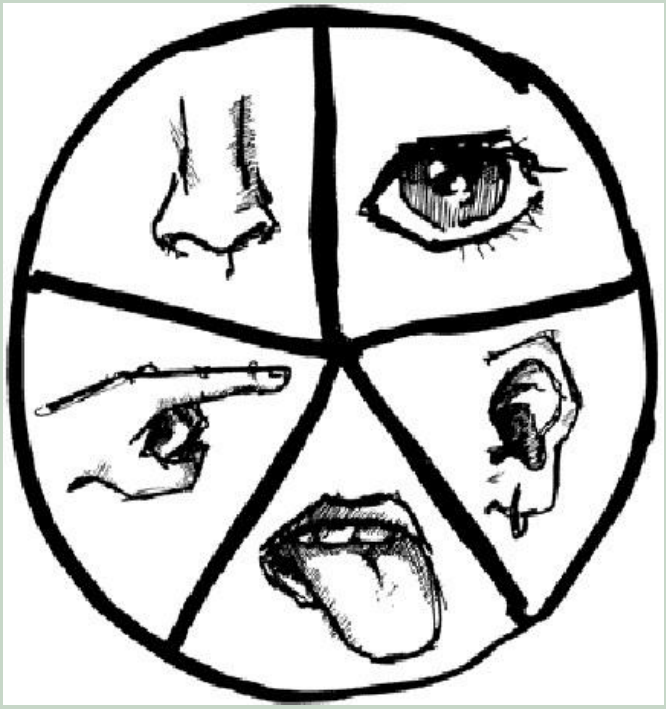
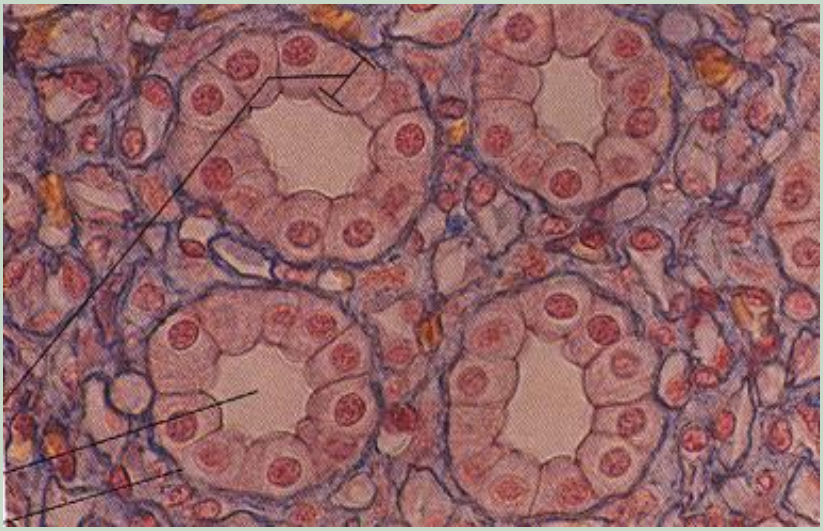
INTRODUCCION A LA BIOLOGIA CELULAR Y MOLECULAR

- BIOLOGIA CELULAR -
Señalización Celular





La comunicación mediante señales extracelulares presenta 6 pasos:

1- Síntesis

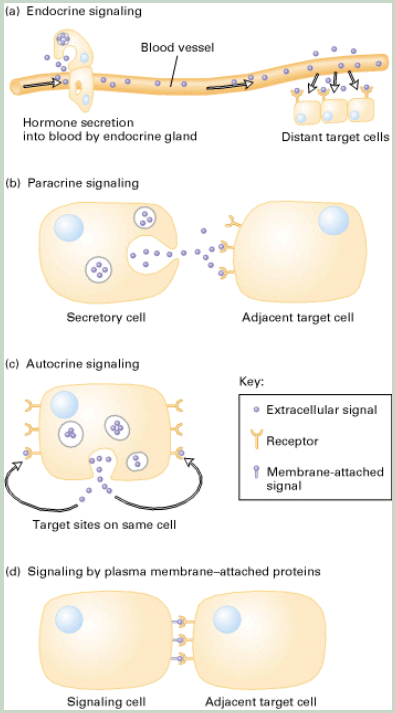
2- Liberación de la molécula señal por la célula productora

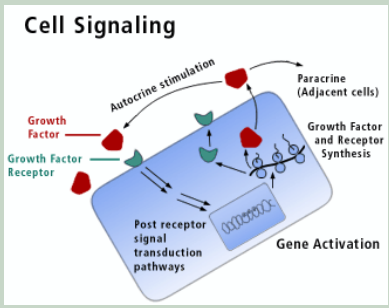
3- Transporte de la señal hacia la célula objetivo

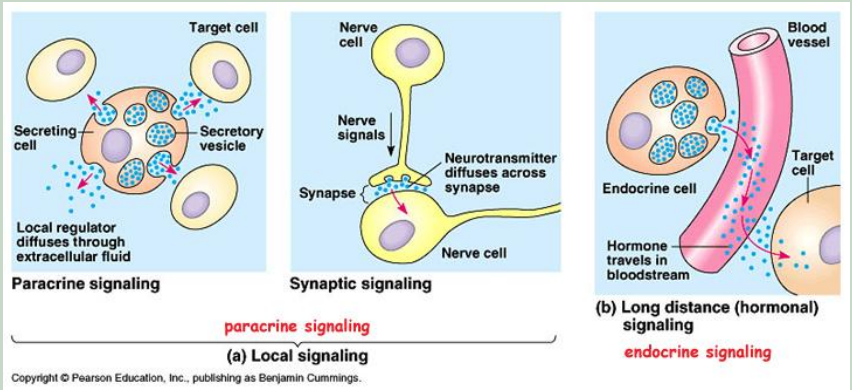
4- Detección de la señal por una proteína receptora específica

5- Cambio del metabolismo, la función o el desarrollo de la célula objetivo

6- Eliminación de la señal


(a) Endocrine signaling
Blood vessel
Hormone secretion into blood by endocrine gland
Distant target cells
(b) Paracrine signaling
Secretory cell
Adjacent target cell
(c) Autocrine signaling
Target sites on same cell
Key:
Extracellular signal
Receptor
Membrane-attached signal
(d) Signaling by plasma membrane–attached proteins
Signaling cell
Adjacent target cell


Cell Signaling
Autocrine stimulation
Paracrine (Adjacent cells)
Growth Factor
Growth Factor Receptor
Growth Factor and Receptor Synthesis
Post receptor signal transduction pathways
Gene Activation


Target cell
Secreting cell
Secretory vesicle
Local regulator diffuses through extracellular fluid
Paracrine signaling
Nerve cell
Nerve signals
Neurotransmitter diffuses across synapse
Synapse
Nerve cell
Synaptic signaling
paracrine signaling
(a) Local signaling
Blood vessel
Endocrine cell
Target cell
Hormone travels in bloodstream
(b) Long distance (hormonal) signaling
endocrine signaling
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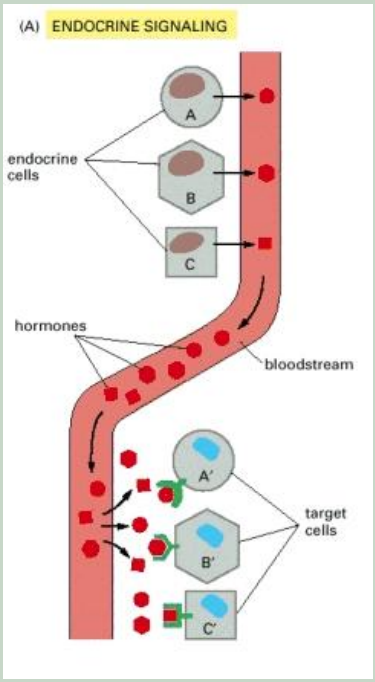
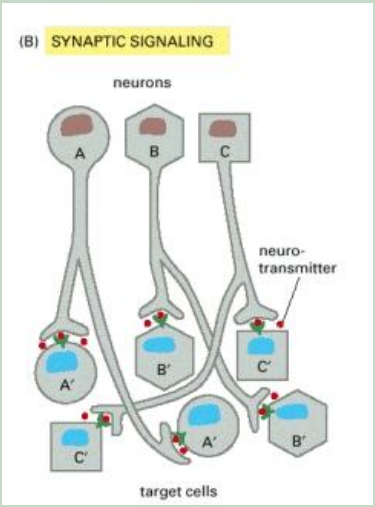
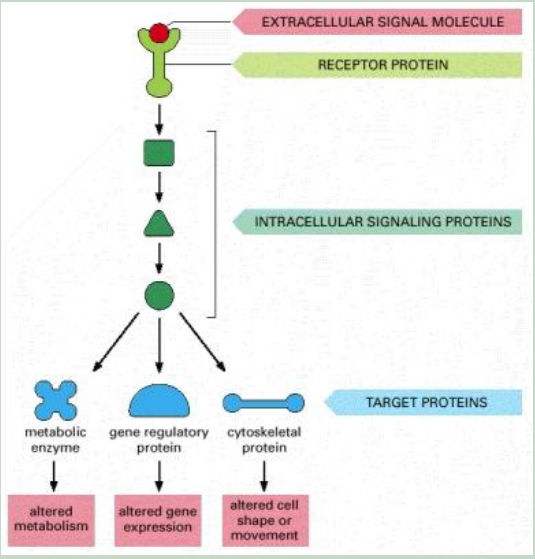
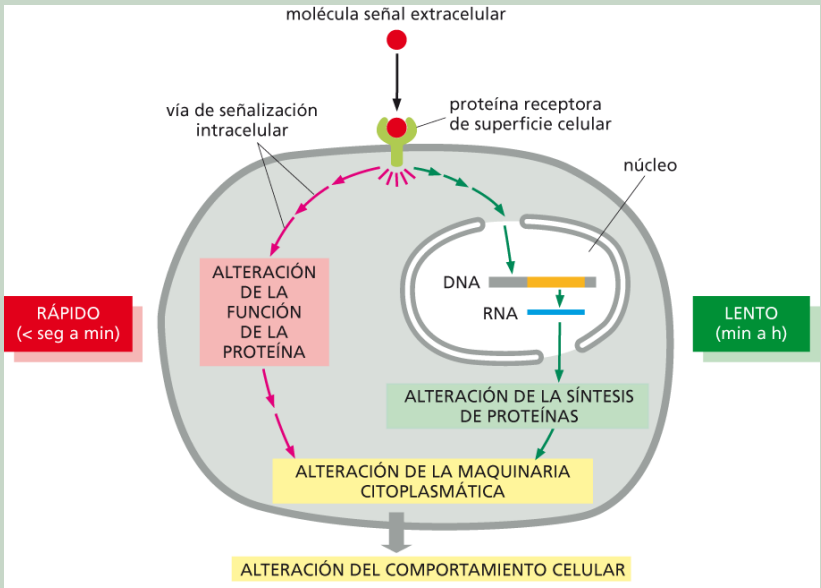
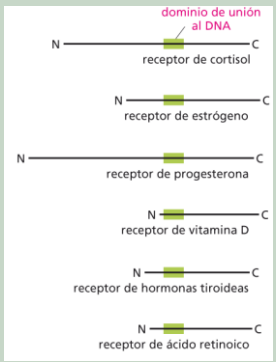
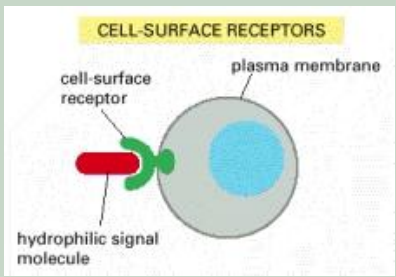

(A) ENDOCRINE SIGNALING
endocrine cells
A
B
C
hormones
bloodstream
A′
B′
C′
target cells

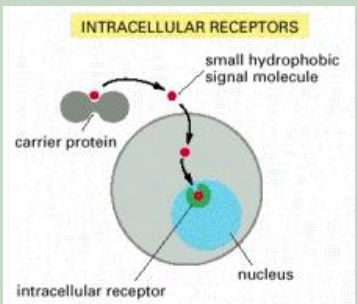

(B) SYNAPTIC SIGNALING
neurons
A
B
C
neuro-transmitter
A′
B′
C′
A′
B′
C′
target cells

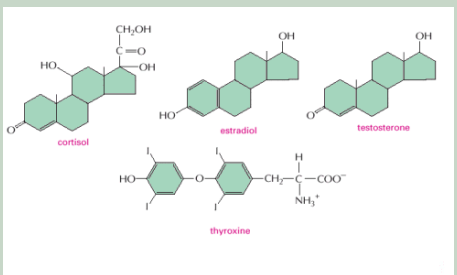

EXTRACELLULAR SIGNAL MOLECULE
RECEPTOR PROTEIN
INTRACELLULAR SIGNALING PROTEINS
TARGET PROTEINS
metabolic enzyme
gene regulatory protein
cytoskeletal protein
altered metabolism
altered gene expression
altered cell shape or movement

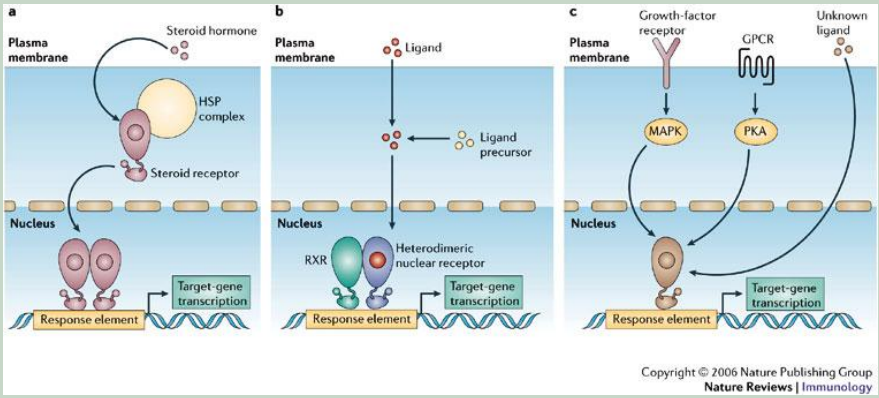

molécula señal extracelular
vía de señalización intracelular
proteína receptora de superficie celular
núcleo
ALTERACIÓN DE LA FUNCIÓN DE LA PROTEÍNA
DNA
RNA
RÁPIDO (< seg a min)
LENTO (min a h)
ALTERACIÓN DE LA SÍNTESIS DE PROTEÍNAS
ALTERACIÓN DE LA MAQUINARIA CITOPLASMÁTICA
ALTERACIÓN DEL COMPORTAMIENTO CELULAR


dominio de unión al DNA
N
C
receptor de cortisol
receptor de estrógeno
receptor de progesterona
receptor de vitamina D
receptor de hormonas tiroideas
receptor de ácido retinoico

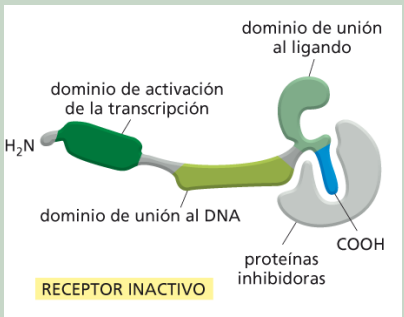

CELL-SURFACE RECEPTORS
cell-surface receptor
plasma membrane
hydrophilic signal molecule

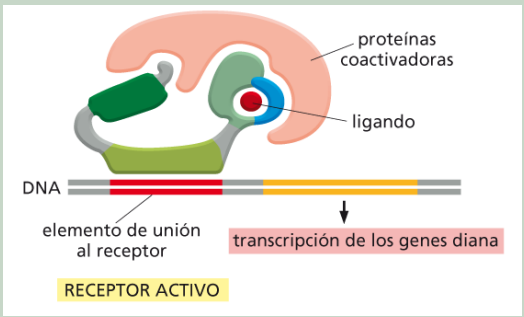

INTRACELLULAR RECEPTORS
small hydrophobic signal molecule
carrier protein
nucleus
intracellular receptor

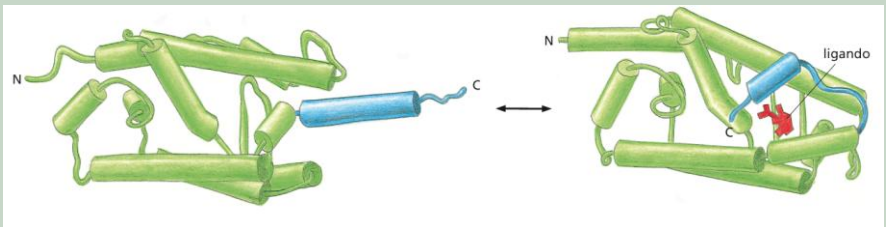

cortisol
estradiol
testosterone
thyroxine

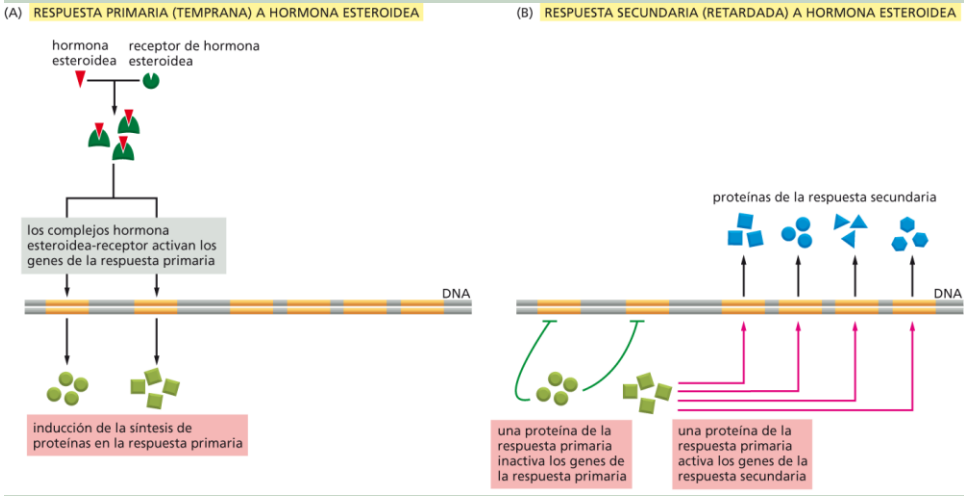


Receptores Nucleares







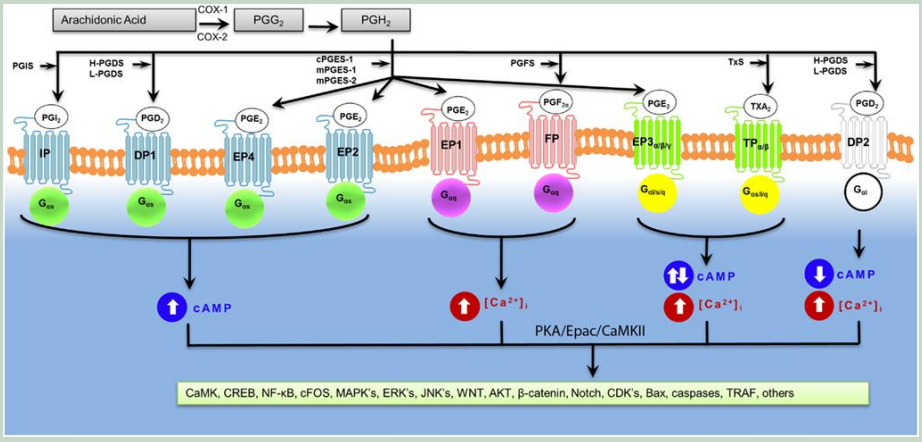


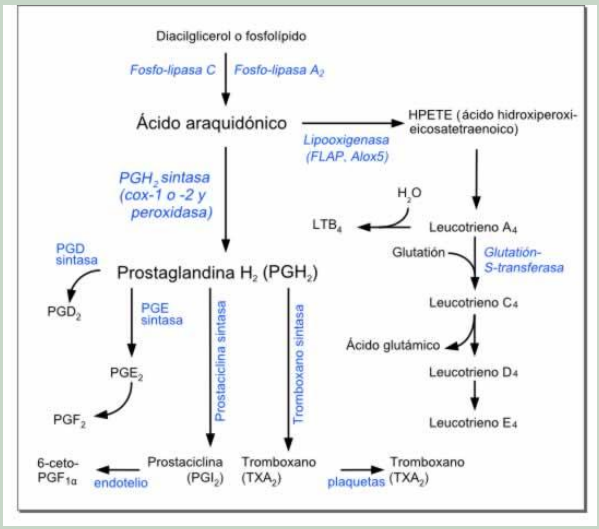
Hormonas lipófilas con receptores de superficie celular

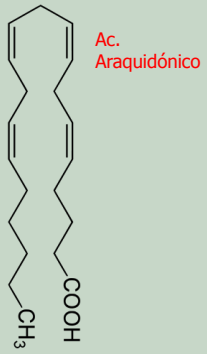
Las principales hormonas que se fijan a receptores de superficie celular son las prostanglandinas.

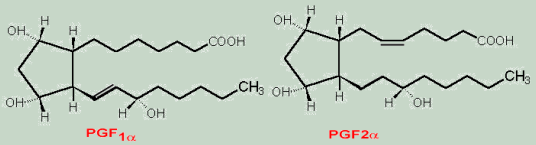
Muchas prostaglandinas actúan como mediadores locales durante las señales paracrinas y autócrinas, y se destruyen cerca del sitio de síntesis; modulan las respuestas de otras hormonas y tienen efectos sobre diversos procesos celulares.

Type	Receptor	Receptor type	Function
PGI_2	IP	G_s	• vasodilation • inhibit platelet aggregation • bronchodilation
PGE_2	EP_1	G_q	• bronchoconstriction • GI tract smooth muscle contraction
	EP_2	G_s	• bronchodilation • GI tract smooth muscle relaxation • vasodilation
	EP_3	G_i	• ↓ gastric acid secretion • ↑ gastric mucus secretion • uterus contraction (when pregnant) • GI tract smooth muscle contraction • lipolysis inhibition • ↑ autonomic neurotransmitters [7] • ↑ platelet response to their agonists [8] [1] and ↑ atherothrombosis in vivo [9][2]
	Unspecified		• hyperalgesia[7] • pyrogenic
$PGF_{2\alpha}$	FP	G_q	• uterus contraction • bronchoconstriction









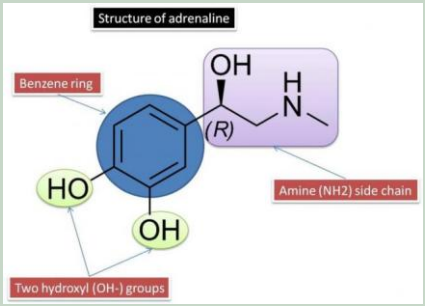
Hormonas hidrosolubles con receptores de superficie celular

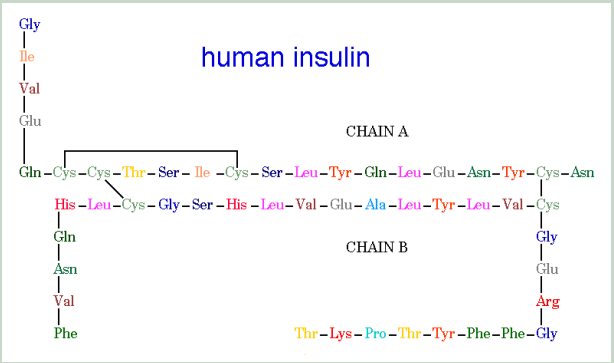
Estas no pueden difundir a través de la membrana plasmática, todas se fijan a receptores de la superficie celular.

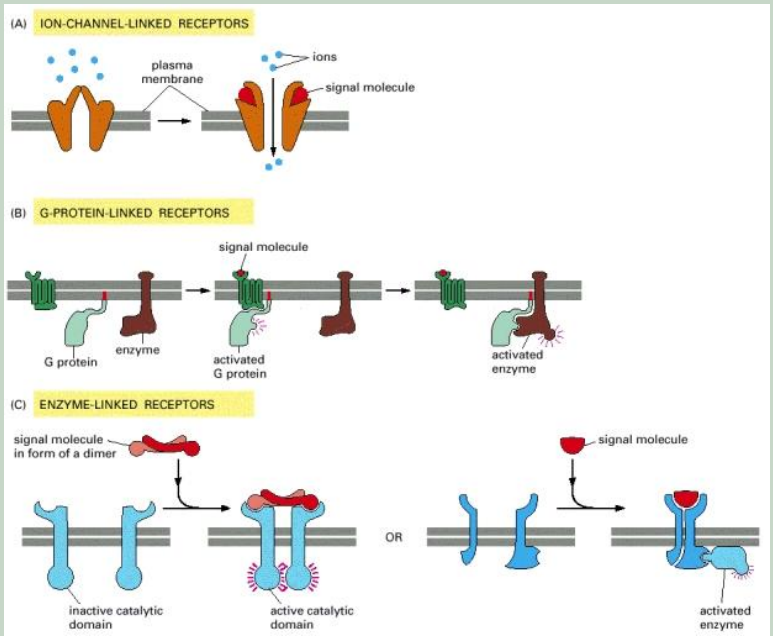
Se reconocen dos grupos:

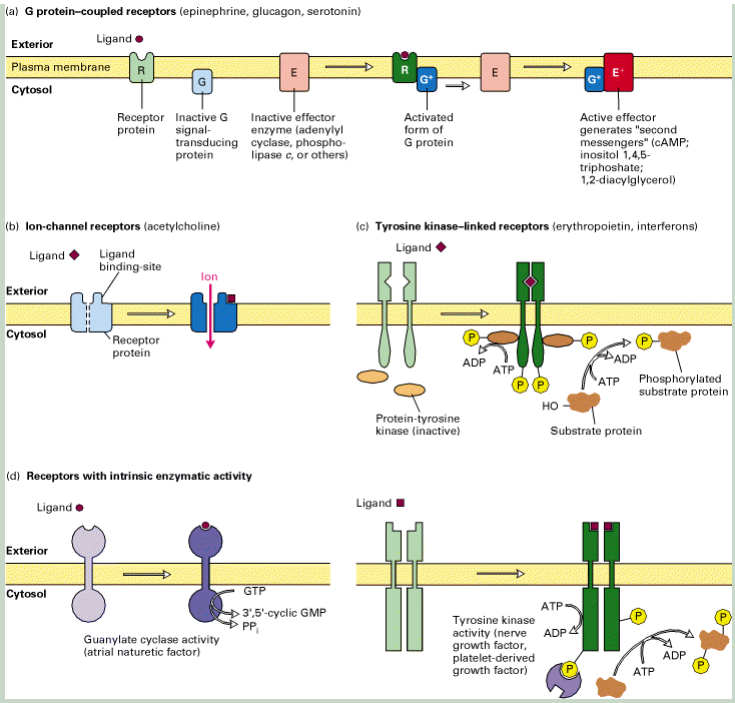
1- Hormonas peptídicas, como la insulina, los factores de crecimiento y glucagón, con tamaños que varían desde unos pocos aminoácidos hasta proteínas.

2- Pequeñas moléculas cargadas, como adrenalina e histamina, derivadas de aminoácidos, con función de hormonas y neurotransmisores.

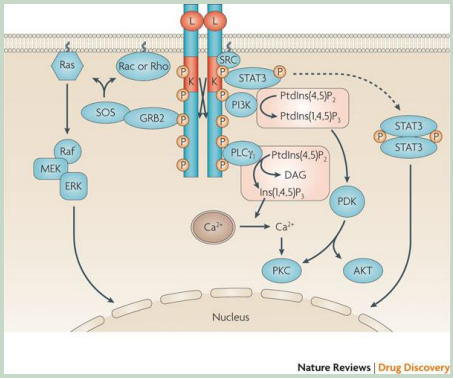

Structure of adrenaline
Benzene ring
OH
H
N
(R)
HO
OH
Amine (NH2) side chain
Two hydroxyl (OH-) groups


human insulin
CHAIN A
CHAIN B
Gly
Ile
Val
Glu
Gln – Cys – Cys – Thr – Ser – Ile – Cys – Ser – Leu – Tyr – Gln – Leu – Glu – Asn – Tyr – Cys – Asn
His – Leu – Cys – Gly – Ser – His – Leu – Val – Glu – Ala – Leu – Tyr – Leu – Val – Cys
Gln
Asn
Val
Phe
Gly
Glu
Arg
Thr – Lys – Pro – Thr – Tyr – Phe – Phe – Gly


(A) ION-CHANNEL-LINKED RECEPTORS
plasma membrane
ions
signal molecule
(B) G-PROTEIN-LINKED RECEPTORS
signal molecule
G protein
enzyme
activated G protein
activated enzyme
(C) ENZYME-LINKED RECEPTORS
signal molecule in form of a dimer
inactive catalytic domain
active catalytic domain
OR
signal molecule
activated enzyme



Receptor Tyr kinase



Receptor G protein

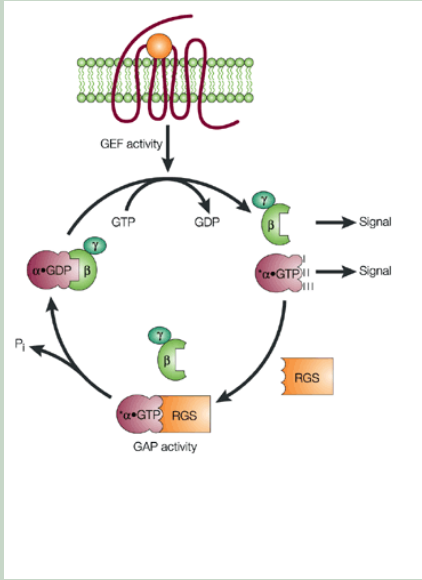
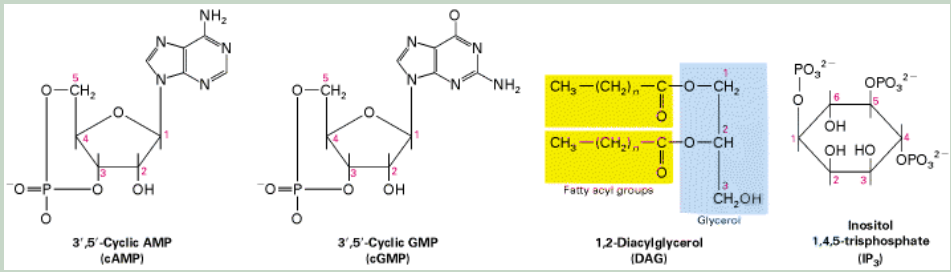


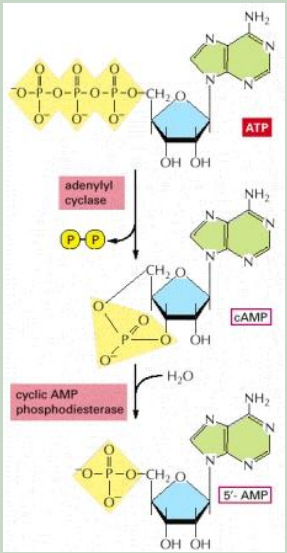
Table 15-4 Some Signaling Proteins That Act Via Receptor Tyrosine Kinases

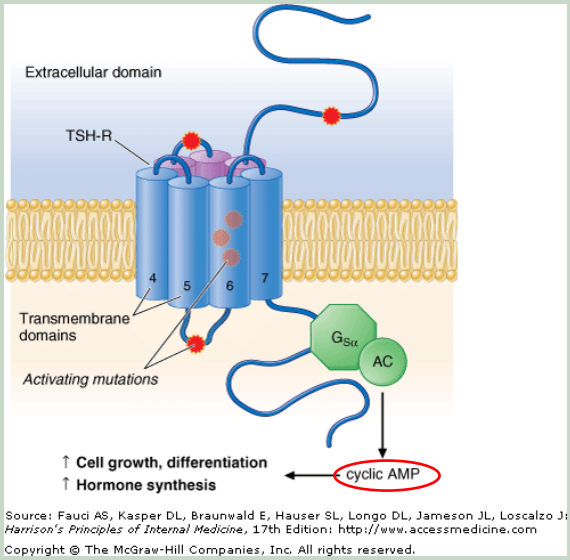
SIGNALING LIGAND	RECEPTORS	SOME RESPONSES
Epidermal growth factor (EGF)	EGF receptor	stimulates proliferation of various
Insulin	insulin receptor	stimulates carbohydrate utilization
Insulin-like growth factors (IGF-1 and IGF-2)	IGF receptor-1	stimulate cell growth and survival
Nerve growth factor (NGF)	Trk A	stimulates survival and growth of s
Platelet-derived growth factors (PDGF AA, BB, AB)	PDGF receptors (α and β)	stimulate survival, growth, and pro
Macrophage-colony-stimulating (M-CSF)	M-CSF receptor factor	stimulates monocyte/macrophage
Fibroblast growth factors (FGF-1 to FGF-24)	FGF receptors (FGF-R1-FGF- R4, plus multiple isoforms of each)	stimulate proliferation of various ce some precursor cells; inductive sig
Vascular endothelial growth factor (VEGF)	VEGF receptor	stimulates angiogenesis
Ephrins (A and B types)	Eph receptors (A and B types)	stimulate angiogenesis; guide cel

Segundos mensajeros



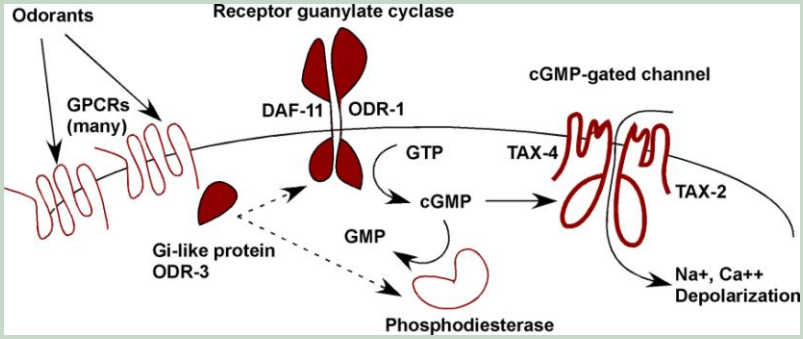
AMPc – TSH hormone

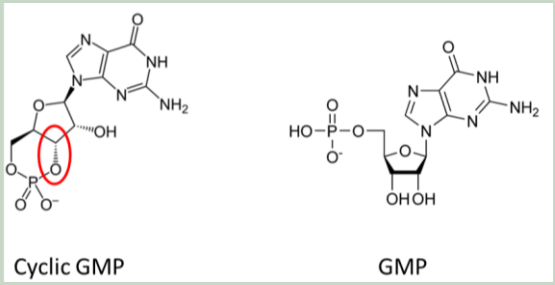


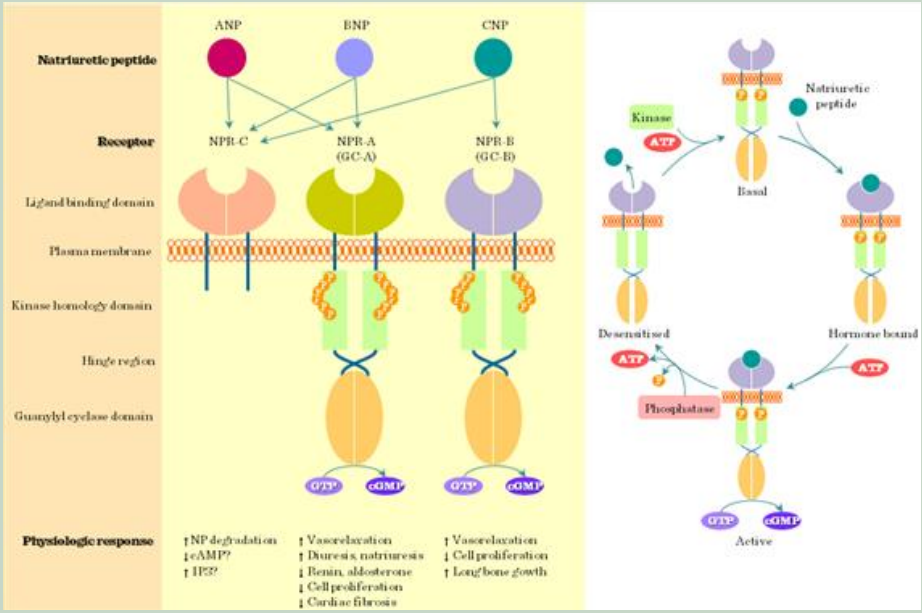


TARGET TISSUE	HORMONE	MAJOR RESPONSE
Thyroid gland	thyroid-stimulating hormone (TSH)	thyroid hormone synthesis and secretion
Adrenal cortex	adrenocorticotrophic hormone (ACTH)	cortisol secretion
Ovary	luteinizing hormone (LH)	progesterone secretion
Muscle	adrenaline	glycogen breakdown
Bone	parathormone	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

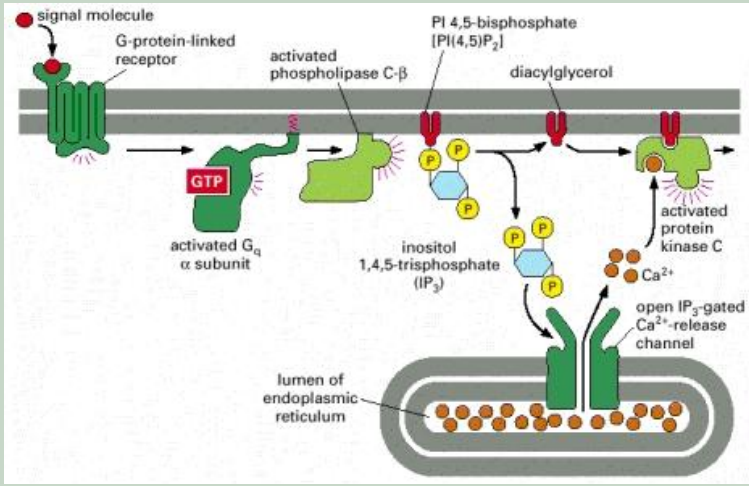
GMPc – NP receptor

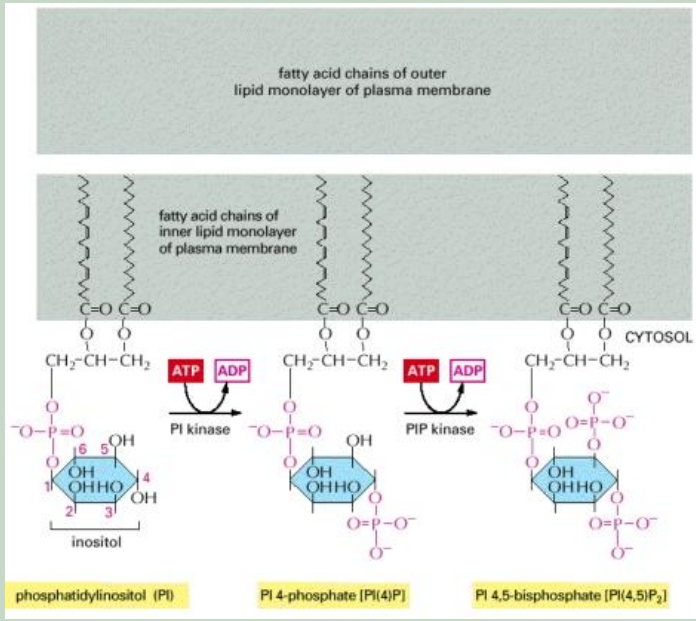






IP and DAG – TSH hormone





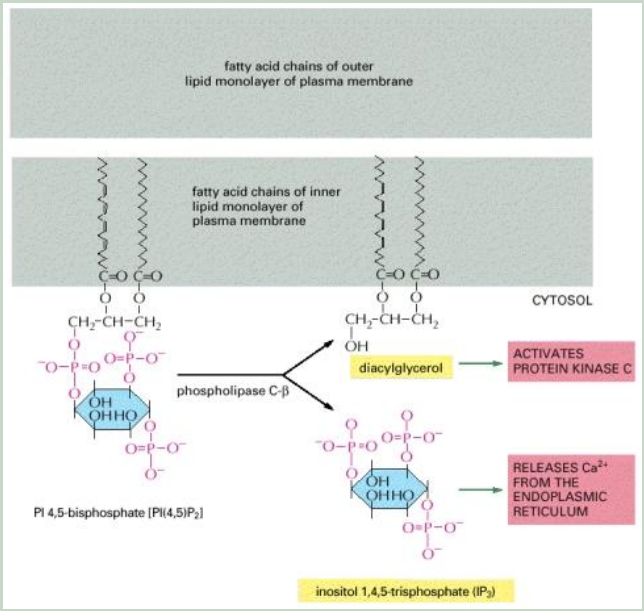
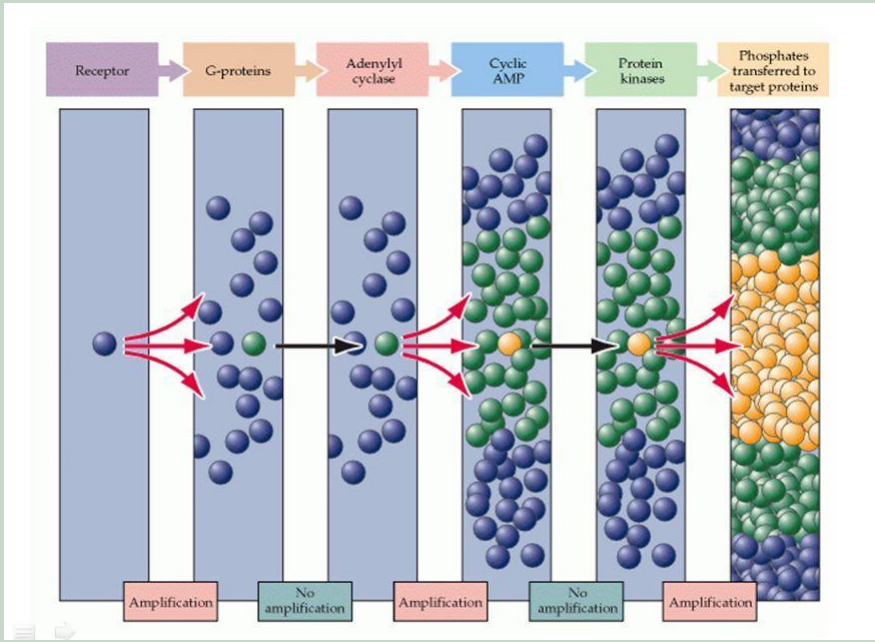
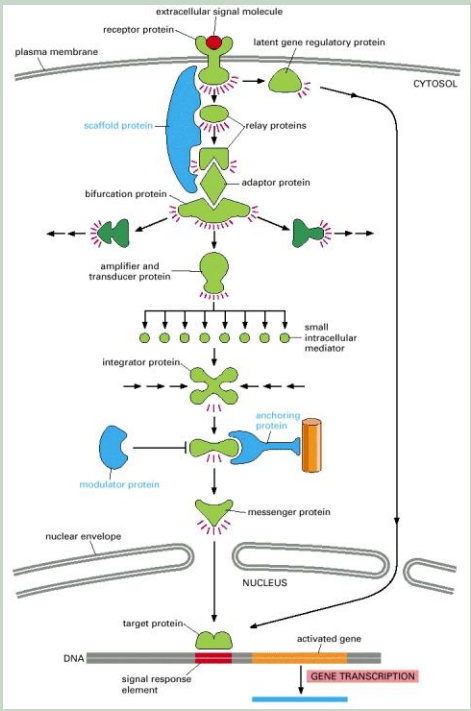
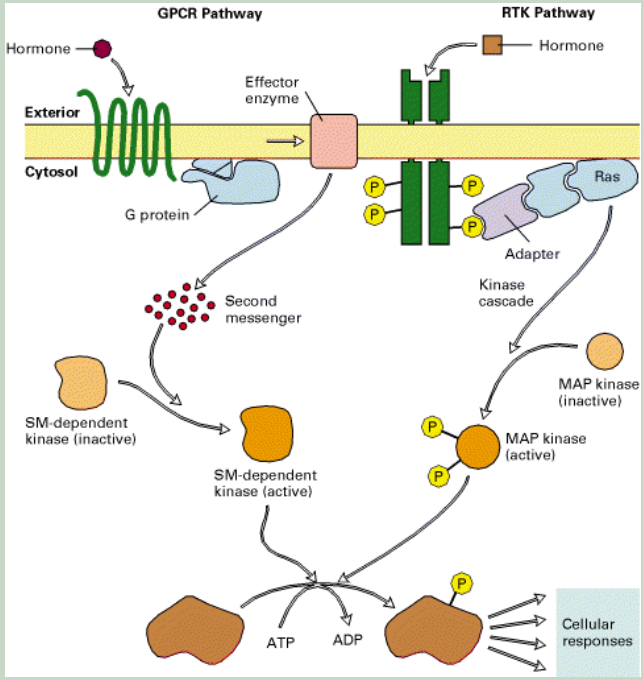


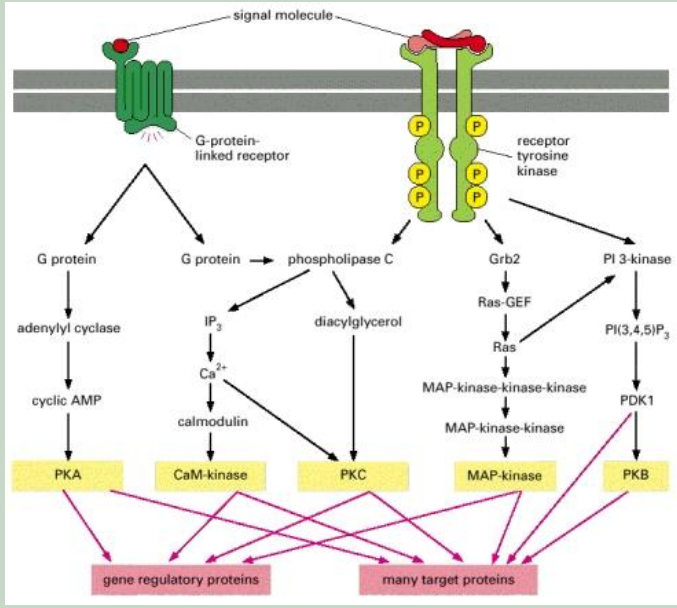
Table 15-2 Some Cell Responses in Which G-Protein-linked Receptors Activate the Inositol-Phospholipid Signaling Pathway

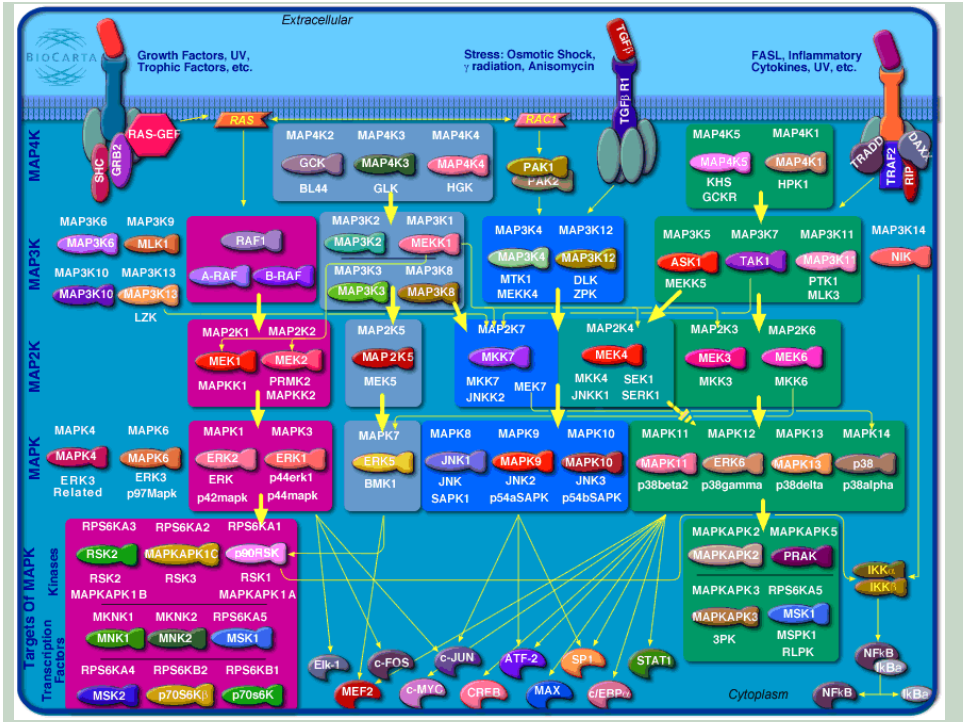
TARGET TISSUE	SIGNALING MOLECULE	MAJOR RESPONSE
Liver	vasopressin	glycogen breakdown
Pancreas	acetylcholine	amylase secretion
Smooth muscle	acetylcholine	contraction
Blood platelets	thrombin	aggregation

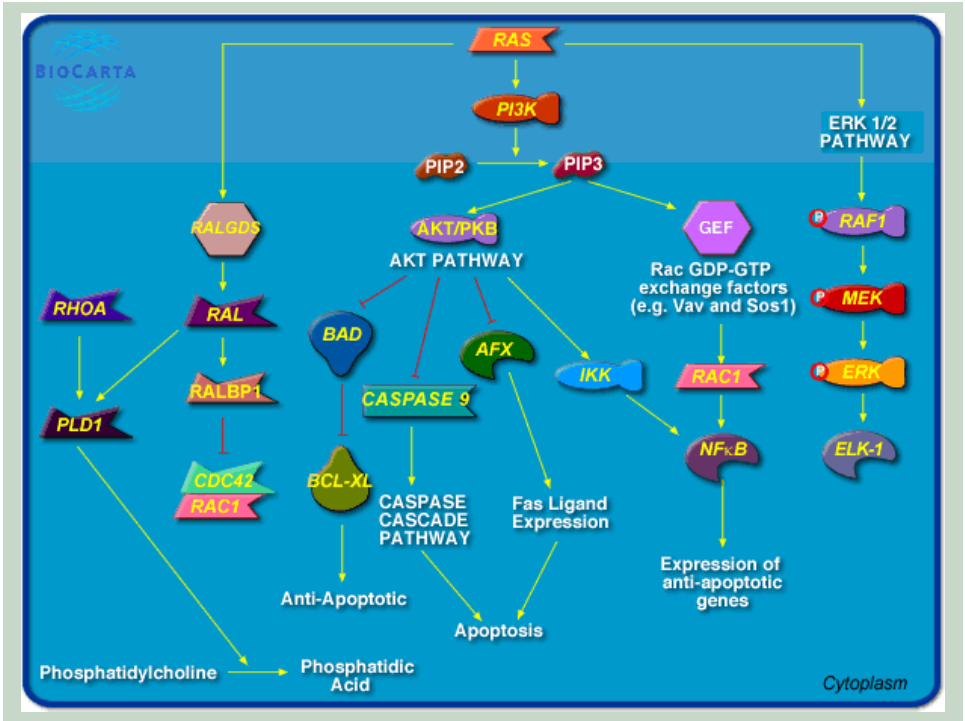

Receptor
G-proteins
Adenylyl cyclase
Cyclic AMP
Protein kinases
Phosphates transferred to target proteins
Amplification
No amplification
Amplification
No amplification
Amplification

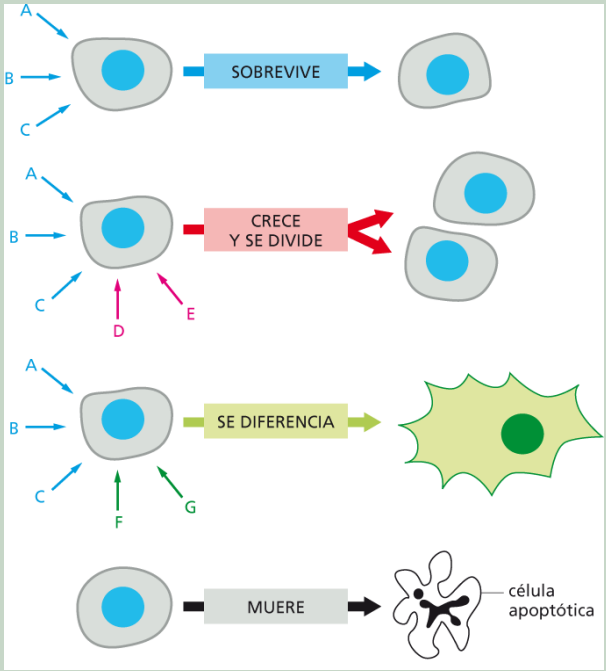

extracellular signal molecule
receptor protein
latent gene regulatory protein
plasma membrane
CYTOSOL
scaffold protein
relay proteins
adaptor protein
bifurcation protein
amplifier and transducer protein
small intracellular mediator
integrator protein
anchoring protein
modulator protein
messenger protein
nuclear envelope
NUCLEUS
target protein
activated gene
DNA
signal response element
GENE TRANSCRIPTION


GPCR Pathway
RTK Pathway
Hormone
Hormone
Effector enzyme
Exterior
Cytosol
G protein
Ras
Adapter
Kinase cascade
Second messenger
MAP kinase (inactive)
SM-dependent kinase (inactive)
MAP kinase (active)
SM-dependent kinase (active)
ATP
ADP
Cellular responses


signal molecule
G-protein-linked receptor
receptor tyrosine kinase
G protein
G protein
phospholipase C
Grb2
PI 3-kinase
adenylyl cyclase
IP3
diacylglycerol
Ras-GEF
Ras
PI(3,4,5)P3
Ca2+
cyclic AMP
calmodulin
MAP-kinase-kinase-kinase
PDK1
MAP-kinase-kinase
PKA
CaM-kinase
PKC
MAP-kinase
PKB
gene regulatory proteins
many target proteins


Extracellular
Growth Factors, UV, Trophic Factors, etc.
Stress: Osmotic Shock, γ radiation, Anisomycin
FASL, Inflammatory Cytokines, UV, etc.
RAS
RAC1
TGFβ R1
TRADD
TRAF2
DAXX
RIP
SHC
GRB2
RAS-GEF
MAP4K
MAP4K2
MAP4K3
MAP4K4
GCK
BL44
GLK
HGK
PAK1
PAK2
MAP4K5
MAP4K1
KHS
GCKR
HPK1
MAP3K
MAP3K6
MAP3K9
MLK1
RAF1
A-RAF
B-RAF
MAP3K10
MAP3K13
LZK
MAP3K2
MAP3K1
MEKK1
MAP3K3
MAP3K8
MAP3K4
MAP3K12
MTK1
MEKK4
DLK
ZPK
MAP3K5
MAP3K7
MAP3K11
MAP3K14
ASK1
TAK1
NIK
MEKK5
PTK1
MLK3
MAP2K
MAP2K1
MAP2K2
MEK1
MEK2
MAPKK1
PRMK2
MAPKK2
MAP2K5
MEK5
MAP2K7
MKK7
MKK7
JNKK2
MEK7
MAP2K4
MEK4
MKK4
JNKK1
SEK1
SERK1
MAP2K3
MAP2K6
MEK3
MEK6
MKK3
MKK6
MAPK
MAPK4
MAPK6
ERK3
Related
ERK3
p97Mapk
MAPK1
MAPK3
ERK2
ERK
p42mapk
ERK1
p44erk1
p44mapk
MAPK7
ERK5
BMK1
MAPK8
MAPK9
MAPK10
JNK1
JNK
SAPK1
MAPK9
JNK2
p54aSAPK
MAPK10
JNK3
p54bSAPK
MAPK11
MAPK12
MAPK13
MAPK14
MAPK11
ERK6
MAPK13
p38
p38beta2
p38gamma
p38delta
p38alpha
Targets Of MAPK
Kinases
RPS6KA3
RPS6KA2
RPS6KA1
RSK2
MAPKAPK1C
p90RSK
RSK2
MAPKAPK1 B
RSK3
RSK1
MAPKAPK1 A
MKNK1
MKNK2
RPS6KA5
MNK1
MNK2
MSK1
Transcription Factors
RPS6KA4
RPS6KB2
RPS6KB1
MSK2
p70S6Kβ
p70s6K
MAPKAPK2
MAPKAPK5
MAPKAPK2
PRAK
MAPKAPK3
RPS6KA5
MAPKAPK3
MSK1
3PK
MSPK1
RLPK
IKKα
IKKβ
NFκB
IκBα
Elk-1
c-FOS
c-JUN
ATF-2
SP1
STAT1
MEF2
c-MYC
CREB
MAX
c/EBPα
Cytoplasm
NFκB
IκBα


RAS
PI3K
PIP2
PIP3
ERK 1/2 PATHWAY
RALGDS
AKT/PKB
AKT PATHWAY
GEF
Rac GDP-GTP exchange factors (e.g. Vav and Sos1)
RAF1
RHOA
RAL
BAD
AFX
IKK
RAC1
MEK
PLD1
RALBP1
CASPASE 9
ERK
NFκB
ELK-1
CDC42
RAC1
BCL-XL
CASPASE CASCADE PATHWAY
Fas Ligand Expression
Expression of anti-apoptotic genes
Anti-Apoptotic
Apoptosis
Phosphatidylcholine
Phosphatidic Acid
Cytoplasm


A
B
C
SOBREVIVE
A
B
C
D
E
CRECE
Y SE DIVIDE
A
B
C
F
G
SE DIFERENCIA
MUERE
célula
apoptótica