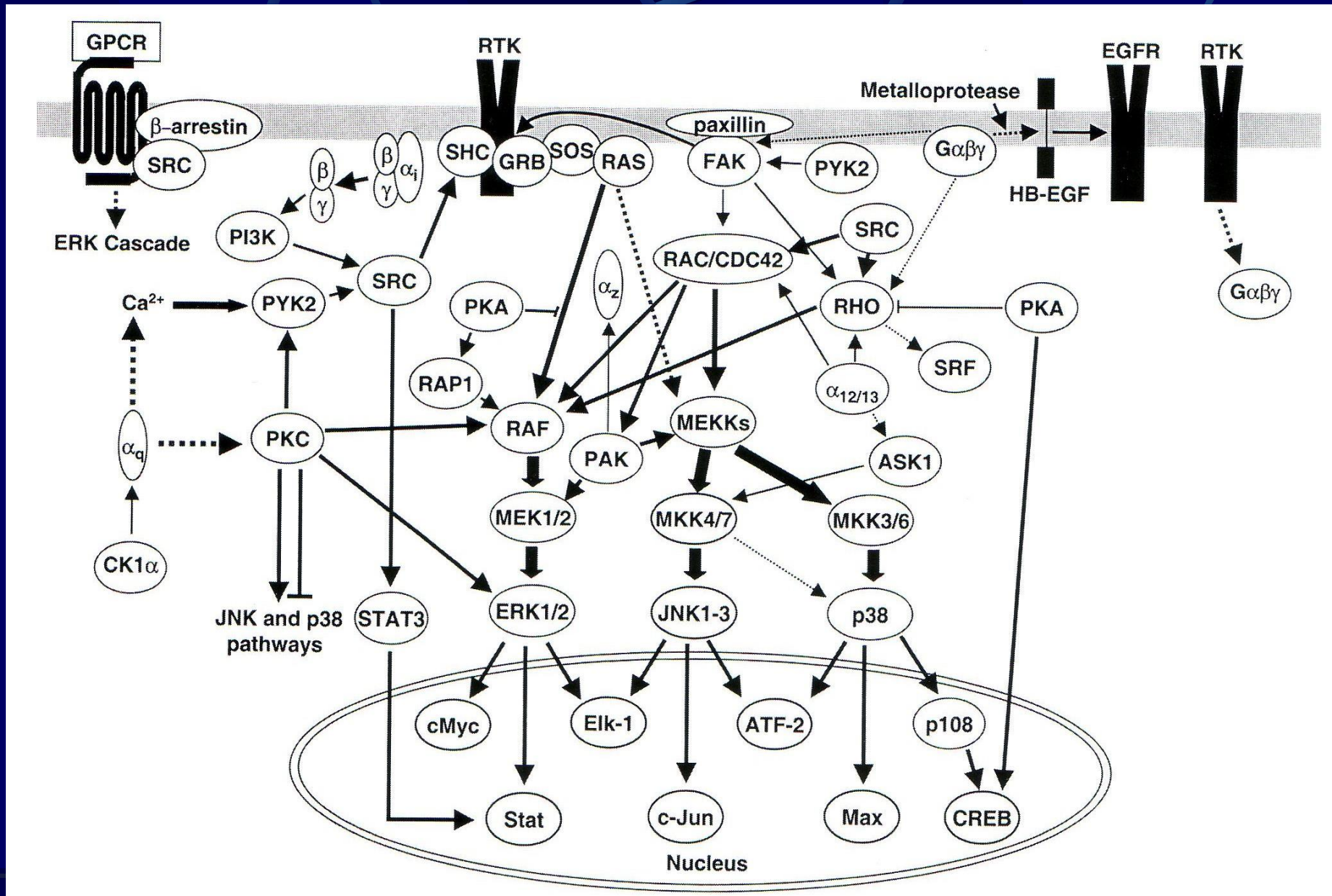
2B. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.

4. Activated genes create new mRNA that moves back to the cytoplasm.

5. Translation produces new proteins for cell processes.

Conversas cruzadas


GPCR
β-arrestin
SRC
ERK Cascade
RTK
SHC
GRB
SOS
RAS
β
γ
α_i
PI3K
SRC
Ca^{2+}
PYK2
α_q
PKC
CK1α
JNK and p38 pathways
STAT3
PKA
α_z
RAP1
RAF
PAK
MEK1/2
ERK1/2
paxillin
FAK
PYK2
Gαβγ
Metalloprotease
HB-EGF
EGFR
RTK
SRC
RAC/CDC42
RHO
PKA
SRF
Gαβγ
$\alpha_{12/13}$
MEKKs
ASK1
MKK4/7
MKK3/6
JNK1-3
p38
cMyc
Elk-1
ATF-2
p108
Stat
c-Jun
Max
CREB
Nucleus

O tema é realmente complexo, embora fascinante!!!