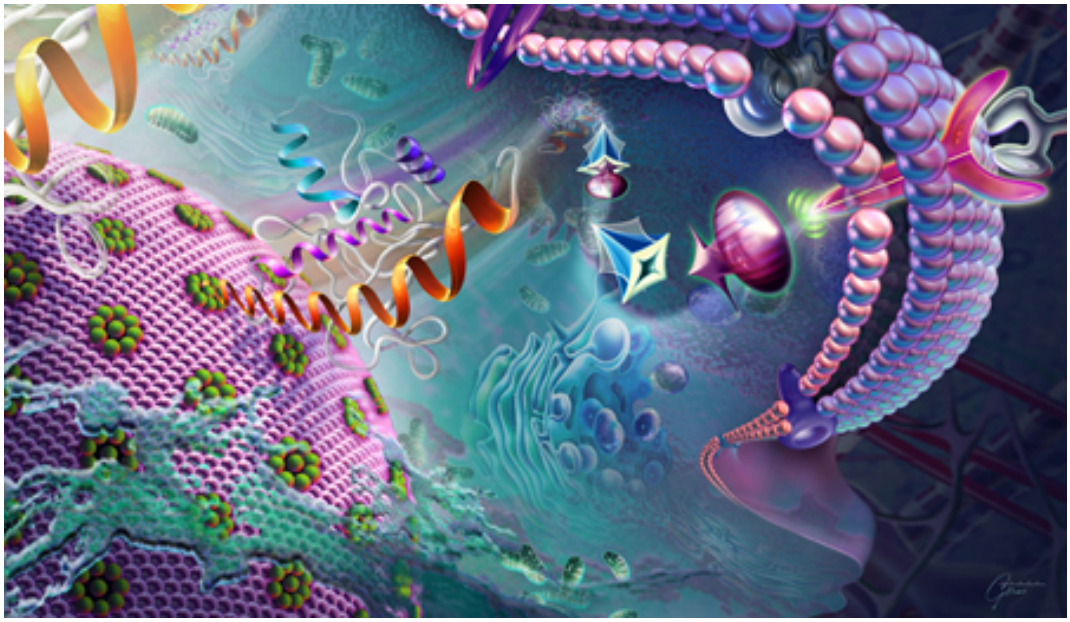
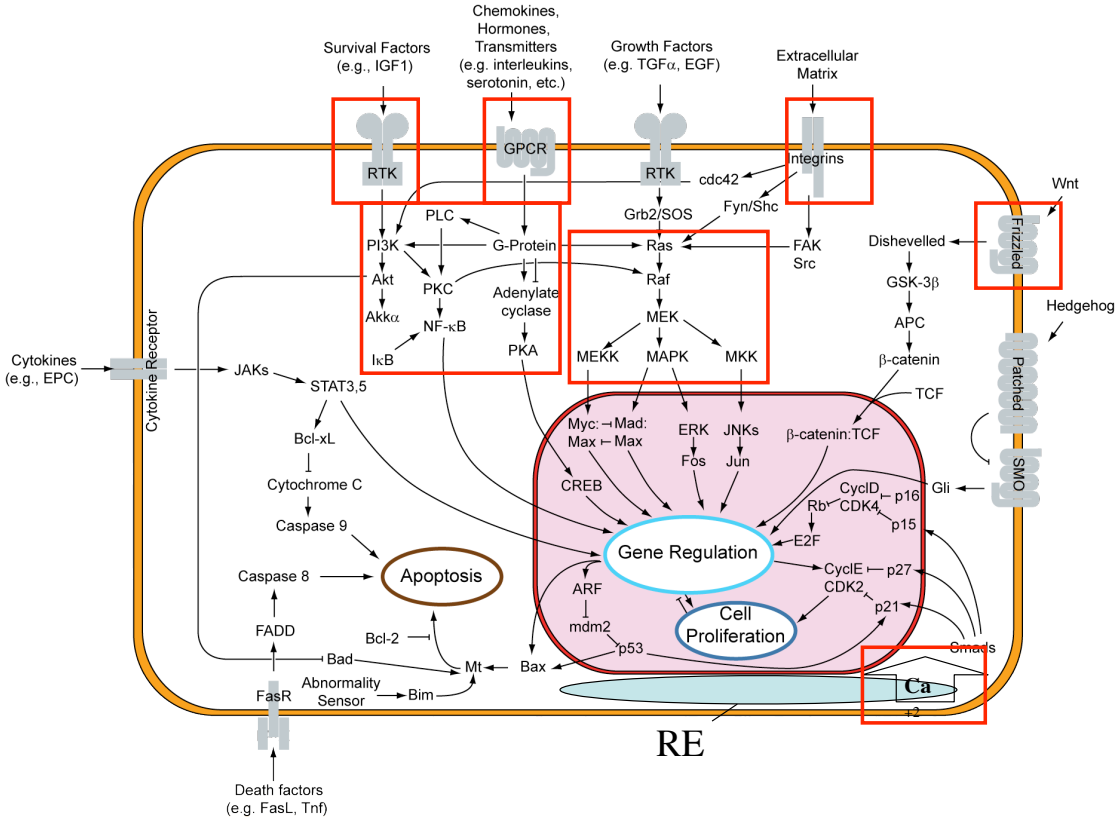
Transducción de Señales



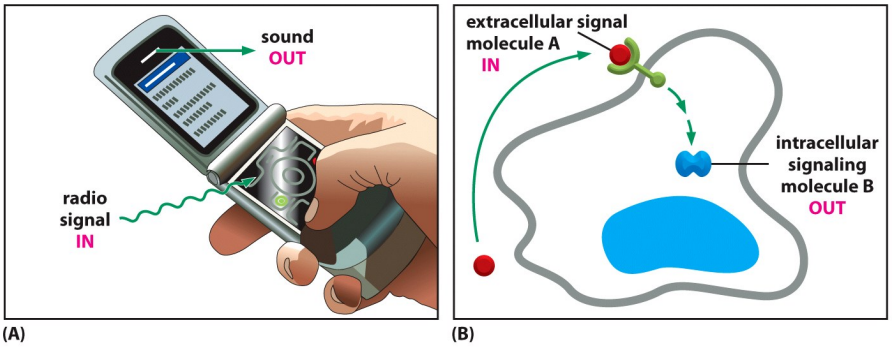
Dr. Alejandro Roth

Fac. Ciencias. Universidad de Chile



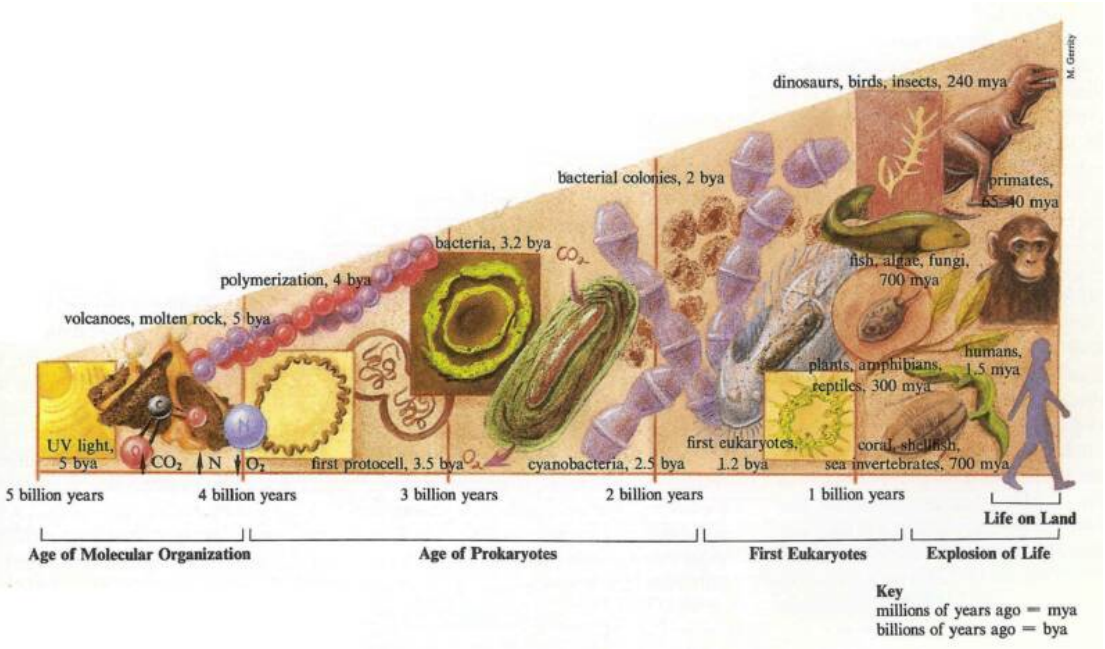
Transducción de Señales: Proceso mediante el cual una célula convierte un tipo de señal o estímulo a uno diferente.

La mayoría de los procesos de transducción de señales requieren reacciones bioquímicas secuenciales en el interior de la célula.



Molecular Biology of the Cell (© Garland Science 2008)

Rumbo a multicelular:

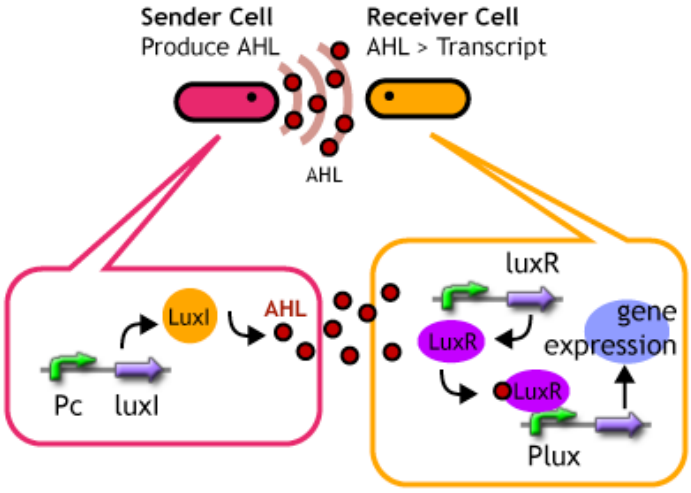


http://www.humanthermodynamics.com/Evolution-diagram_op_800x467.jpg

Comunicación entre unicelulares:

- Bacterias:
  - Quorum sensing

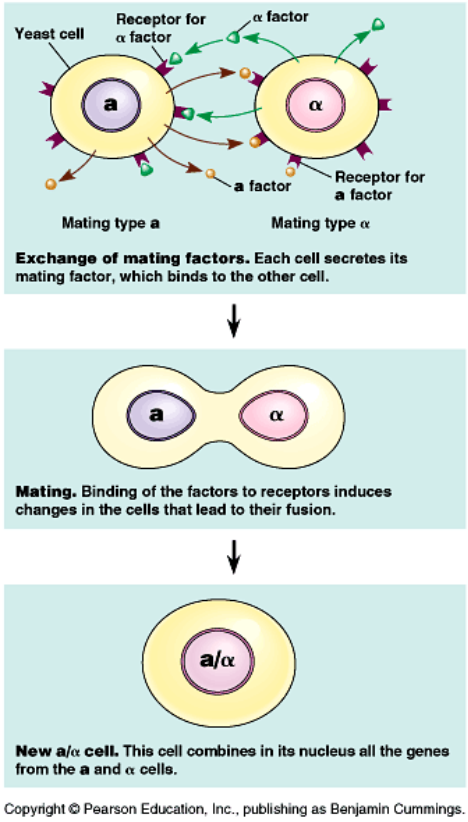
    Mecanismo de regulació genética dependiente de concentración de células en un ambiente



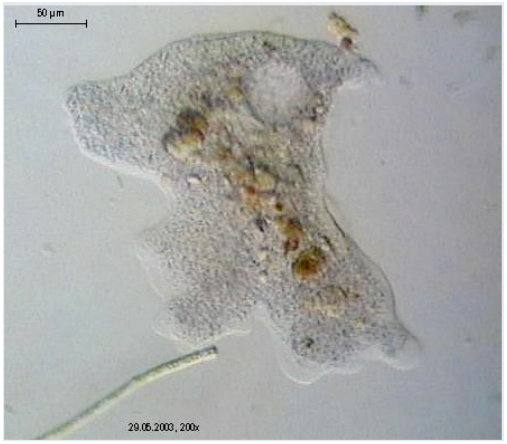
Comunicación entre unicelulares:

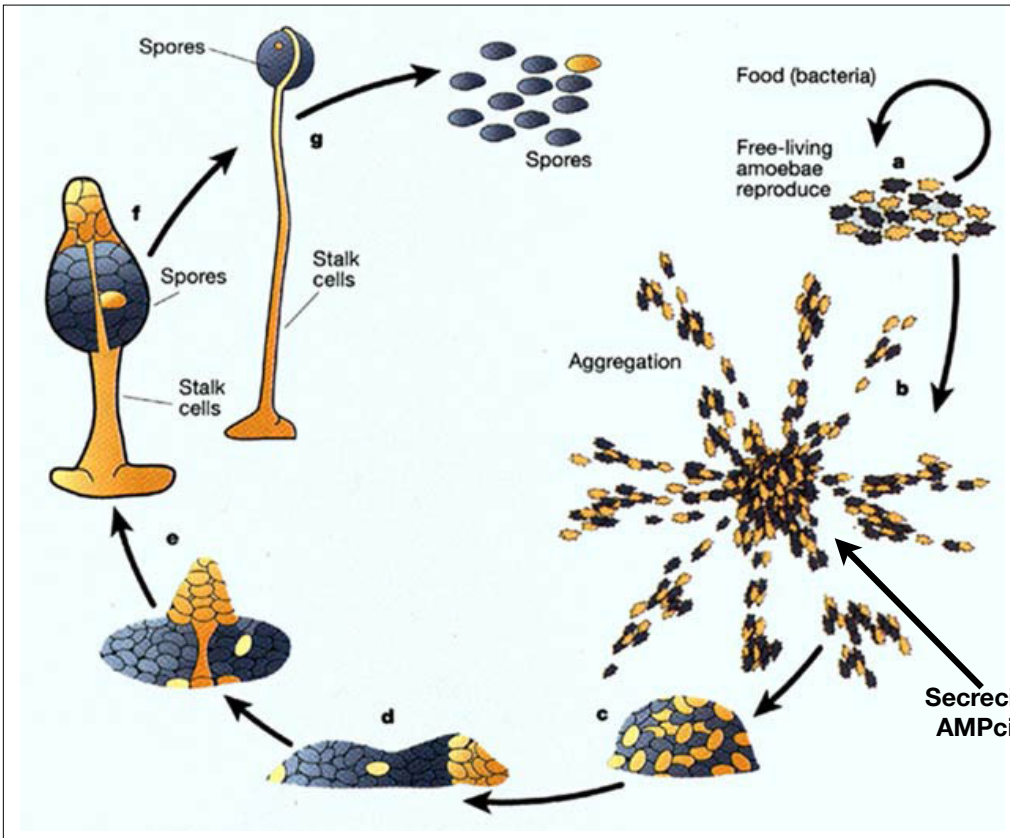
- Levaduras:
  - reproducción sexual

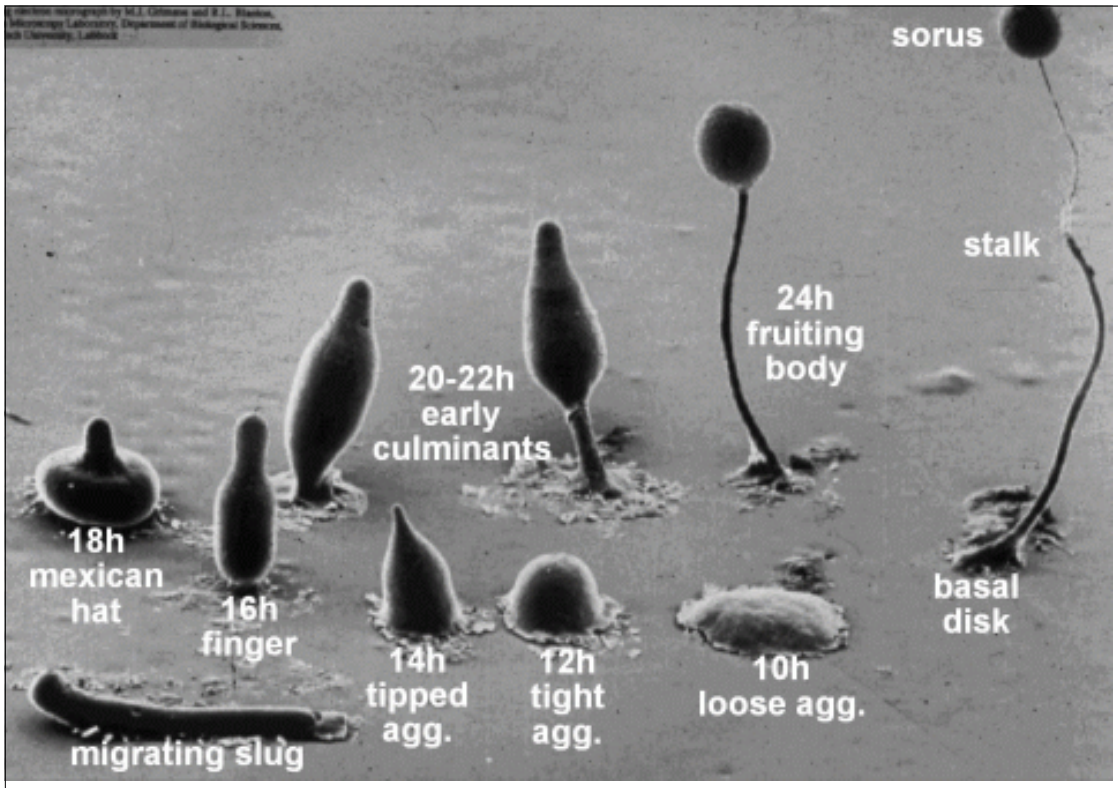
    Mecanismo para el reconocimiento intersexual entre levaduras. Posibilita el apareamiento.



Rumbo a multicelular







9

http://carabuxa.wordpress.com/2008/04/27/quorum-sensing/

Definiciones básicas:

- **Señal**:molécula que transmite una información, y con ello coordina una respuesta, desde una tipo celular a otras células o moléculas del organismo. La señal puede ser grande (proteína) o pequeña (neurotransmisor), hidrofílica(proteína, amino ácido) o hidrofóbica(hormonas esteroidales, retinoides).
- **Receptor**: proteína intra o extracelular de la célula blanco que une específicamente la molécula señal, también llamada ligando. Una célula responderá a una señal solo si tiene receptores para ella.
- **Cascada de señalización**: La unión de ligando al receptor induce la activación de enzimas que a su vez dan origen a reacciones intracelulares concatenadas. Ejemplos: activación de proteínas quinasas, proteínas fosfatasas, proteínas que unen guanidín nucleótidos (proteínas G) y proteínas que se unen a promotores en la secuencia de ADN.

- **La señal es generalmente transitoria. Una vez que la señal produce una respuesta celular esta es destruida (ligandos proteicos por down-regulation).**

¿Qué le dijo una célula a otra célula?

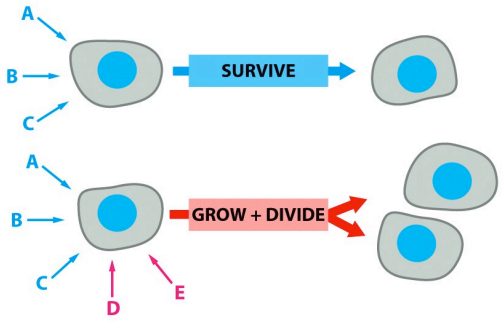


Figure 15-8 *Molecular Biology of the Cell* (© Garland Science 2008)

¿Qué le dijo una célula a otra célula?

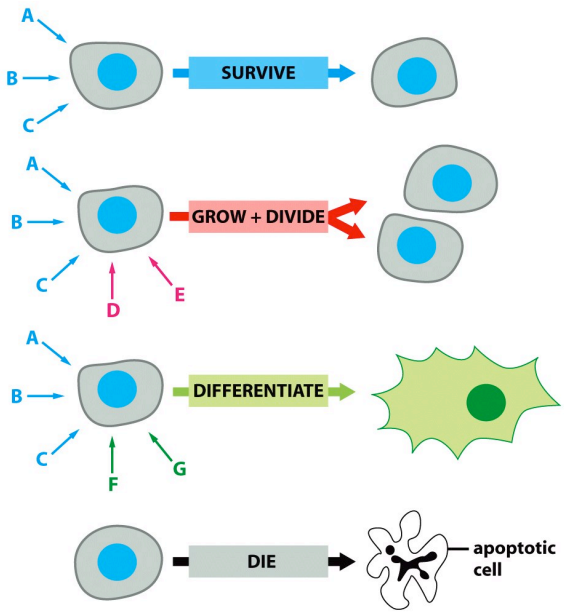


Figure 15-8 *Molecular Biology of the Cell* (© Garland Science 2008)

y ¿Cómo se lo dijo?

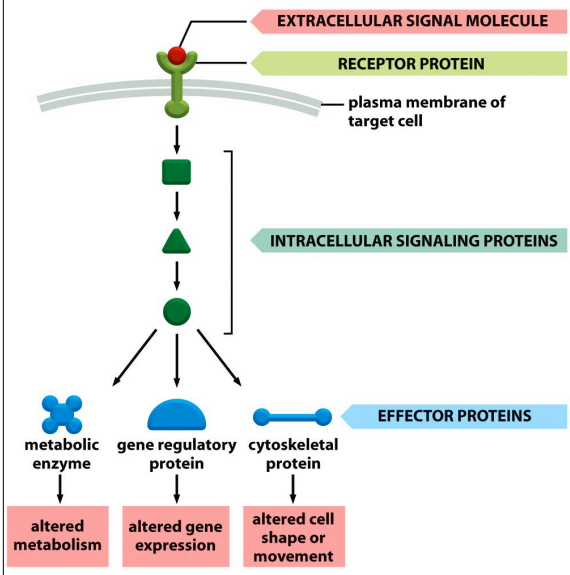


Figure 15-1 *Molecular Biology of the Cell* (© Garland Science 2008)

La organización concatenada de estas reacciones las convierte en **VIAS**, o incluso una **RED** de señalización.

Las reacciones de transducción de señales son realizadas por enzimas producen "segundos mensajeros" (y, que en una vía han sido activadas por los segundos de enzimas previas).

Los procesos enzimáticos actúan como una cascada de señales, aumentando el número de moléculas participantes, lo que sirve como amplificador de la señal. Es aquí donde una señal pequeña da origen a una respuesta de la célula completa.

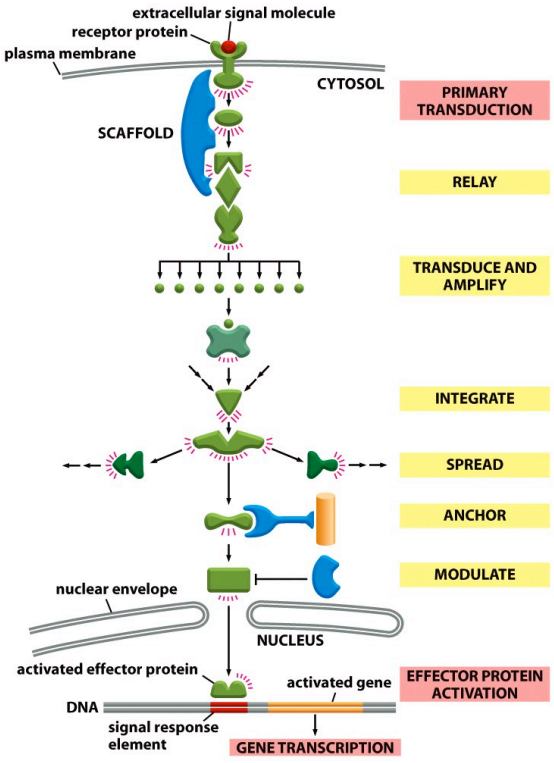
Estos procesos son normalmente rápidos, varían desde milisegundos (apertura de un canal y entrada de iones), a minutos (cascadas de quinasas activadas por péptidos, proteínas o lípidos) o hasta horas y días (receptores nucleares).

Su impacto puede ser medirse en diferentes niveles de la célula:

Membrana

Citoesqueleto

Núcleo (velocidad de transducción)



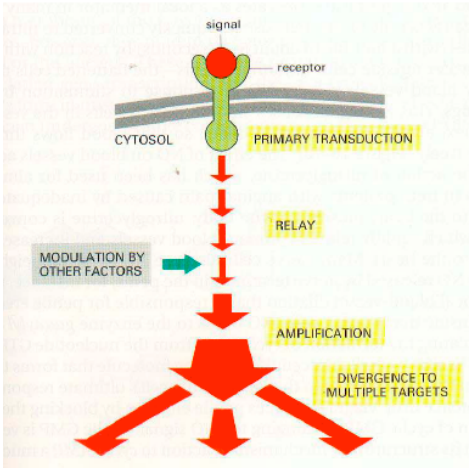


Figure 15-17 *Molecular Biology of the Cell* (© Garland Science 2008)

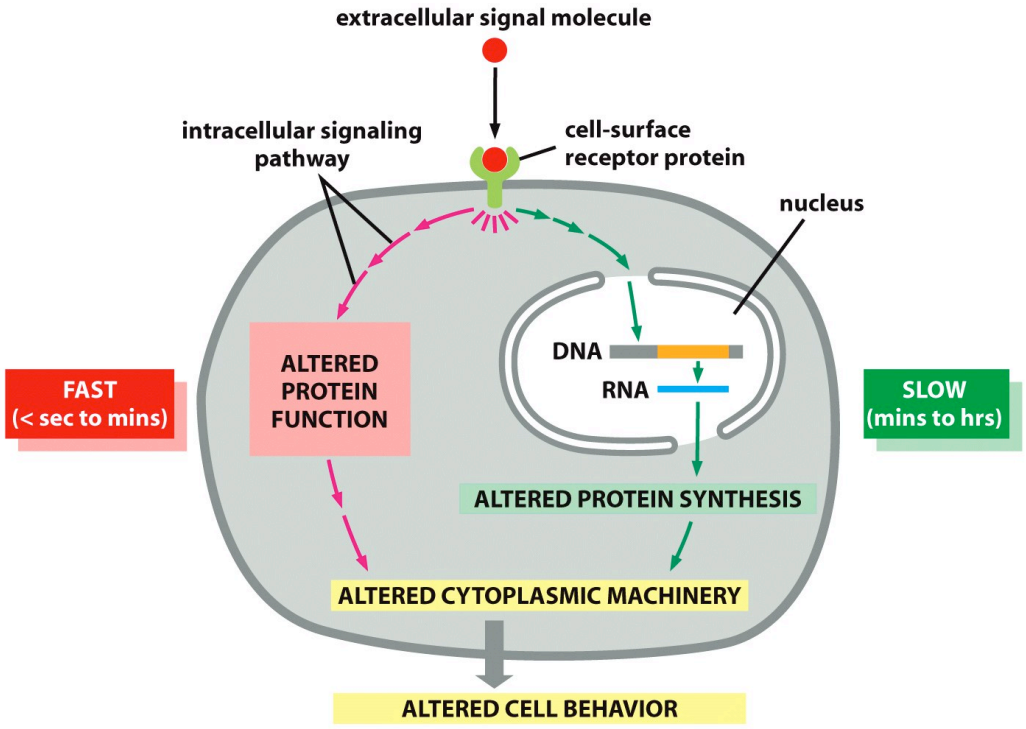


Figure 15-6 *Molecular Biology of the Cell* (© Garland Science 2008)

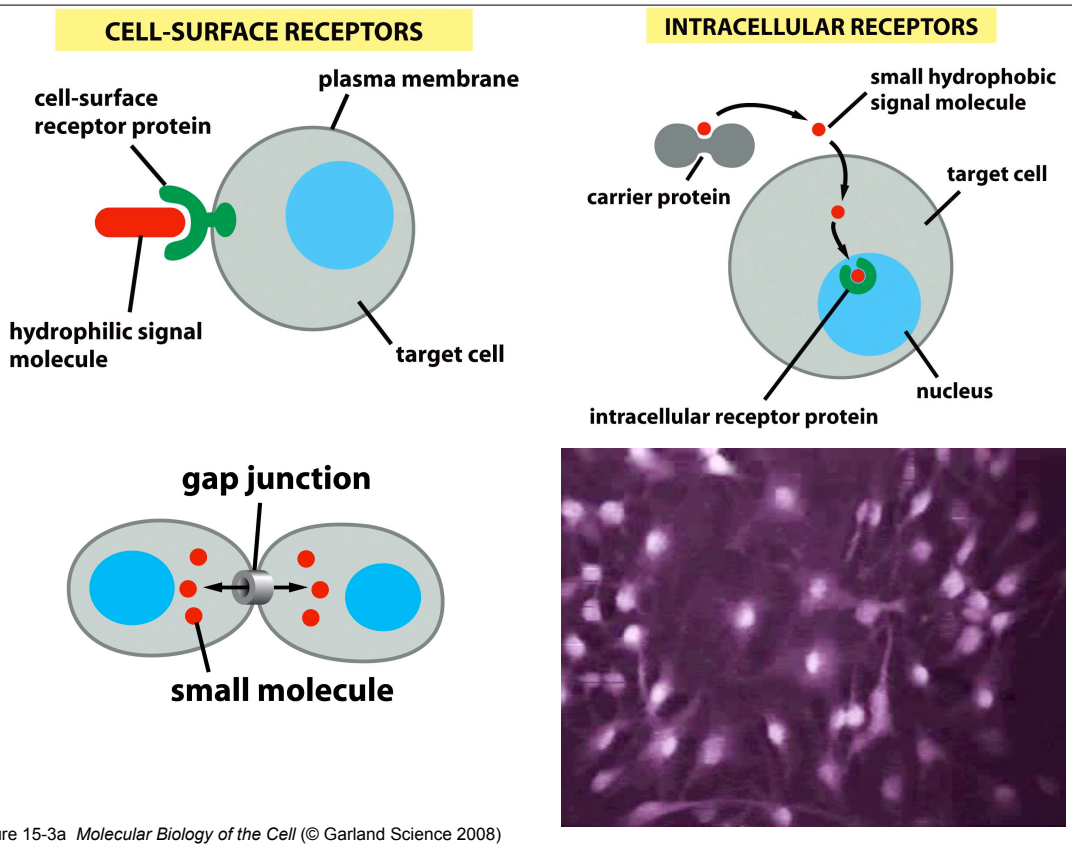


Figure 15-3a *Molecular Biology of the Cell* (© Garland Science 2008)

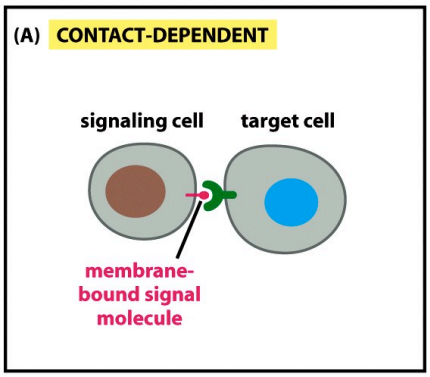


Figure 15-4 *Molecular Biology of the Cell* (© Garland Science 2008)

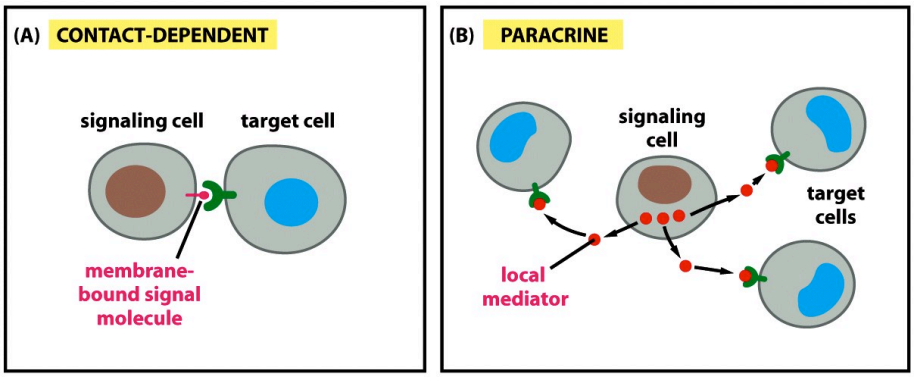


Figure 15-4 *Molecular Biology of the Cell* (© Garland Science 2008)

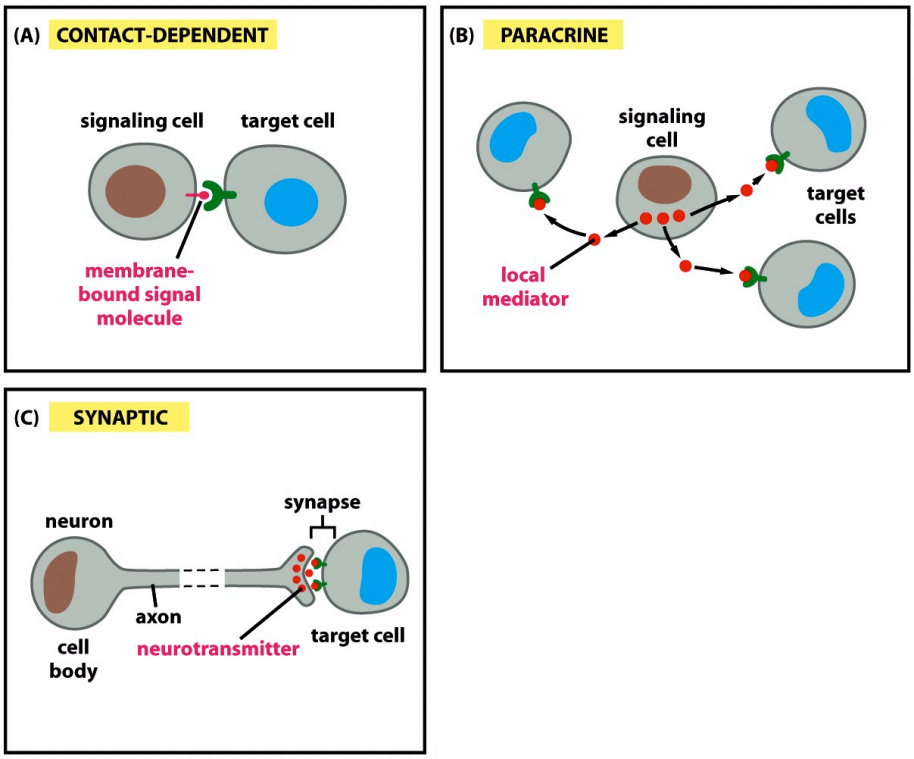


Figure 15-4 *Molecular Biology of the Cell* (© Garland Science 2008)

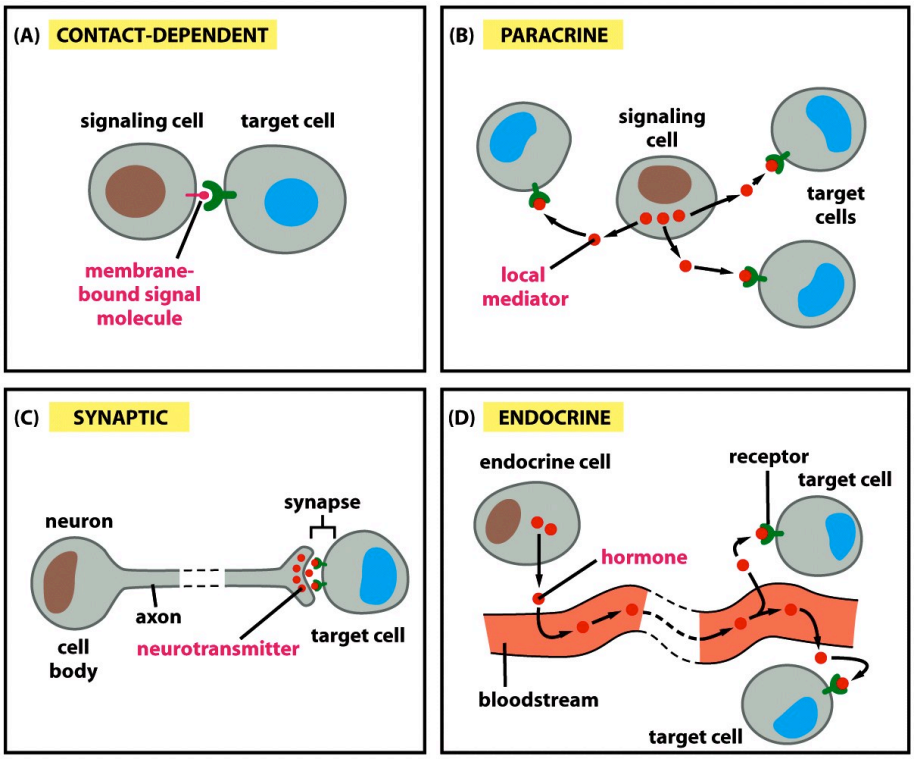


Figure 15-4 *Molecular Biology of the Cell* (© Garland Science 2008)

La misma señal, diferente contexto

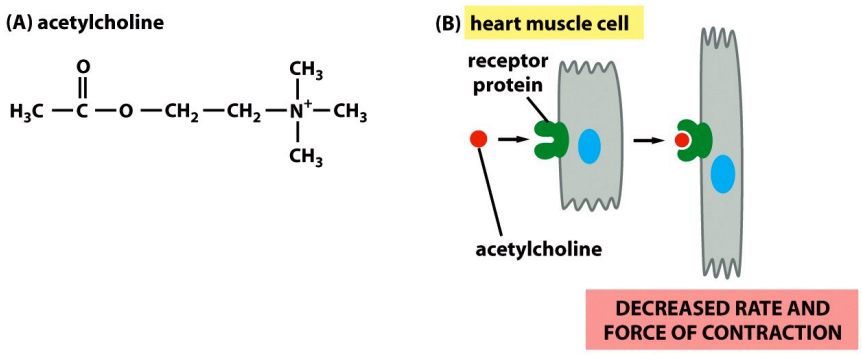
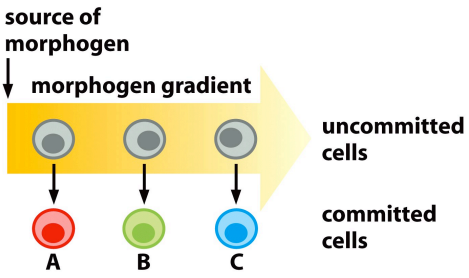


Figure 15-9 *Molecular Biology of the Cell* (© Garland Science 2008)

Gradientes y difusión de las señales:

- Las células derivan su información posicional gracias a la existencia de gradientes.
- La identidad de la célula (o su respuesta), depende de el número de receptores activados (proporcional a la concentración de ligando/señal). Esto genera diferencias en la **expresión génica de cada célula.**



- Las señales paracrinas no deben difundir (solo actuar sobre células vecinas), su migración eslimitada por su unión a proteínas ricas en *heparán sulfato*.

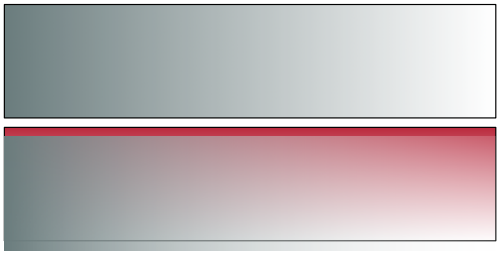


Figure 15-10 *Molecular Biology of the Cell* (© Garland Science 2008)

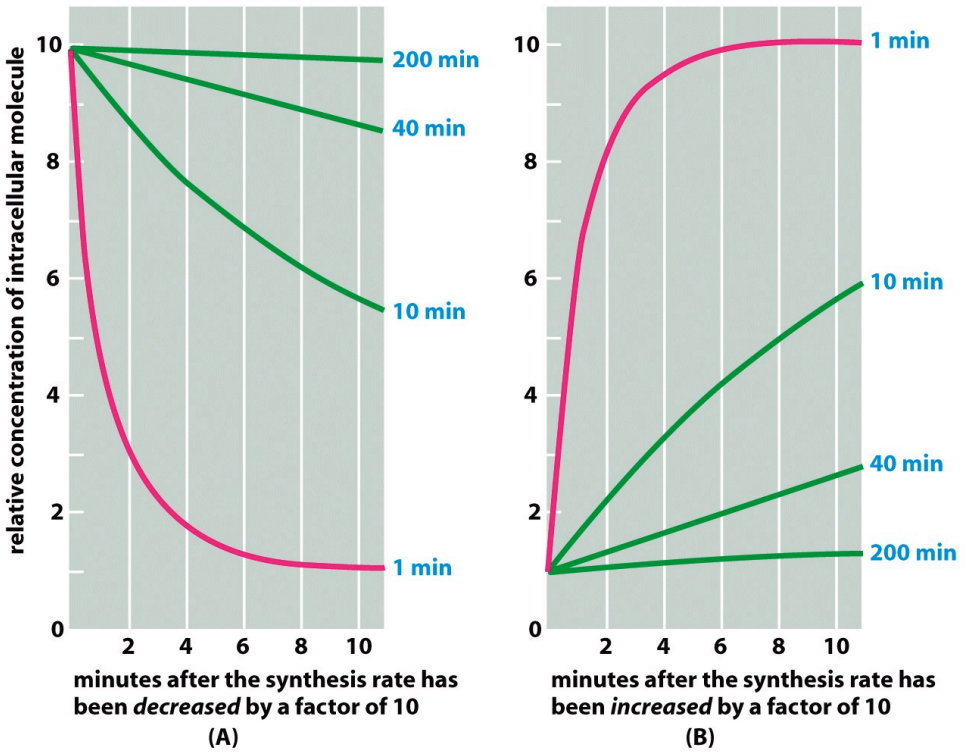


Figure 15-11 *Molecular Biology of the Cell* (© Garland Science 2008)

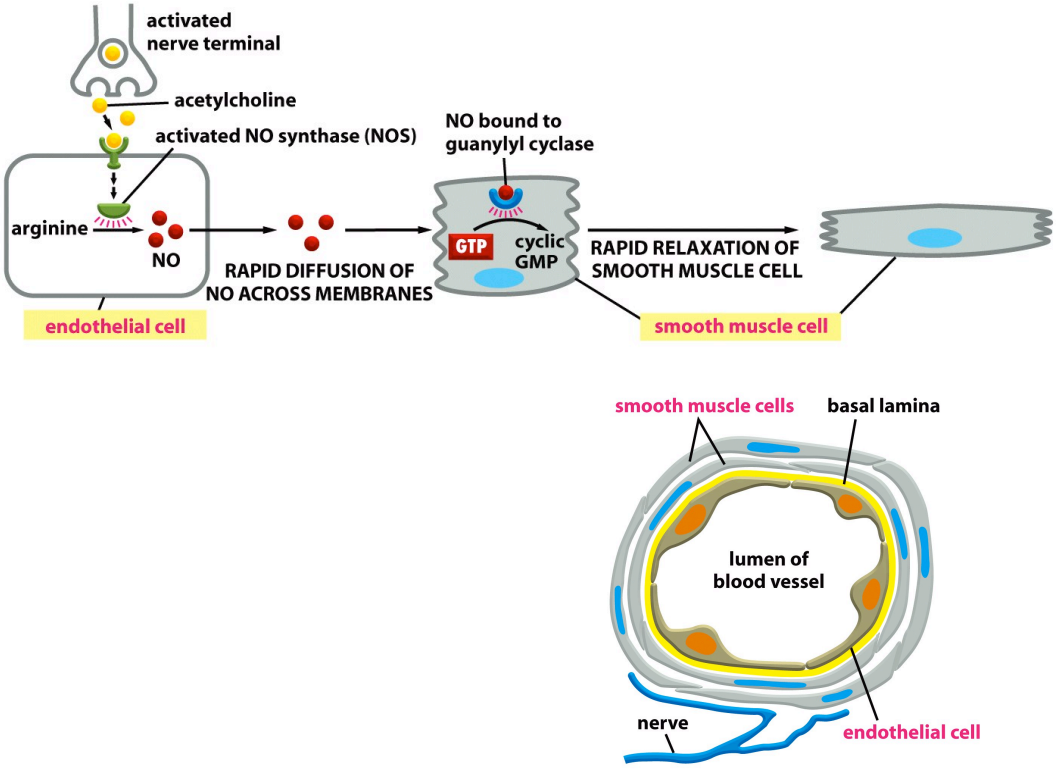


Figure 15-12b *Molecular Biology of the Cell* (© Garland Science 2008)

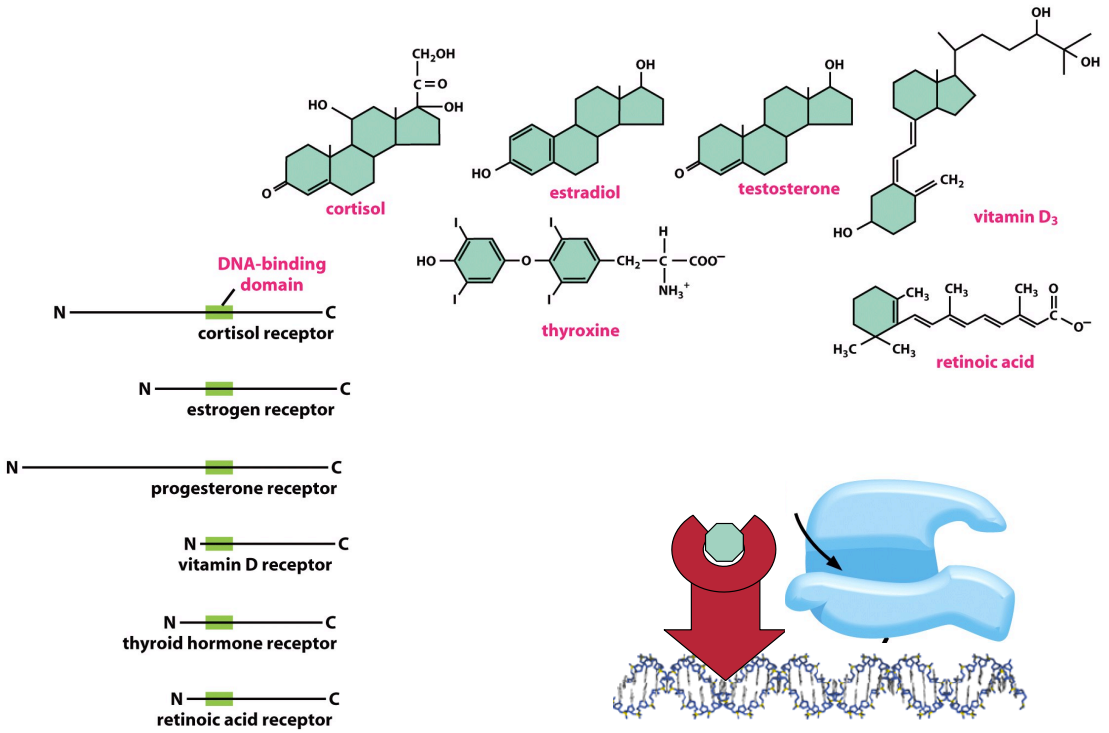


Figure 15-13 *Molecular Biology of the Cell* (© Garland Science 2008)

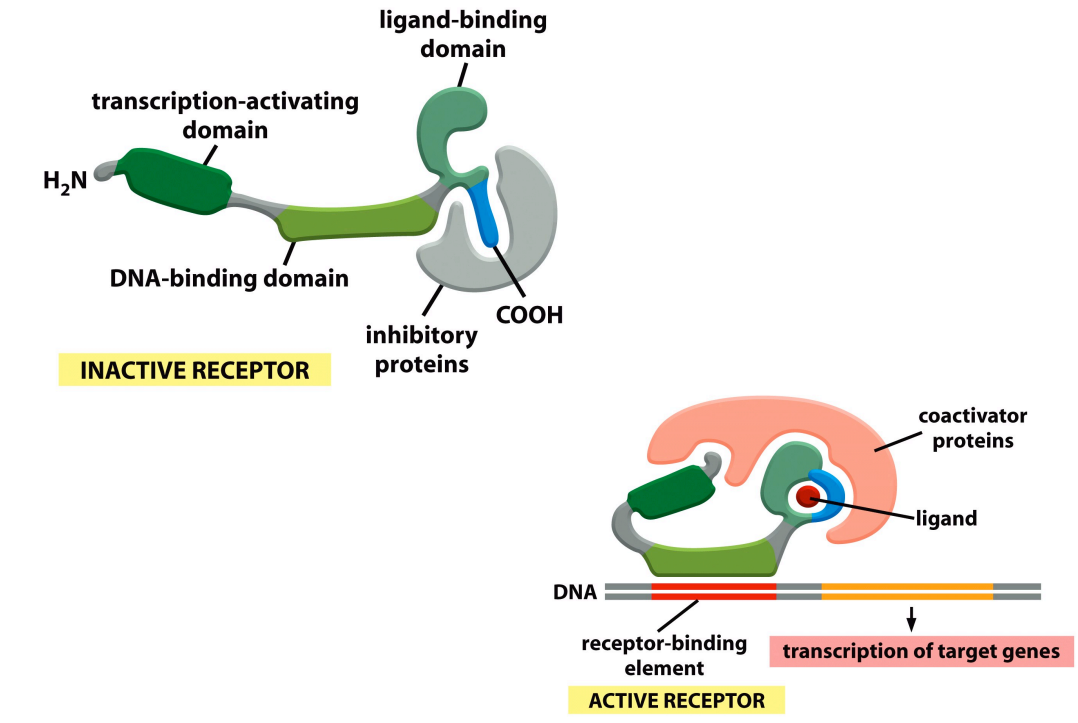


Figure 15-14b *Molecular Biology of the Cell* (© Garland Science 2008)

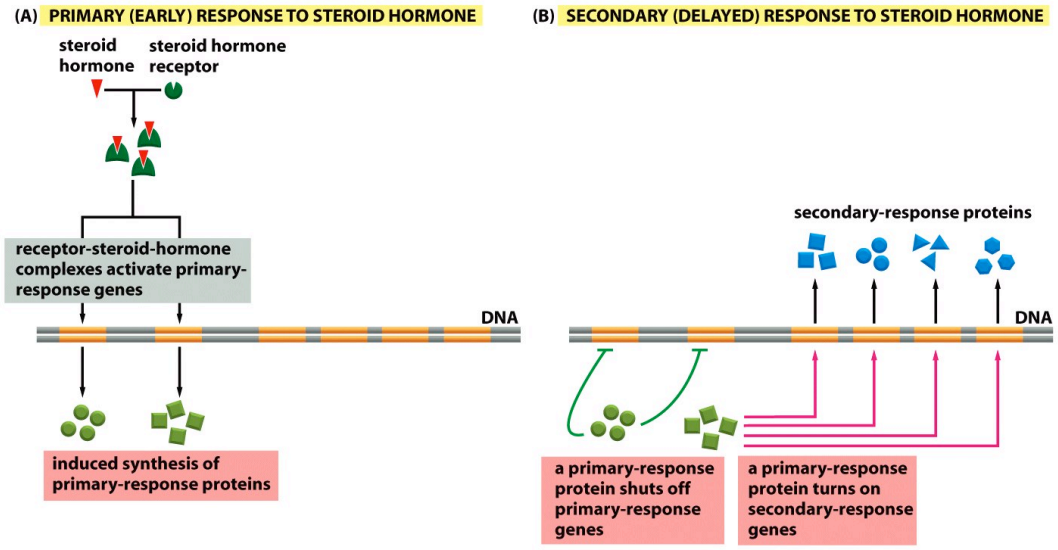
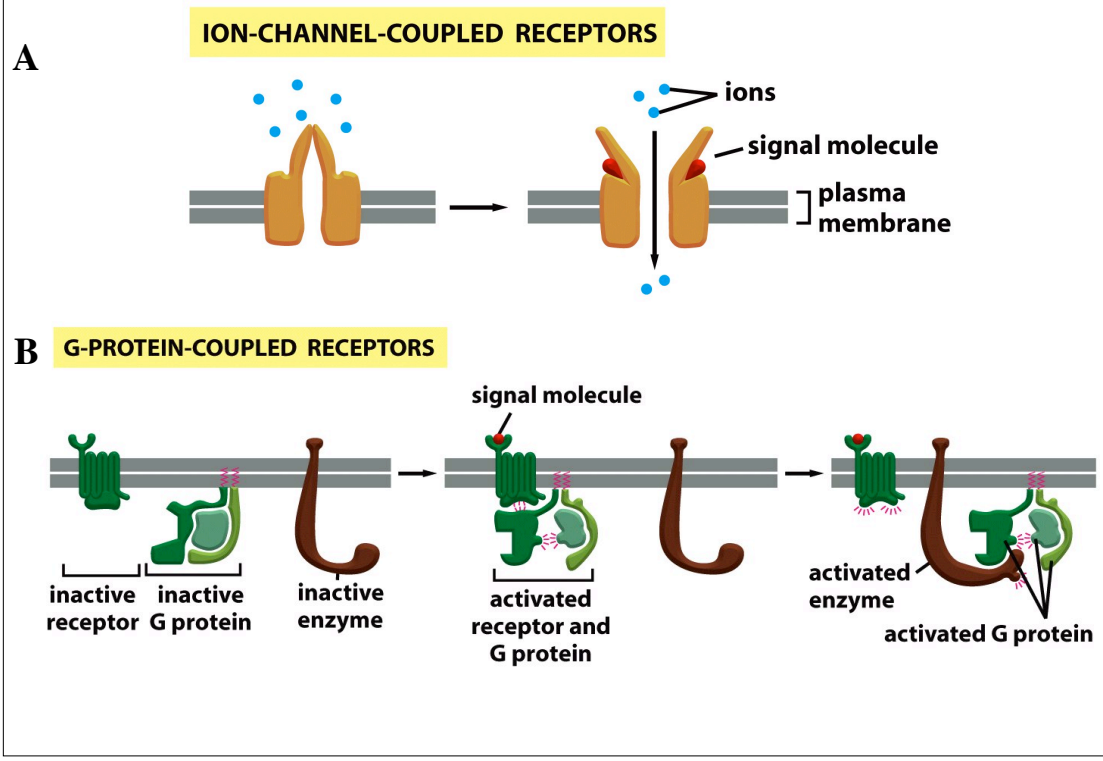


Figure 15-15 *Molecular Biology of the Cell* (© Garland Science 2008)

Señales desde la superficie



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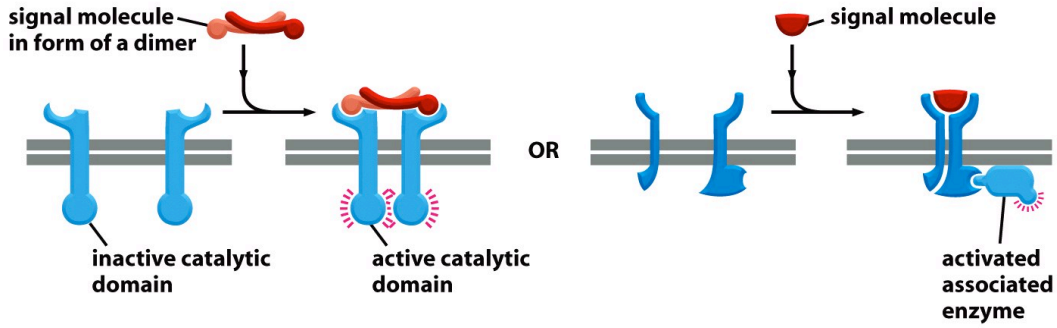
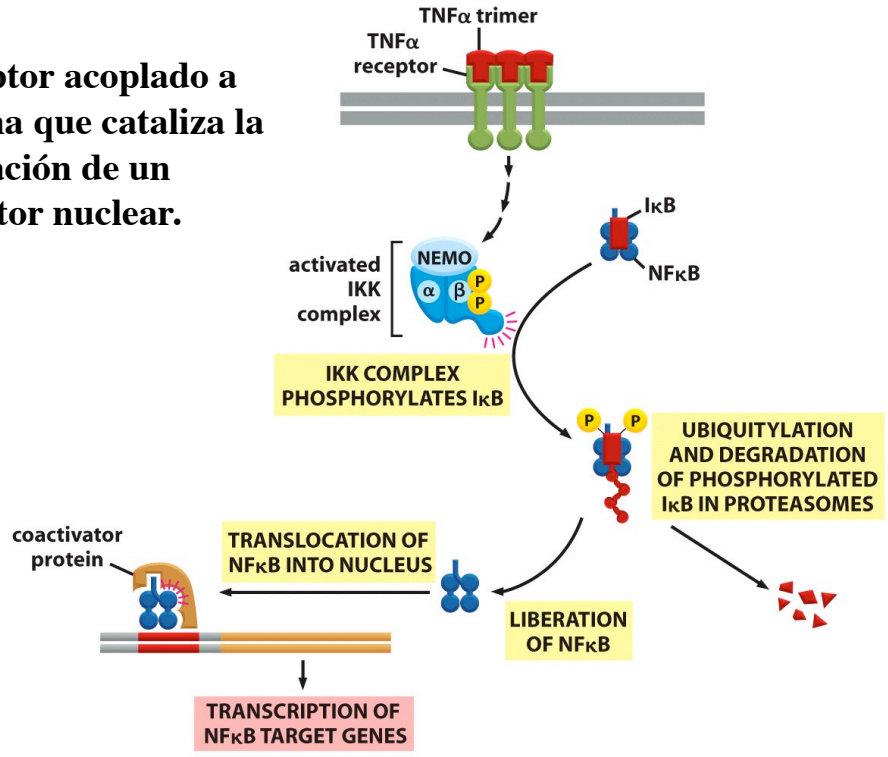


Vía NF-kB

Receptor acoplado a enzima que cataliza la activación de un receptor nuclear.



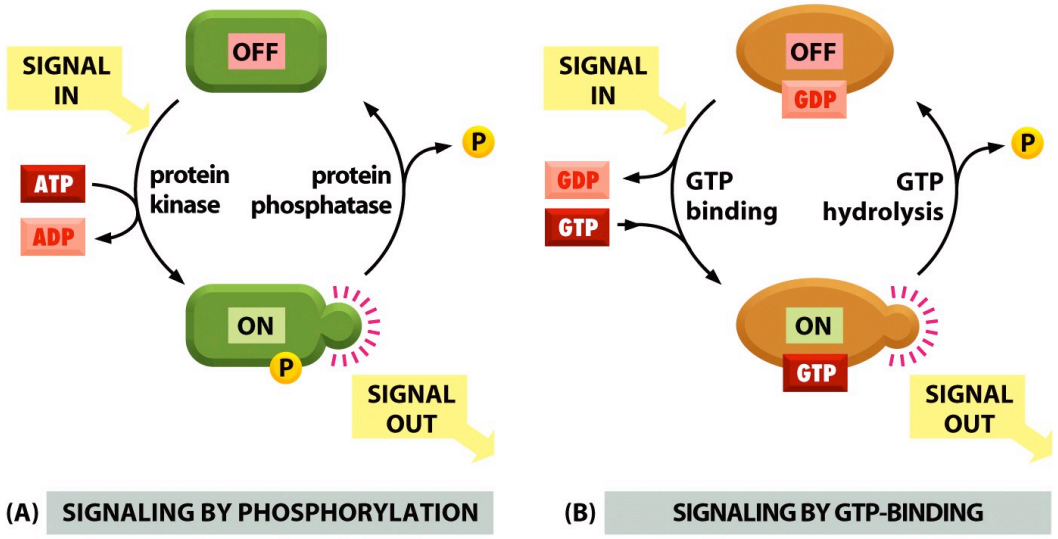


Figure 15-18 *Molecular Biology of the Cell* (© Garland Science 2008)

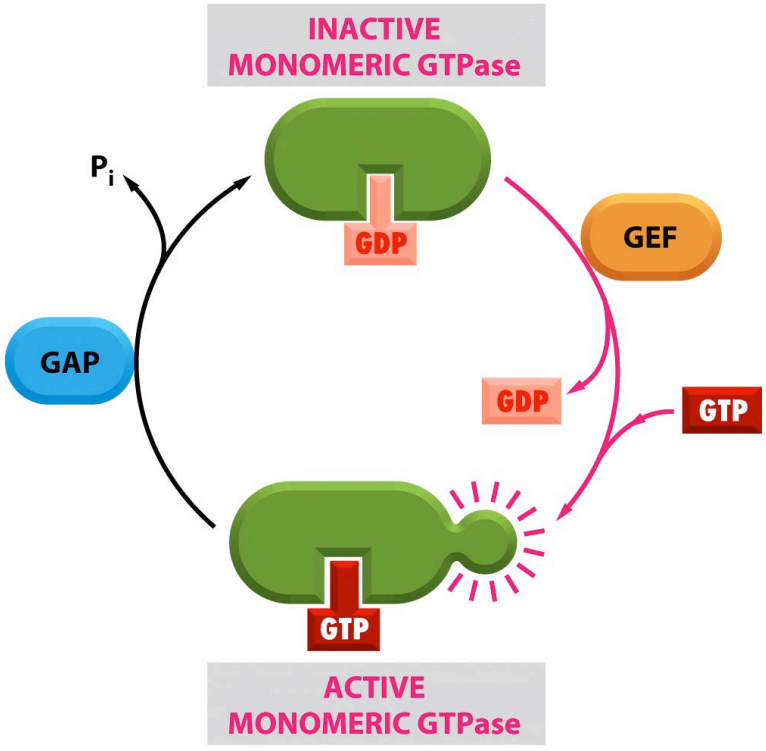


Figure 15-19 *Molecular Biology of the Cell* (© Garland Science 2008)

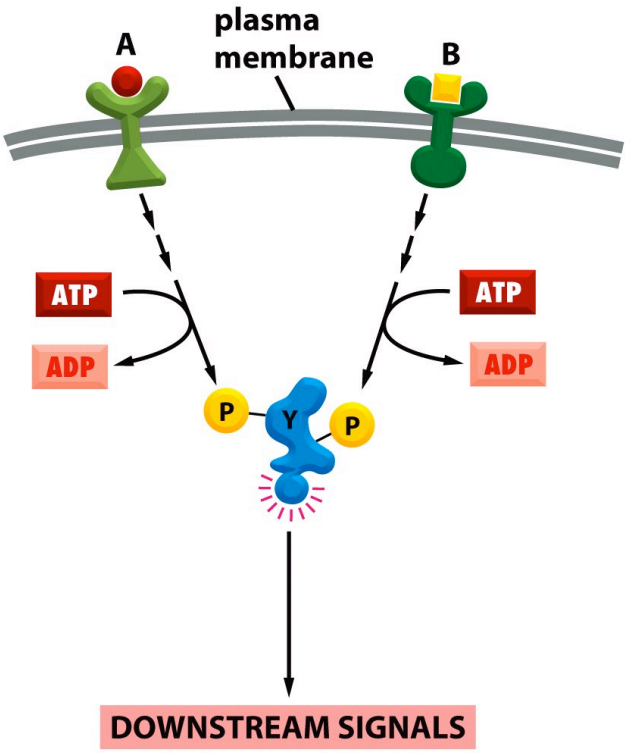


Figure 15-20 *Molecular Biology of the Cell* (© Garland Science 2008)

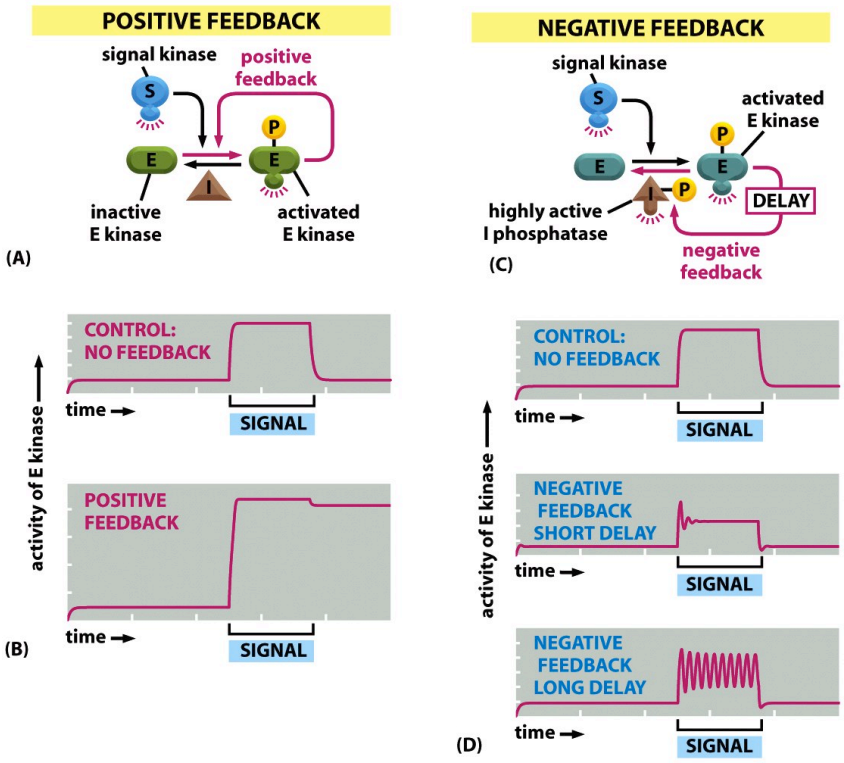


Figure 15-28 *Molecular Biology of the Cell* (© Garland Science 2008)

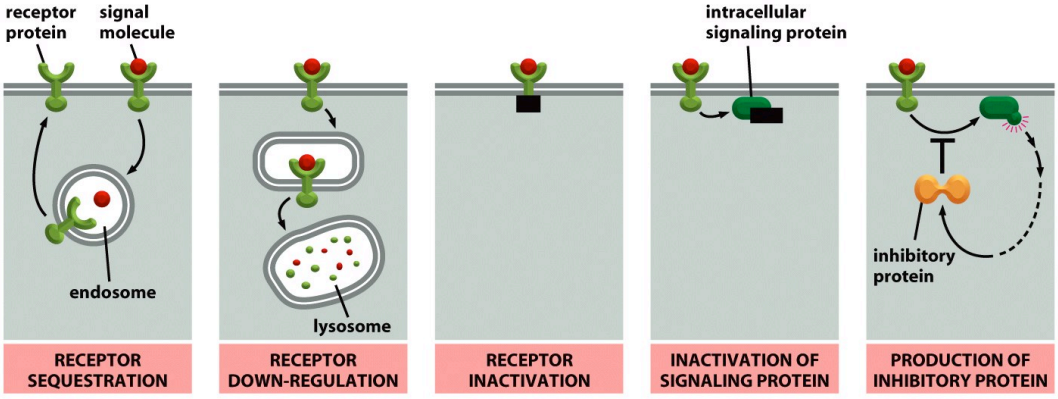
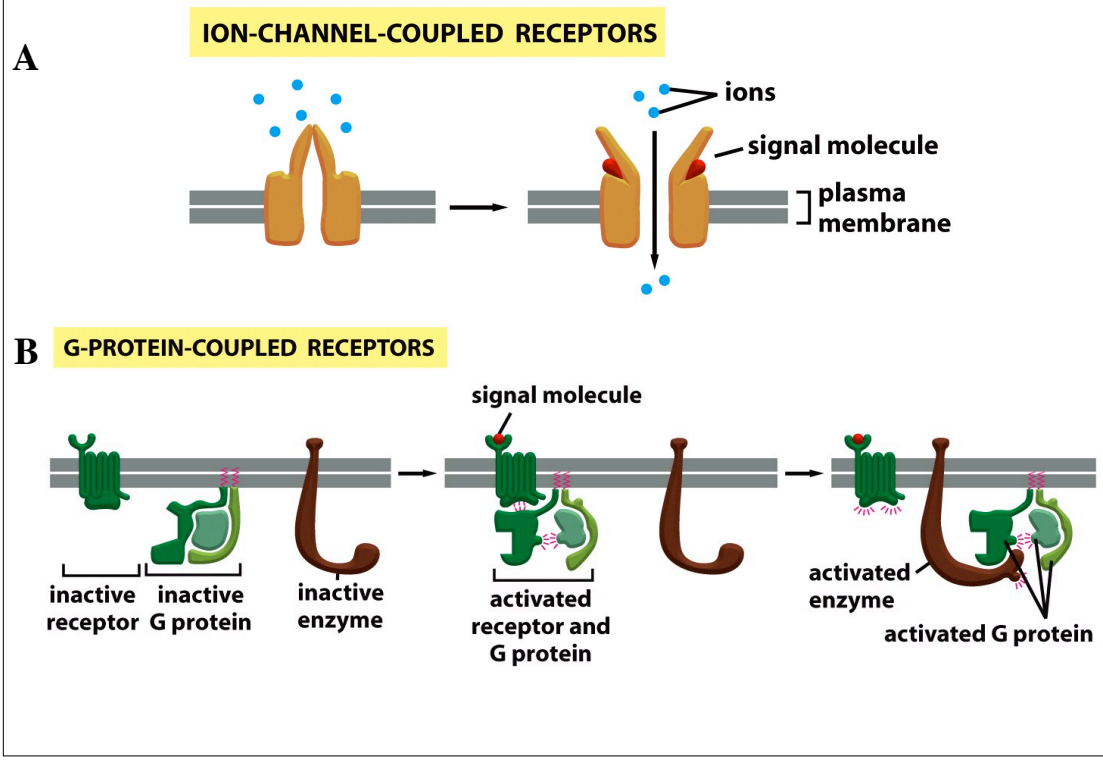


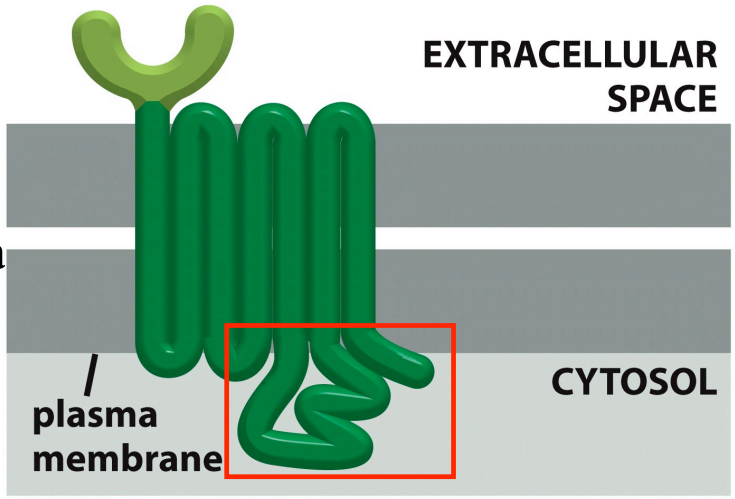
Figure 15-29 *Molecular Biology of the Cell* (© Garland Science 2008)

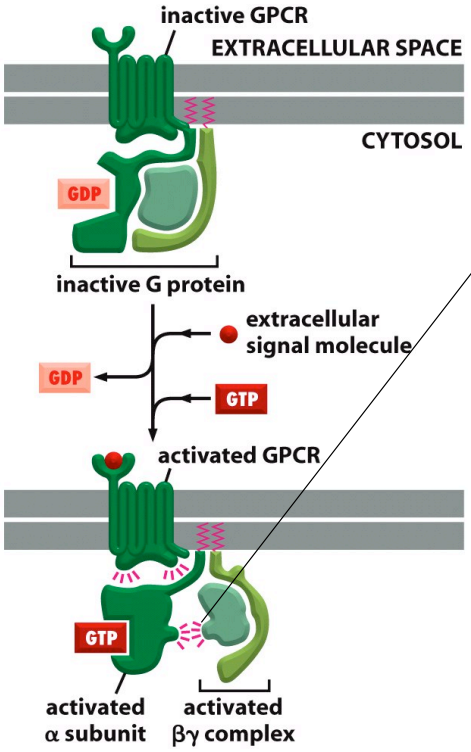
Señales desde la superficie



Receptores Metabotrópicos con 7 segmentos Transmembrana

(7 magníficos)





Efectos de Beta y Gamma activados:

SOME FUNCTIONS
activates adenylyl cyclase; activates Ca^{2+} channels
activates adenylyl cyclase in olfactory sensory neurons
inhibits adenylyl cyclase
activates K^+ channels
activates K^+ channels; inactivates Ca^{2+} channels
activates phospholipase C-β
activates cyclic GMP phosphodiesterase in vertebrate rod photoreceptors
activates phospholipase C-β
activates Rho family monomeric GTPases (via Rho-GEF) to regulate the actin cytoskeleton

Figure 15-32 *Molecular Biology of the Cell* (© Garland Science 2008)

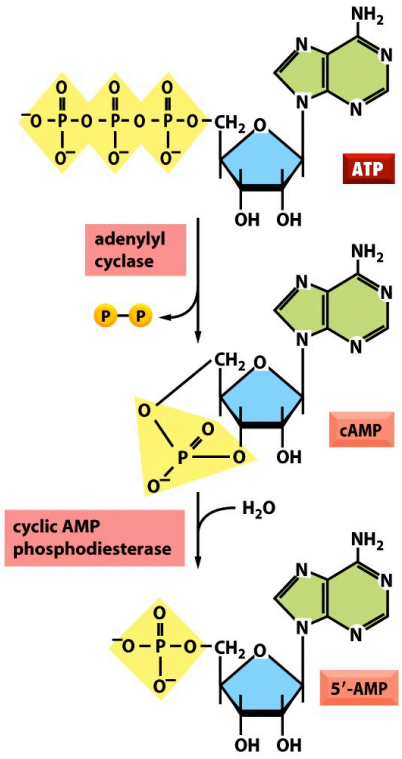
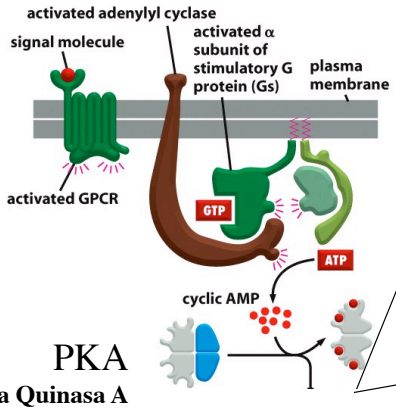


Figure 15-34 *Molecular Biology of the Cell* (© Garland Science 2008)



PKA

Proteína Quinasa A

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

Por ejemplo:

5-HT: Serotonina

1. **Aumento de AMPc**
2. **Activación de PKA**
   - a) **Fosforilación de Ca-K (inactivación del canal).**
     - **Bloqueo de corriente de salida de K+**
     - **Aumento de la respuesta al facilitar la despolarización.**
   - b) **Efectos a largo plazo**
     - **Aumento del número de Ca-K**

Figure 15-36 *Molecular Biology of the Cell* (© Garland Science 2008)

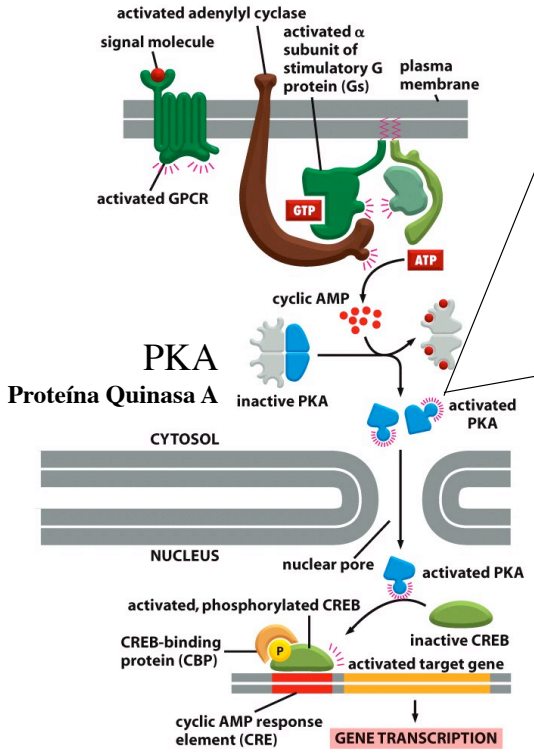


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Figure 15-36 *Molecular Biology of the Cell* (© Garland Science 2008)

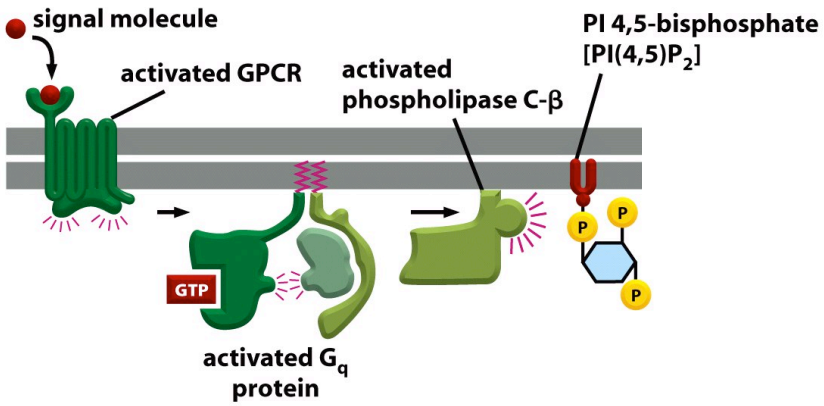


Figure 15-39 *Molecular Biology of the Cell* (© Garland Science 2008)

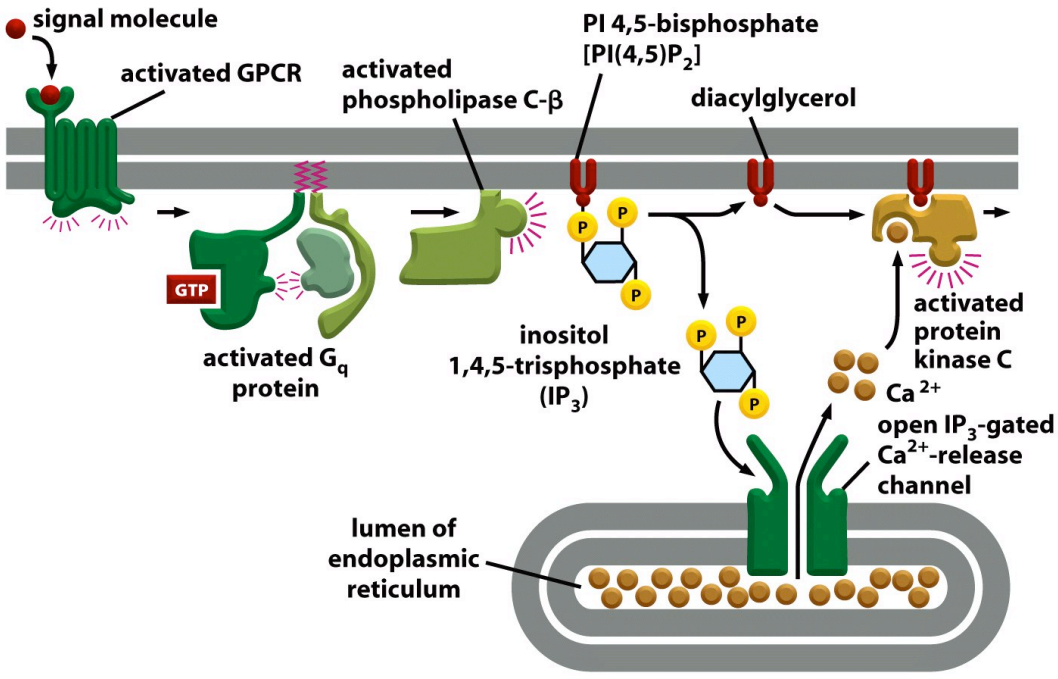


Figure 15-39 *Molecular Biology of the Cell* (© Garland Science 2008)

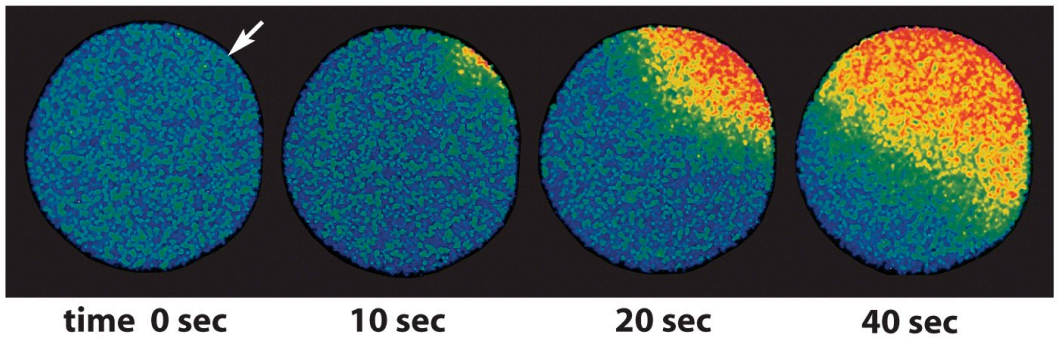


Figure 15-40 *Molecular Biology of the Cell* (© Garland Science 2008)

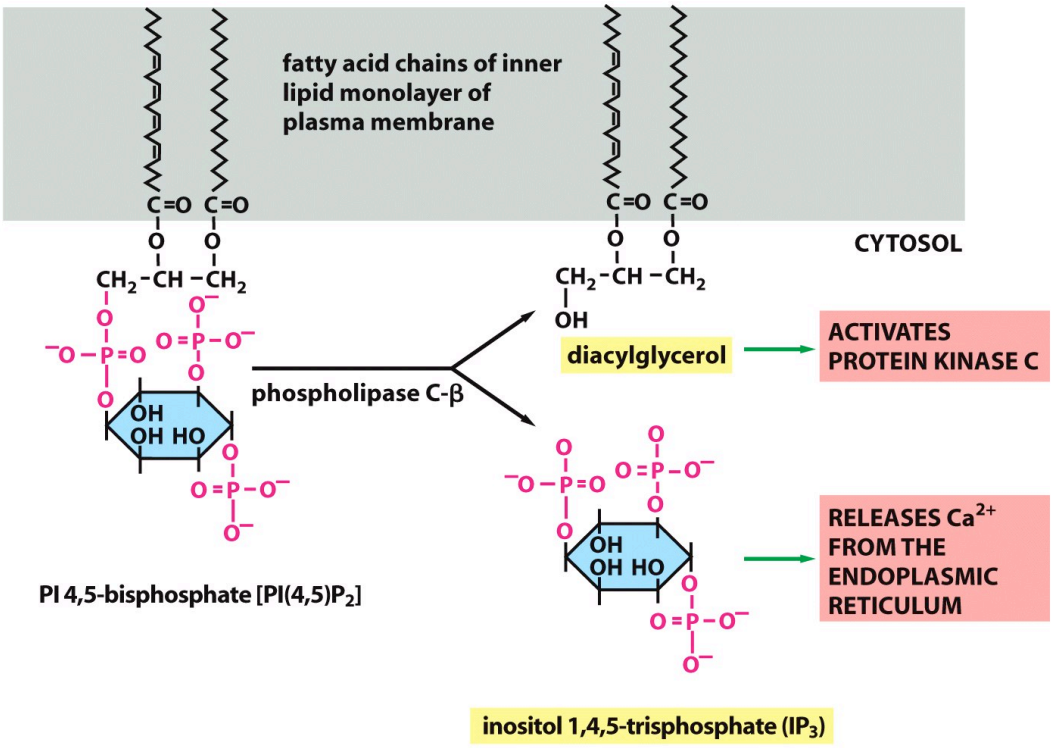


Figure 15-38 *Molecular Biology of the Cell* (© Garland Science 2008)

Regulación de las concentraciones de Calcio

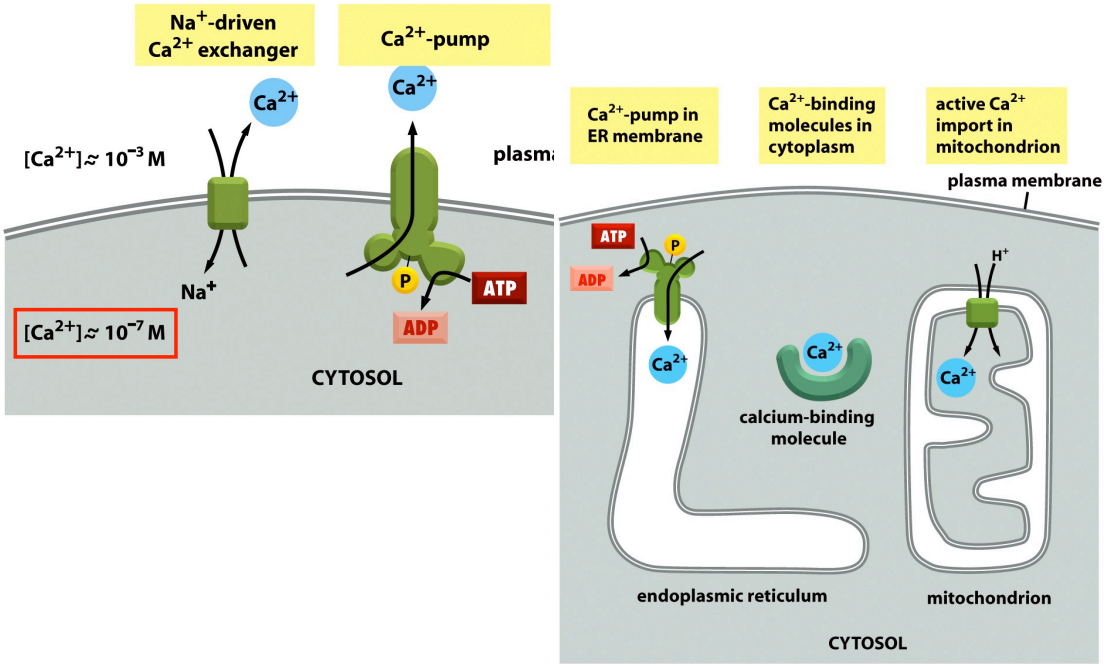
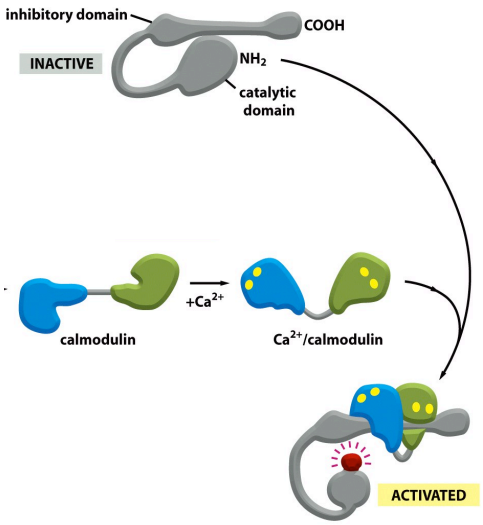


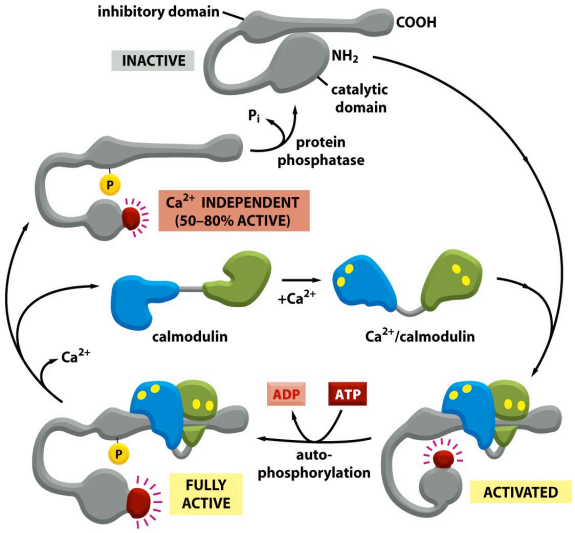
Figure 15-41a *Molecular Biology of the Cell* (© Garland Science 2008)



Efectos de la activación de Calmodulina

- Unión y activación de la bomba de Ca^{+2} (fin de pulso de Ca^{+2}).
- Activación de las Quinasas dependientes de Ca^{+2}/ Calmodulina.
  - Fosforilación inhibitoria de CREB.
  - Actividad quinasa mantenida (CamK II), memoria de pulso de Ca^{+2} previo.

Figure 15-44 *Molecular Biology of the Cell* (© Garland Science 2008)



Efectos de la activación de Calmodulina

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  - Actividad quinasa mantenida (CamK II), memoria de pulso de Ca^{+2} previo.

Figure 15-44 *Molecular Biology of the Cell* (© Garland Science 2008)

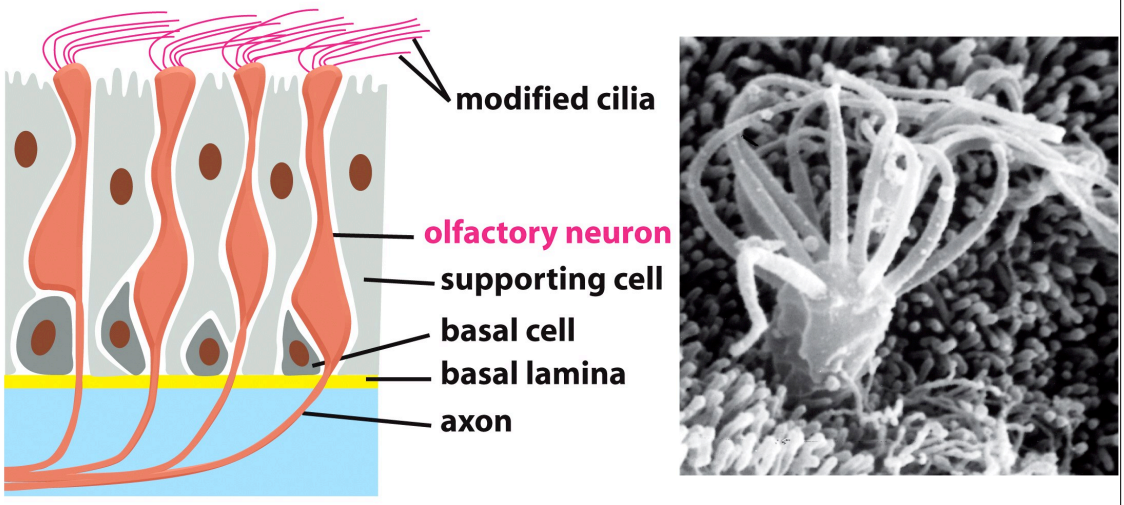
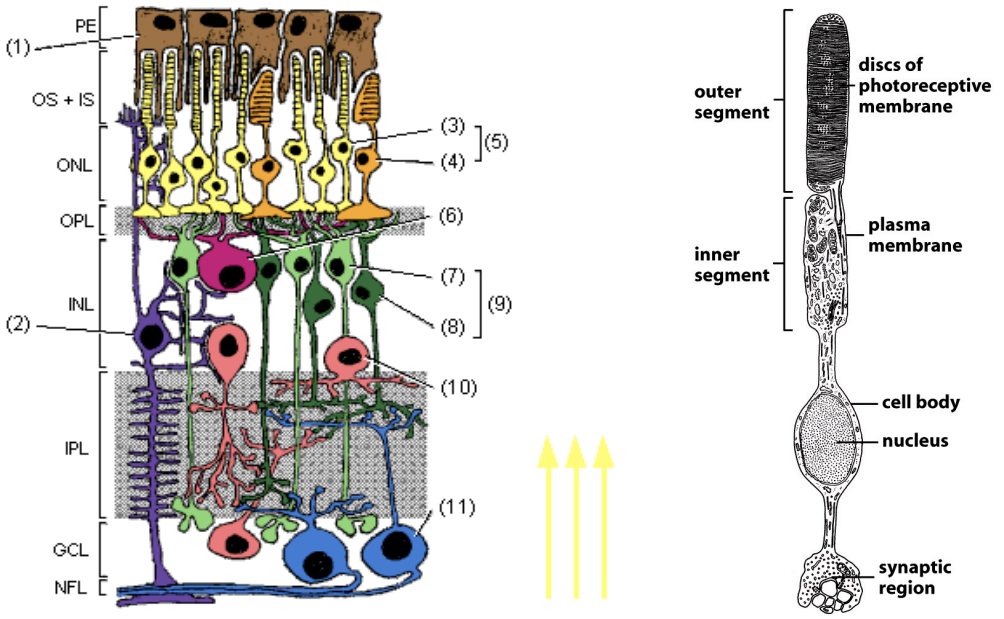


Figure 15-46a *Molecular Biology of the Cell* (© Garland Science 2008)



The following cell types are shown: retinal pigment epithelium (PE, 1), Müller cells (2), photoreceptors (5): rods (3) and cones (4), horizontal cells (6), bipolar cells (9): rod- (7) and cone bipolar cells (8), amacrine cells (10), ganglion cells (11). The arrows show the direction of the light falling into the eye (and through the layers of the retina).

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Transducción de la señal
Por los fotoreceptores

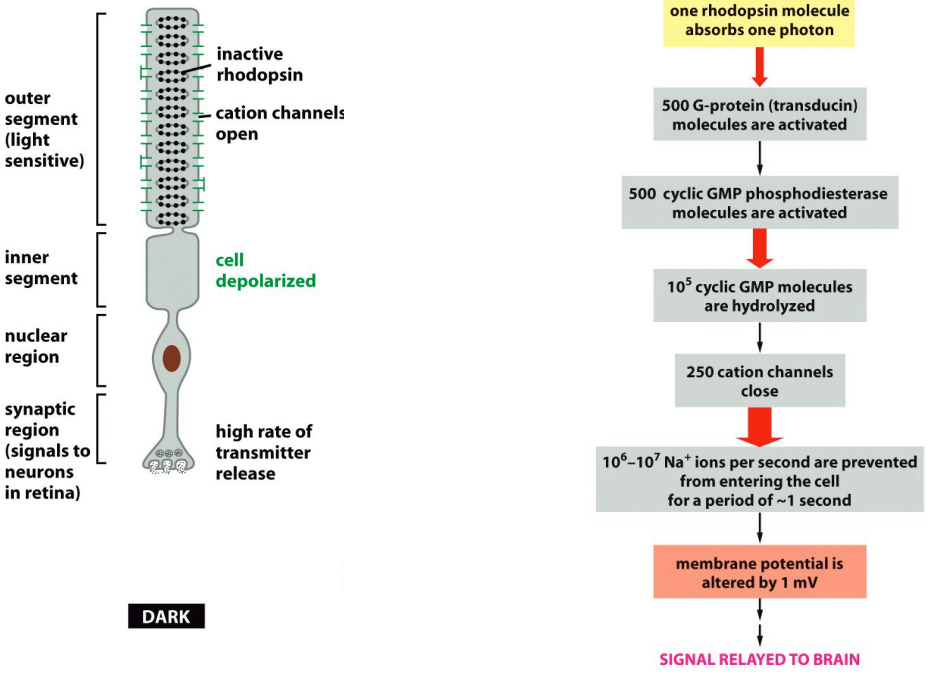


Figure 15-49 *Molecular Biology of the Cell* (© Garland Science 2008)

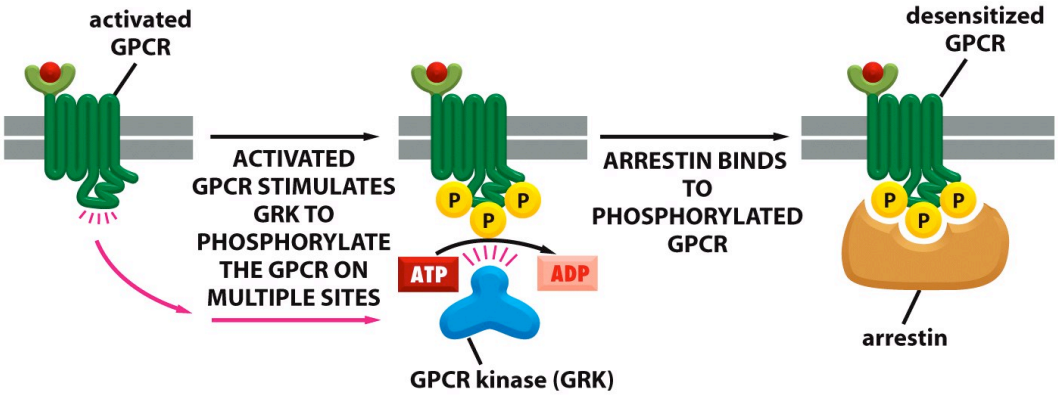


Figure 15-51 *Molecular Biology of the Cell* (© Garland Science 2008)

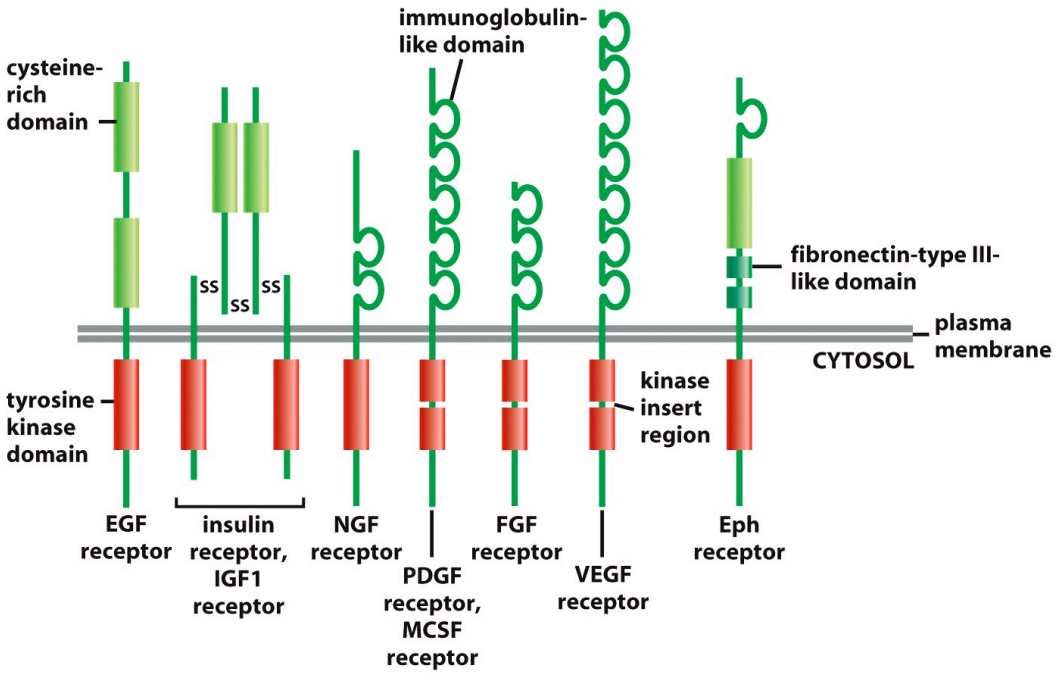


Figure 15-52 *Molecular Biology of the Cell* (© Garland Science 2008)

Table 15–4 Some Signal Proteins That Act Via RTKs

SIGNAL PROTEIN	RECEPTORS	SOME REPRESENTATIVE RESPONSES
Epidermal growth factor (EGF)	EGF receptors	stimulates cell survival, growth, proliferation, or differentiation of various cell types; acts as inductive signal in development
Insulin	insulin receptor	stimulates carbohydrate utilization and protein synthesis
Insulin-like growth factors (IGF1 and IGF2)	IGF receptor-1	stimulate cell growth and survival in many cell types
Nerve growth factor (NGF)	Trk A	stimulates survival and growth of some neurons
Platelet-derived growth factors (PDGF AA, BB, AB)	PDGF receptors (α and β)	stimulate survival, growth, proliferation, and migration of various cell types
Macrophage-colony-stimulating factor (MCSF)	MCSF receptor	stimulates monocyte/macrophage proliferation and differentiation
Fibroblast growth factors (FGF1 to FGF24)	FGF receptors (FGFR1–FGFR4, plus multiple isoforms of each)	stimulate proliferation of various cell types; inhibit differentiation of some precursor cells; act as inductive signals in development
Vascular endothelial growth factor (VEGF)	VEGF receptors	stimulates angiogenesis
Ephrins (A and B types)	Eph receptors (A and B types)	stimulate angiogenesis; guide cell and axon migration

Table 15-4 *Molecular Biology of the Cell* (© Garland Science 2008)

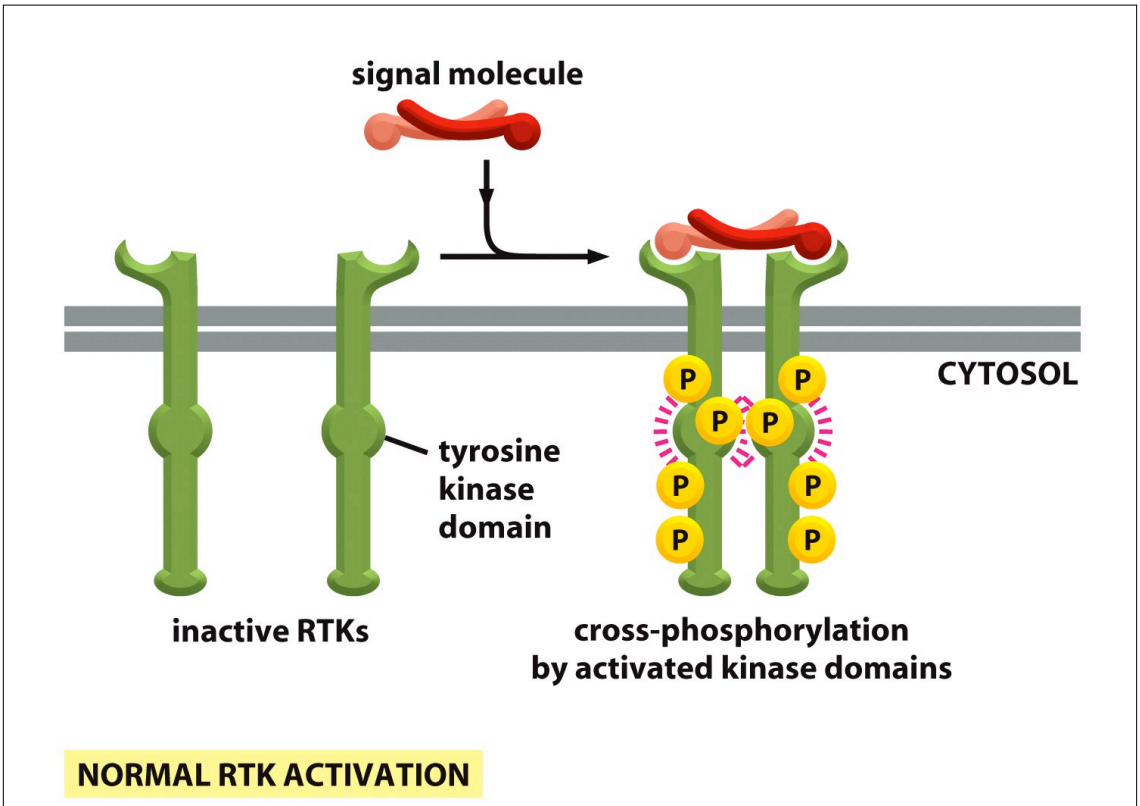


Figure 15-53a *Molecular Biology of the Cell* (© Garland Science 2008)

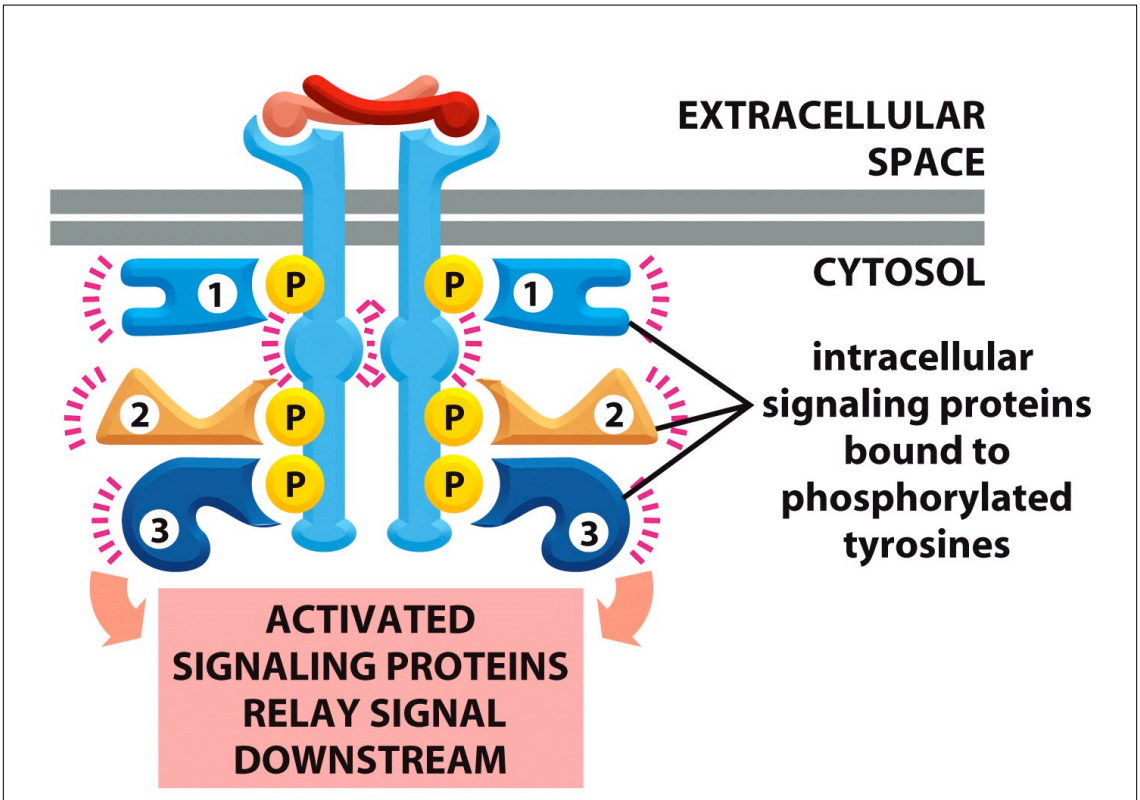


Figure 15-54 *Molecular Biology of the Cell* (© Garland Science 2008)

Table 15–5 The Ras Superfamily of Monomeric GTPases

FAMILY	SOME FAMILY MEMBERS	SOME FUNCTIONS
Ras	H-Ras, K-Ras, N-Ras	relay signals from RTKs
	Rheb	activates mTOR to stimulate cell growth
	Rep1	activated by a cyclic-AMP-dependent GEF; influences cell adhesion by activating integrins
Rho*	Rho, Rac, Cdc42	relay signals from surface receptors to the cytoskeleton and elsewhere
ARF*	ARF1–ARF6	regulate assembly of protein coats on intracellular vesicles
Rab*	Rab1–60	regulate intracellular vesicle traffic
Ran*	Ran	regulates mitotic spindle assembly and nuclear transport of RNAs and proteins

*The Rho family is discussed in Chapter 16, the ARF and Rab proteins in Chapter 13, and Ran in Chapters 12 and 17. The three-dimensional structure of Ras is shown in Figure 3–72.

Table 15-5 *Molecular Biology of the Cell* (© Garland Science 2008)

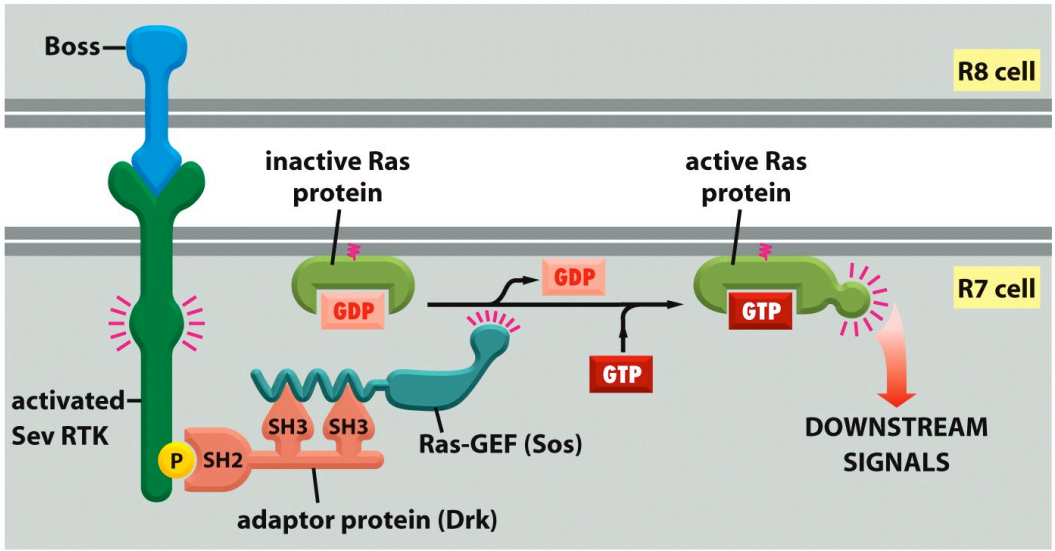


Figure 15-58 *Molecular Biology of the Cell* (© Garland Science 2008)

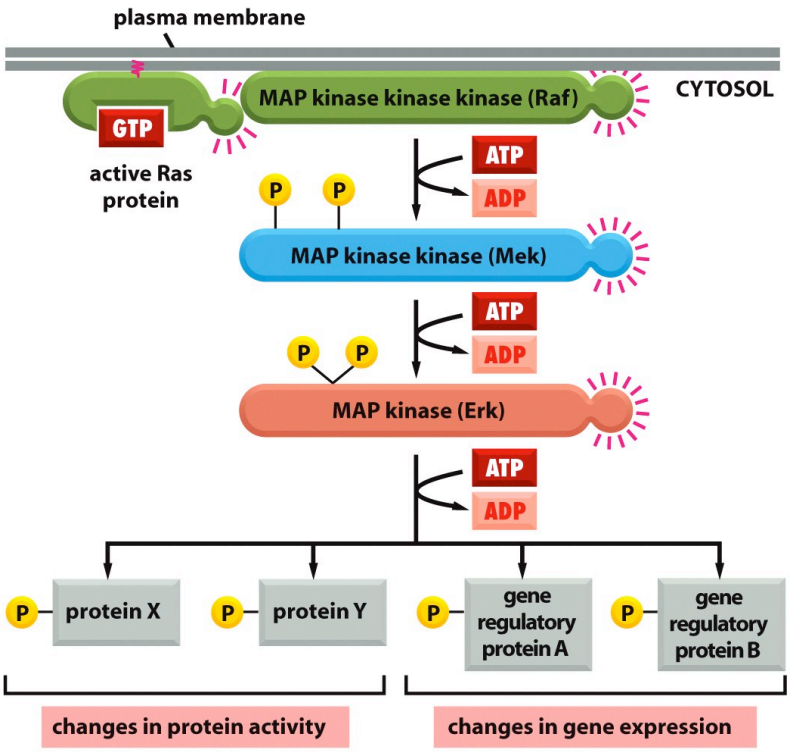


Figure 15-60 *Molecular Biology of the Cell* (© Garland Science 2008)

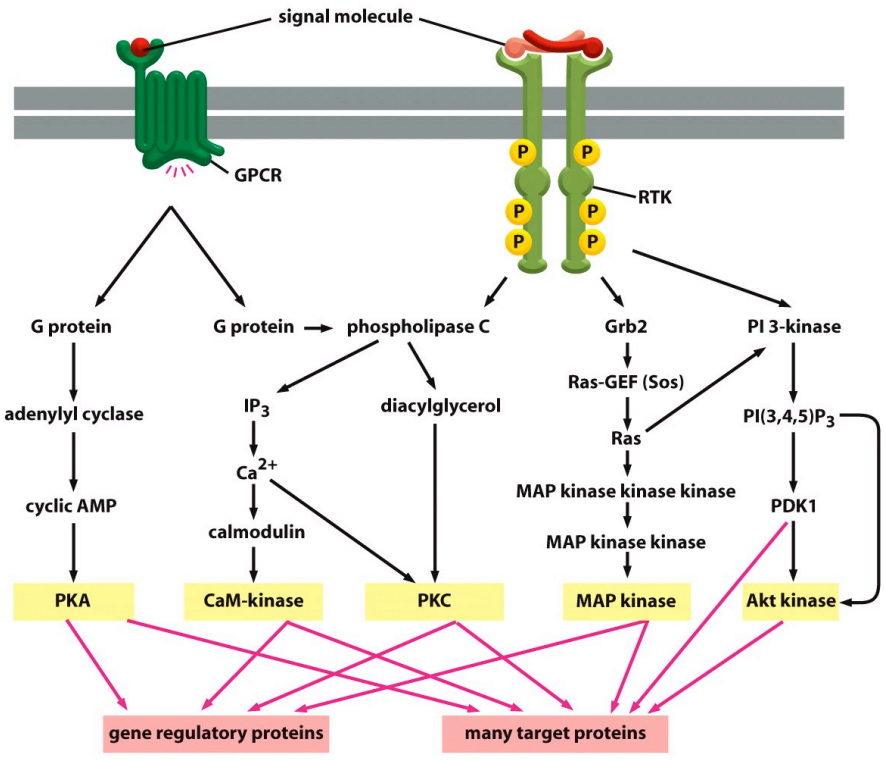


Figure 15-66 *Molecular Biology of the Cell* (© Garland Science 2008)

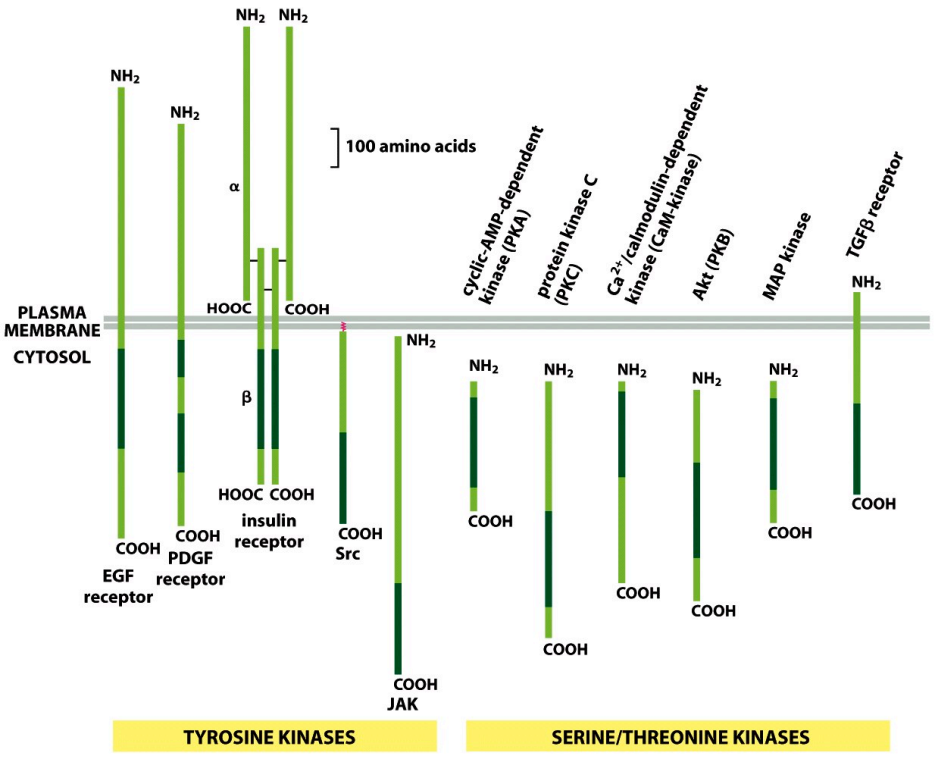


Figure 15-70 *Molecular Biology of the Cell* (© Garland Science 2008)

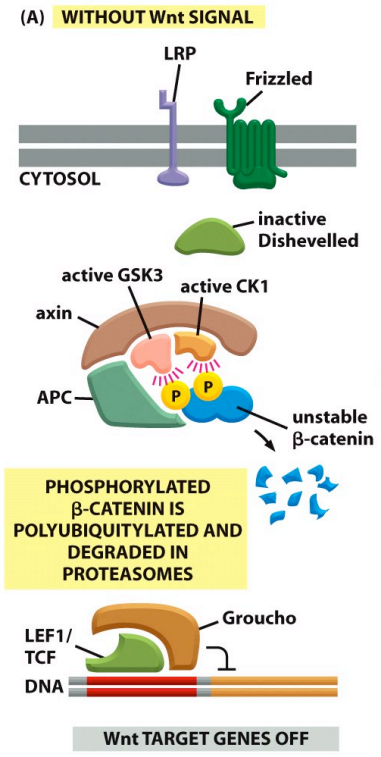
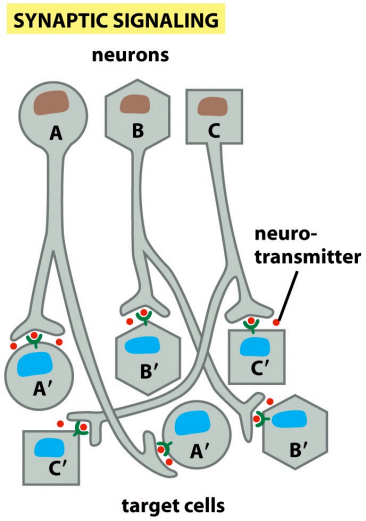


Figure 15-77 *Molecular Biology of the Cell* (© Garland Science 2008)

Comunicación y señales



Sistema Nervioso, Una metáfora geográfica: 2.000.000 x

Cuerpo Neuronal:	Campo de futbol
Dendrita:	2.4 Km (5 bifurcaciones)
Axón:	ancho de una calle (+ mielina)
Largo de un Axón:	Santiago a Pto Mont (1.200 km)
Membrana celular	1 cm
Espacio Sináptico	3 cm
Receptor de Ach	0.4 cm

Pto Mont a Santiago toma el mismo tiempo que los últimos 3 cm!

Diego Fernandez-Duque
Villanova University

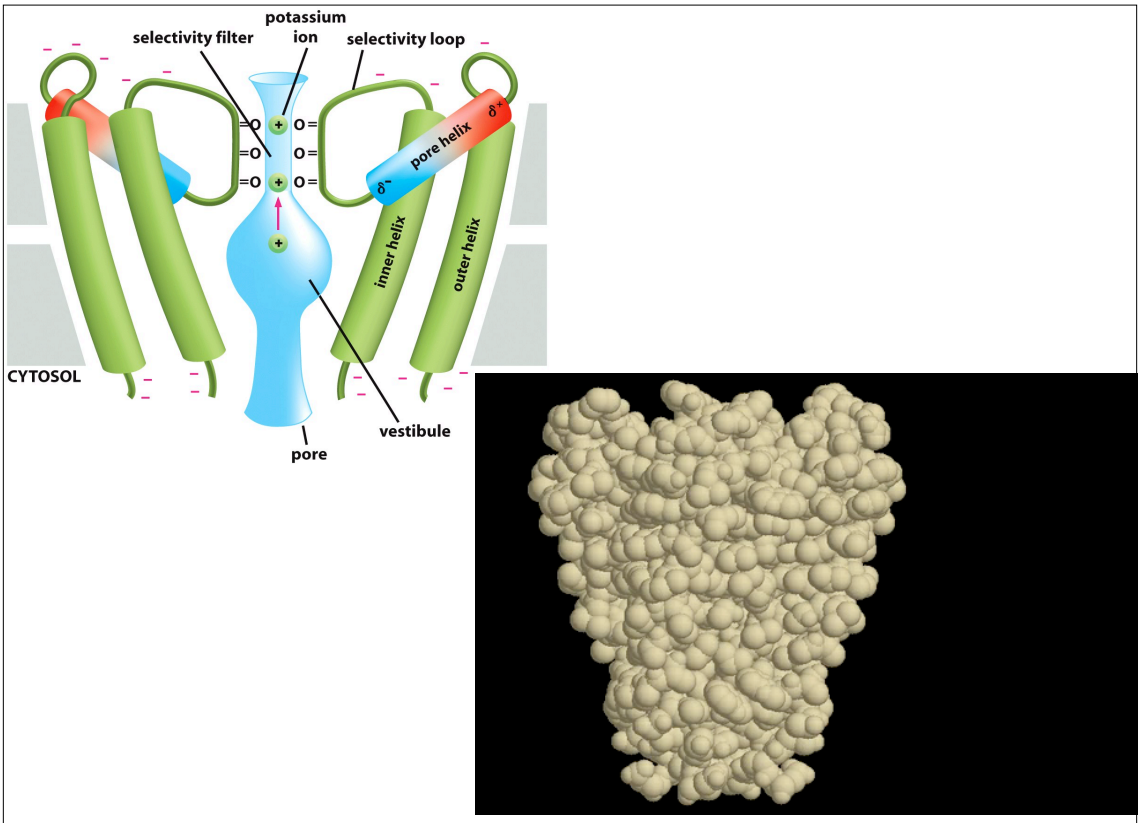


Figure 11-23a *Molecular Biology of the Cell* (© Garland Science 2008)

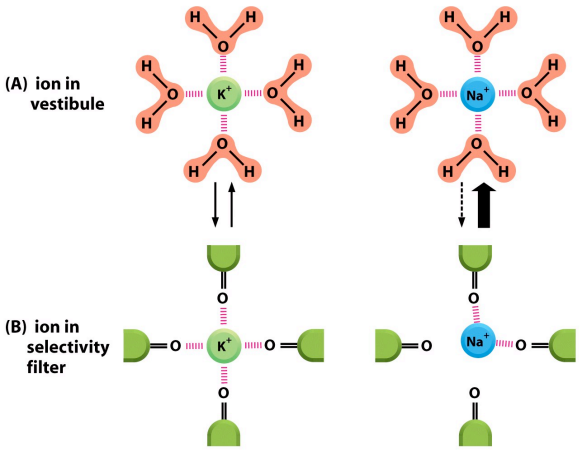


Figure 11-24 *Molecular Biology of the Cell* (© Garland Science 2008)

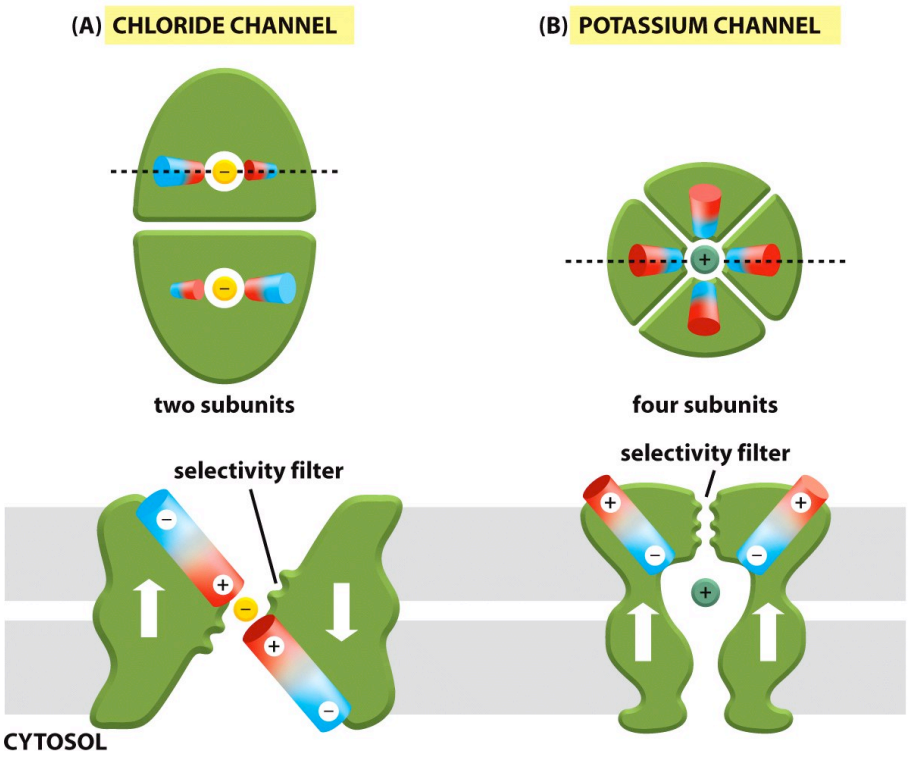


Figure 11-26 *Molecular Biology of the Cell* (© Garland Science 2008)

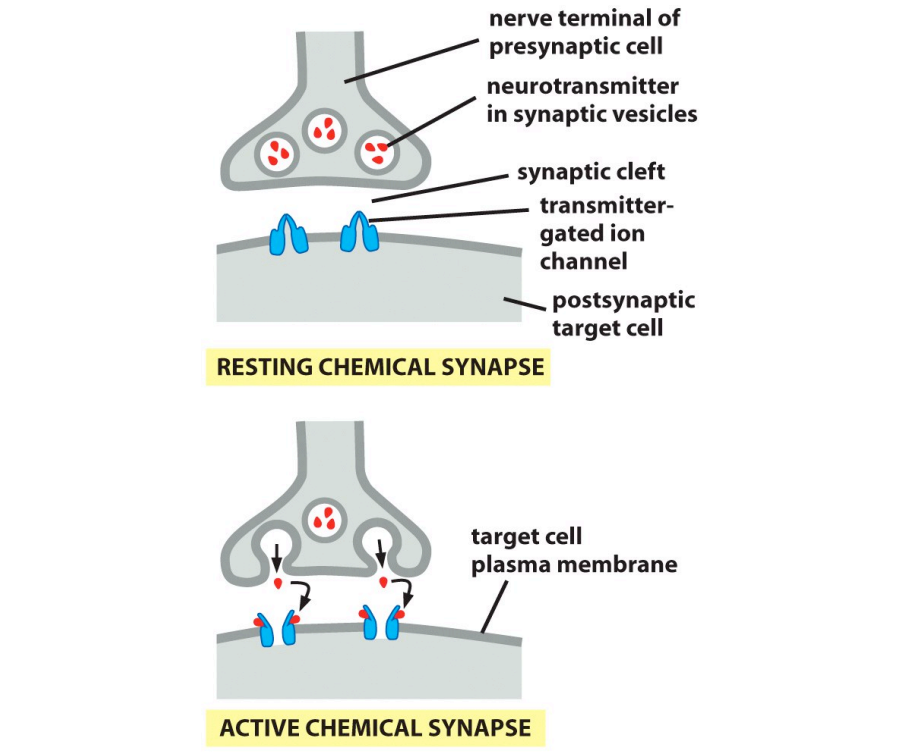


Figure 11-35a *Molecular Biology of the Cell* (© Garland Science 2008)

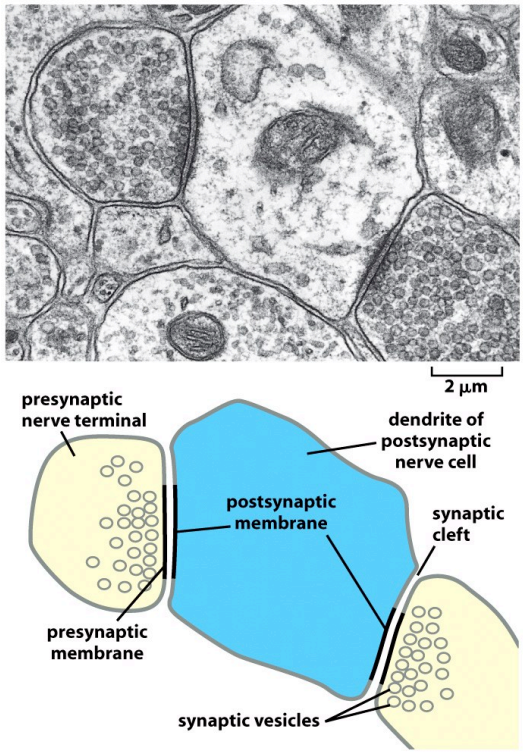


Figure 11-35b *Molecular Biology of the Cell* (© Garland Science 2008)

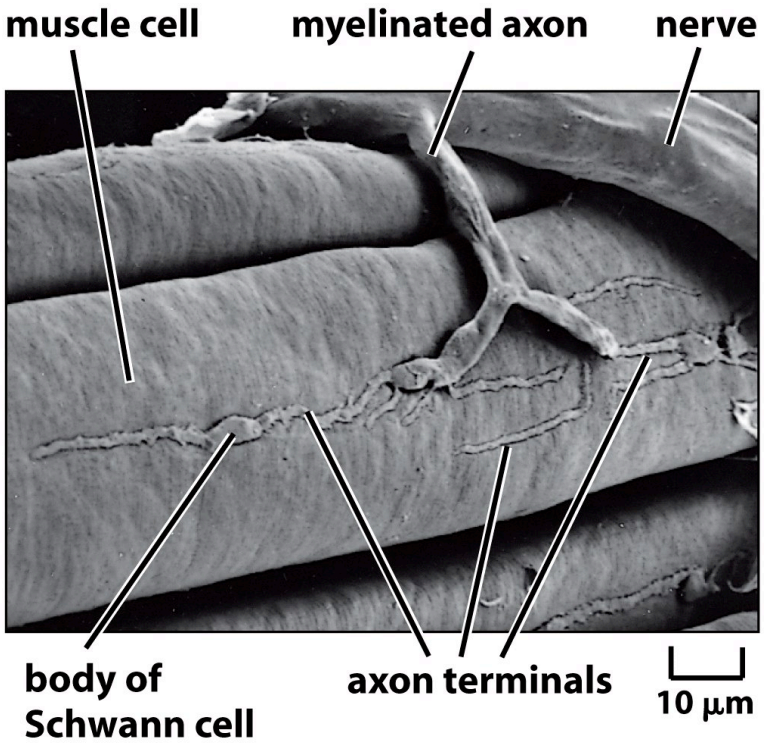


Figure 11-36 *Molecular Biology of the Cell* (© Garland Science 2008)

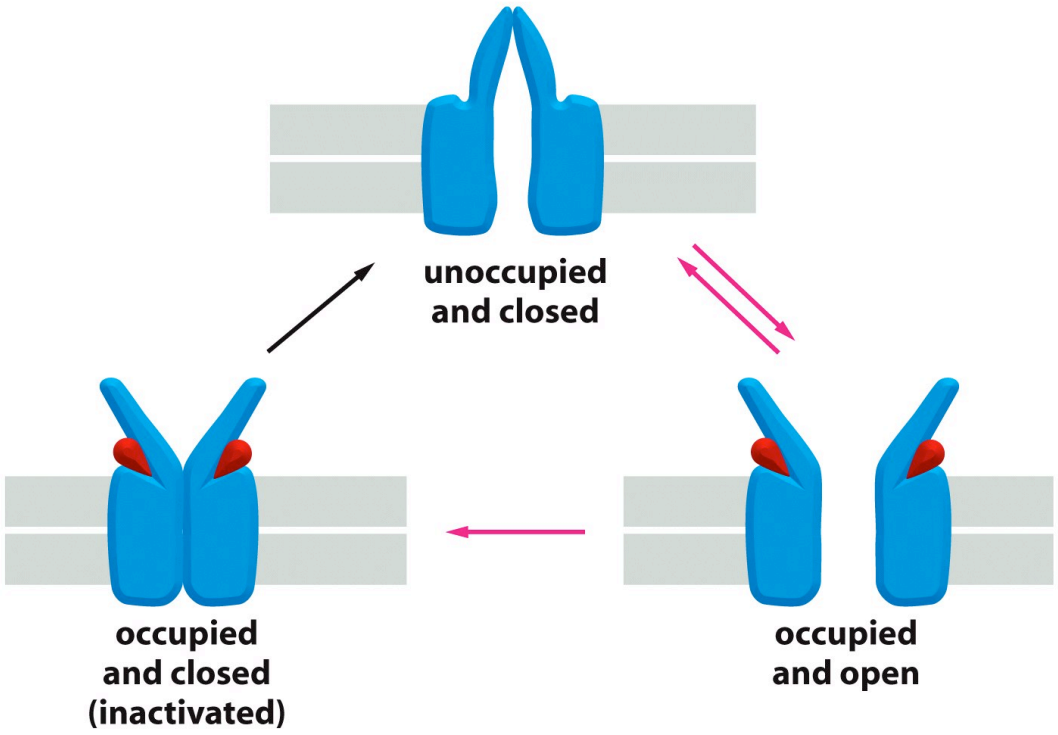
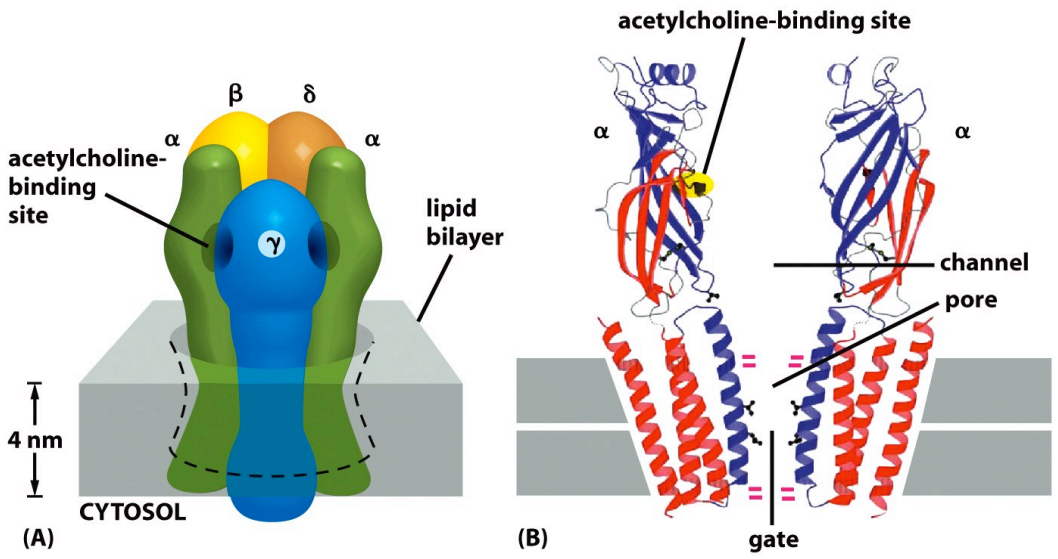


Figure 11-37 *Molecular Biology of the Cell* (© Garland Science 2008)



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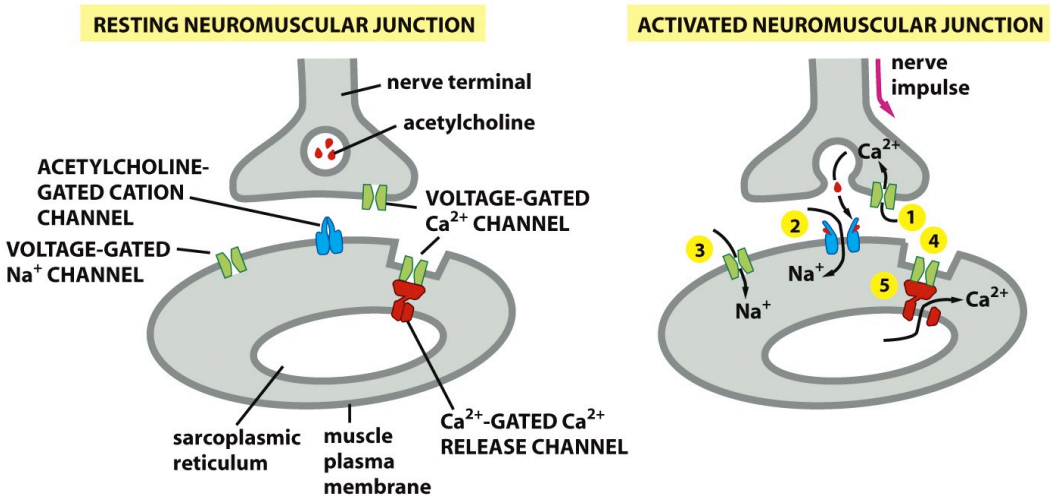

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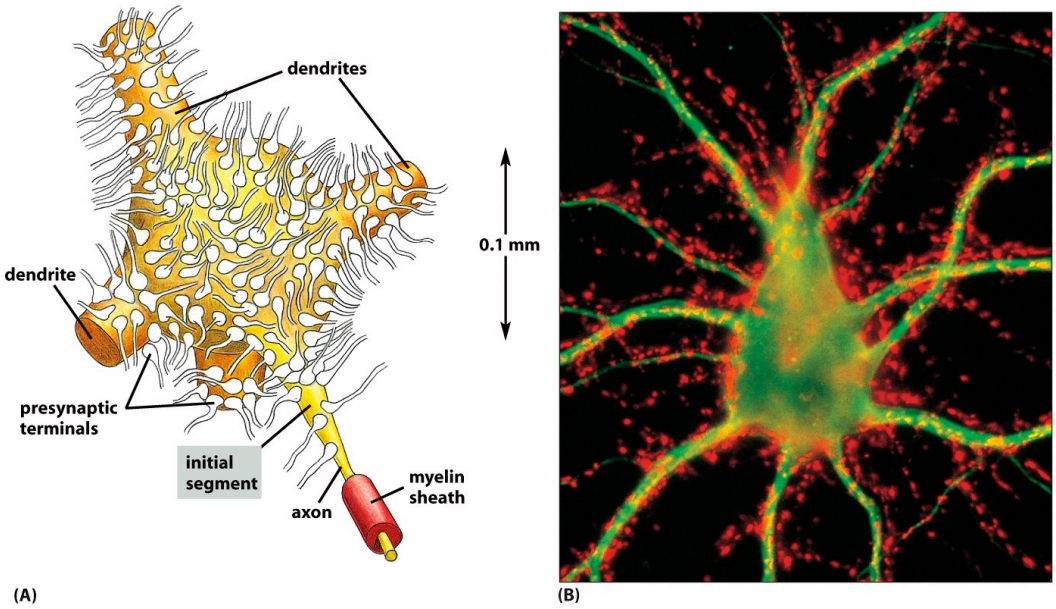

Figure 11-40 *Molecular Biology of the Cell* (© Garland Science 2008)

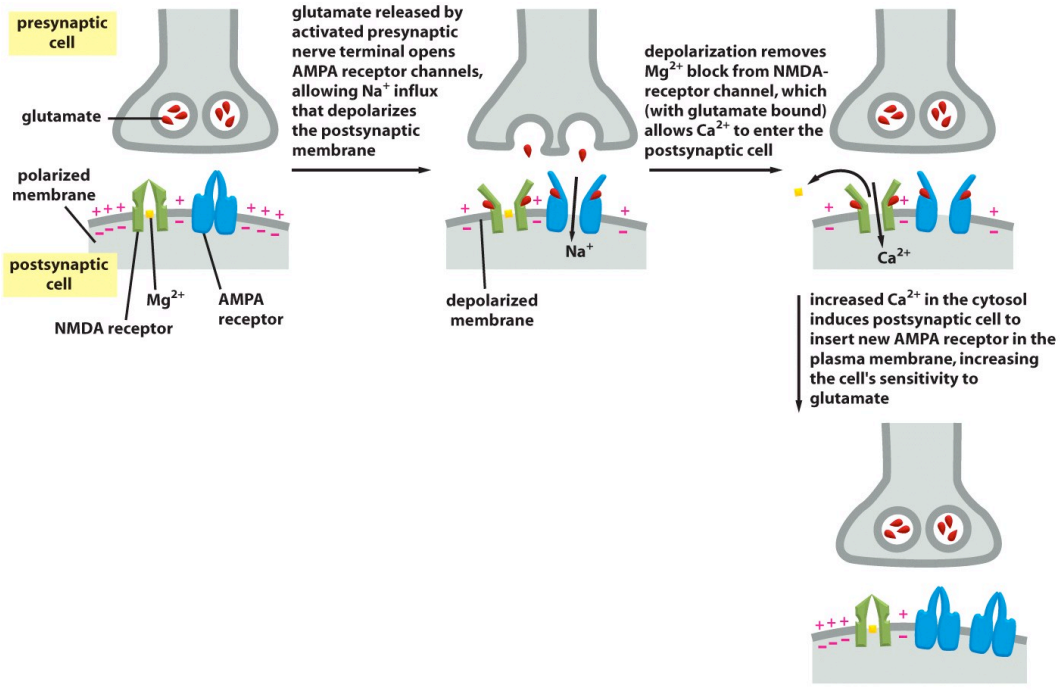

Figure 11-42 *Molecular Biology of the Cell* (© Garland Science 2008)

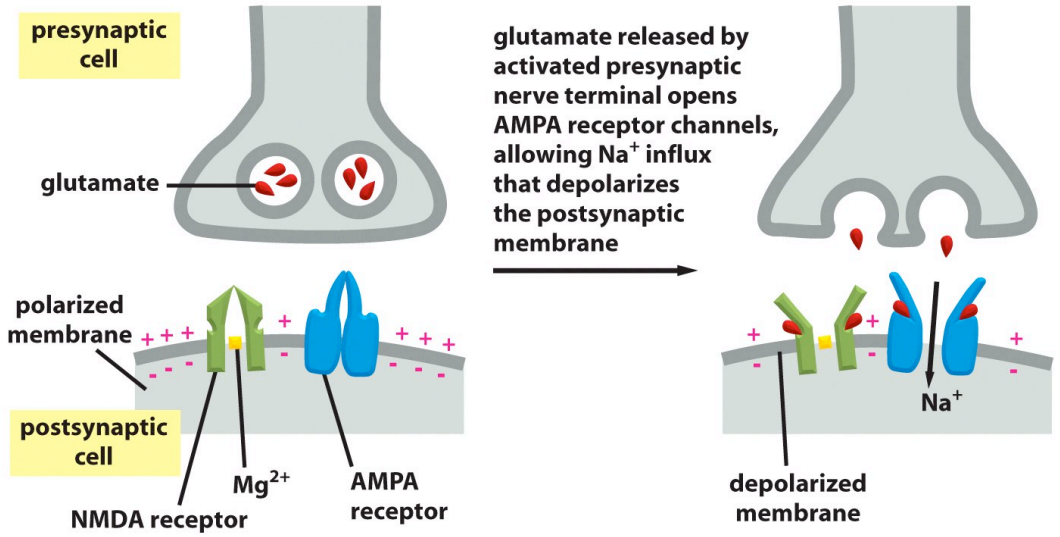

Figure 11-42 (part 1 of 3) *Molecular Biology of the Cell* (© Garland Science 2008)

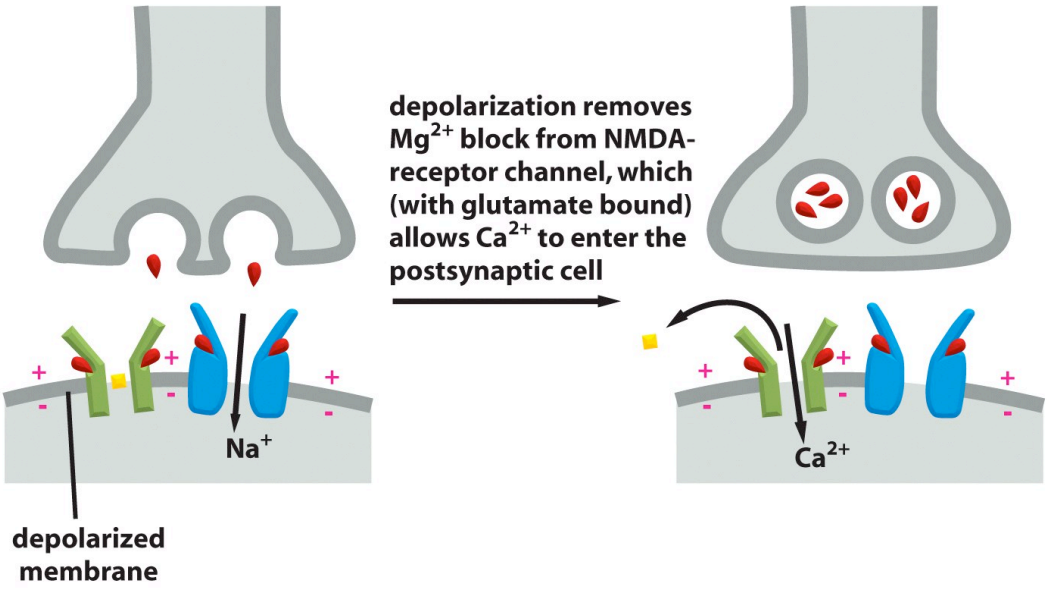

Figure 11-42 (part 2 of 3) *Molecular Biology of the Cell* (© Garland Science 2008)

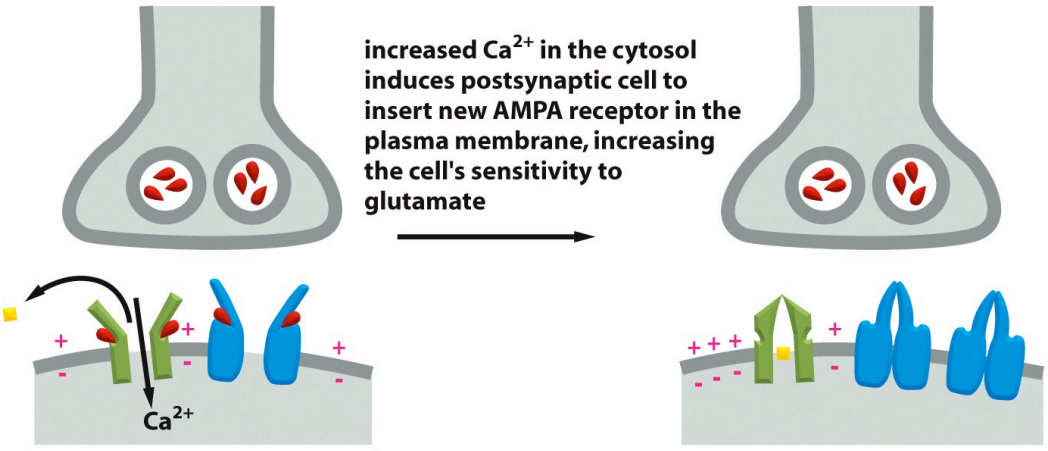

Figure 11-42 (part 3 of 3) *Molecular Biology of the Cell* (© Garland Science 2008)

Table 11–2 Some Ion Channel Families

CHANNEL TYPE	REPRESENTATIVE EXAMPLE	
Voltage-gated cation channels	voltage-gated Na^+ channels voltage-gated K^+ channels (including delayed and early) voltage-gated Ca^{2+} channels	
Transmitter-gated ion channels	acetylcholine-gated cation channels glutamate-gated Ca^{2+} channels serotonin-gated cation channels	excitatory
	GABA-gated Cl^- channels glycine-gated Cl^- channels	inhibitory

Table 11-2 *Molecular Biology of the Cell* (© Garland Science 2008)