Jelátviteli mechanizmusok

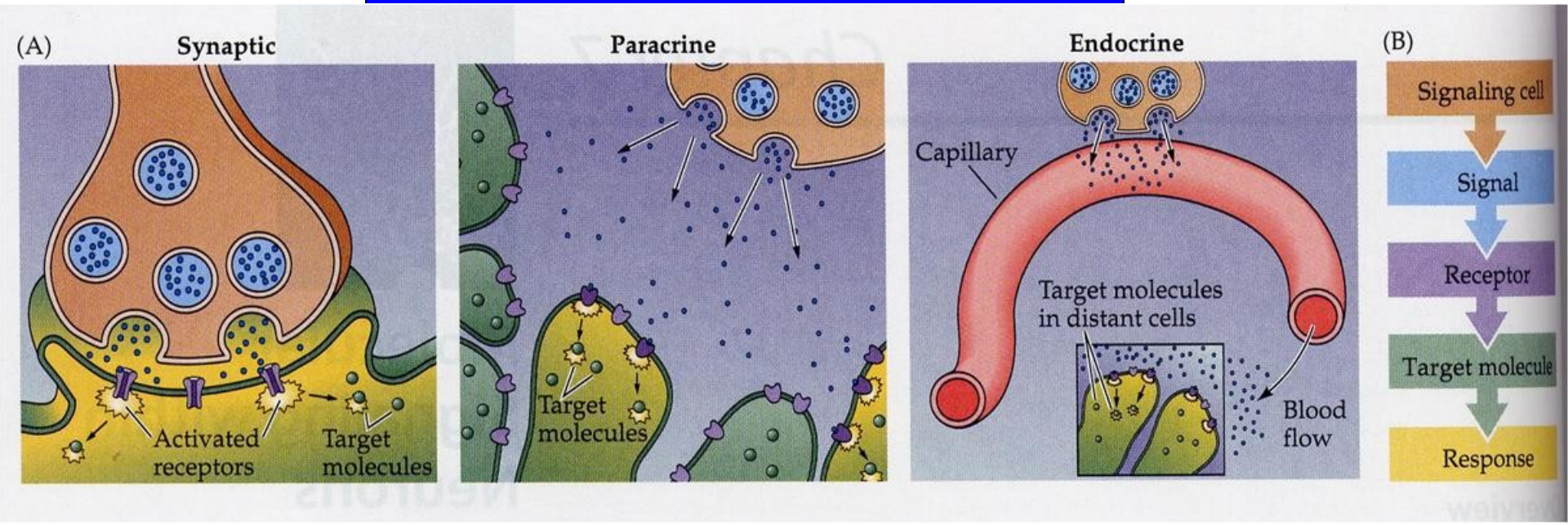
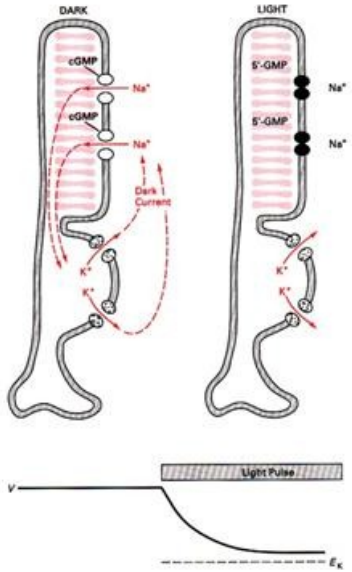
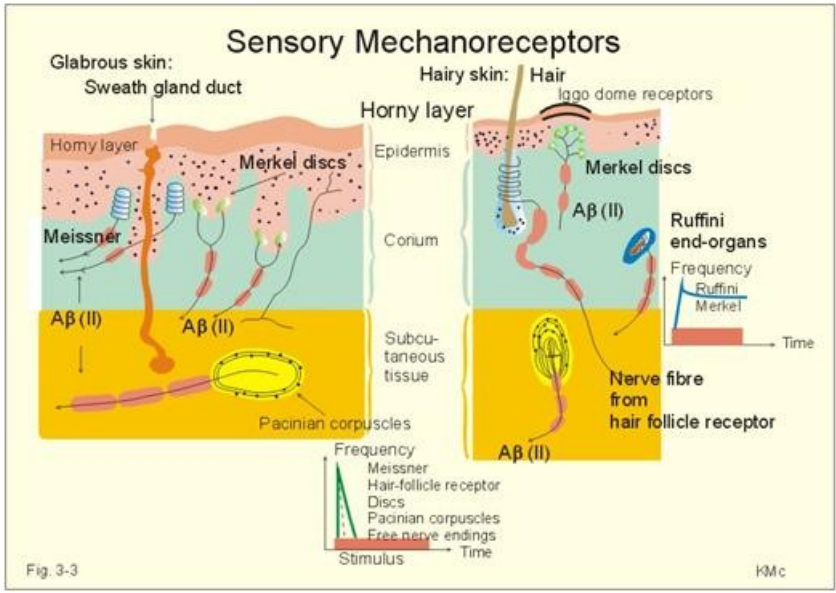


Figure 7.1 Chemical signaling mechanisms. (A) Forms of chemical communication include synaptic transmission, paracrine signaling, and endocrine signaling. (B) The essential components of chemical signaling are: cells that initiate the process by releasing signaling molecules; specific receptors on target cells; second messenger target molecules; and subsequent cellular responses.





http://www.bergen.org/ACADEMY/Bio/AnP/AnP1/AnP1Tri2/FIGS/TRANS/phototransduction.html

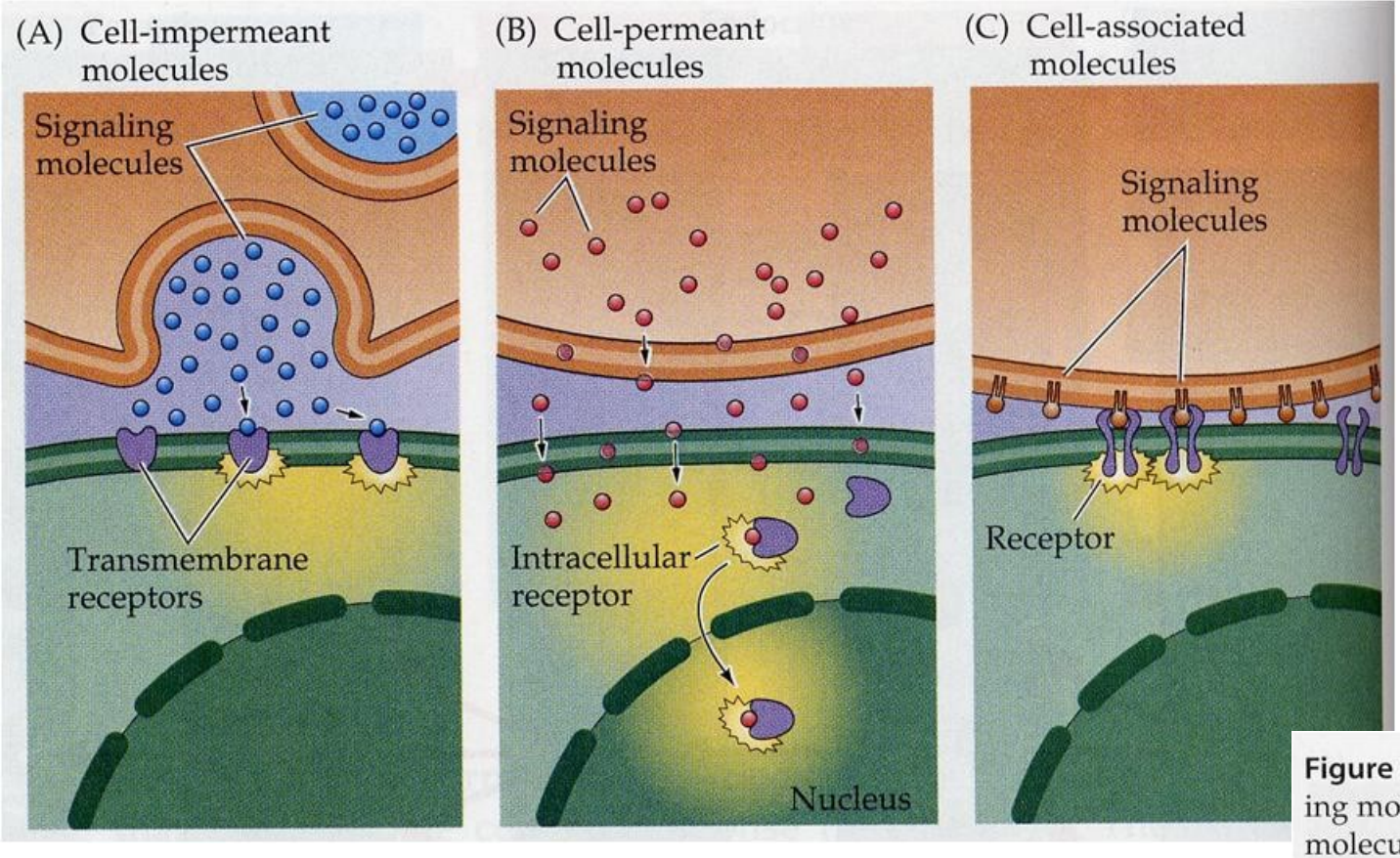


Figure 7.3 Three classes of cell signaling molecules. (A) Cell-impermeant molecules, such as neurotransmitters, cannot readily traverse the plasma membrane of the target cell and must bind to the extracellular portion of transmembrane receptor proteins. (B) Cell-permeant molecules are able to cross the plasma membrane and bind to receptors in the cytoplasm or nucleus of target cells. (C) Cell-associated molecules are presented on the extracellular surface of the plasma membrane. These signals activate receptors on target cells only if they are directly adjacent to the signaling cell.

Jelátvivő molekulák:
-Sejtmembránon átjutó
- vagy át nem jutó molekulák
- kontakt szignáling

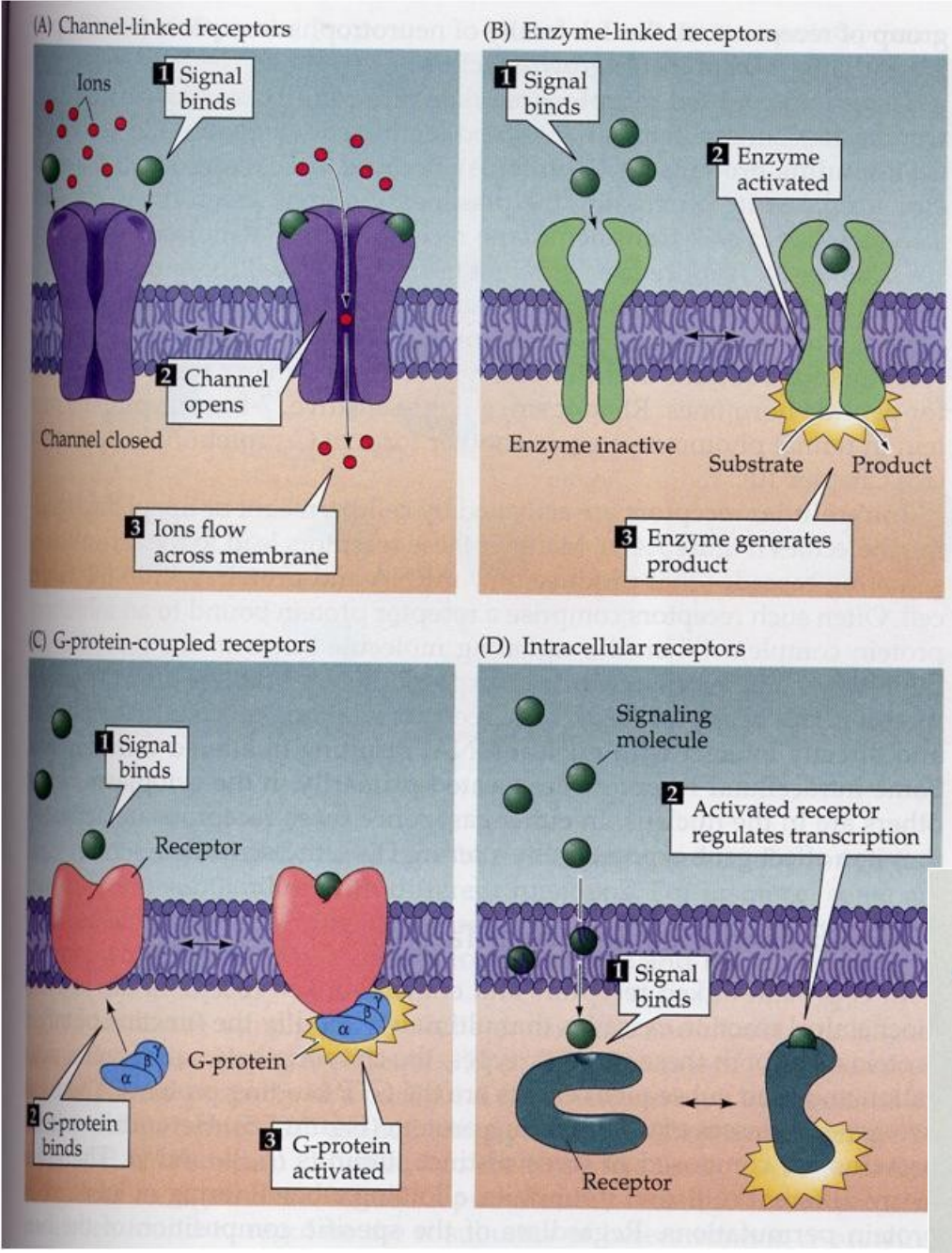


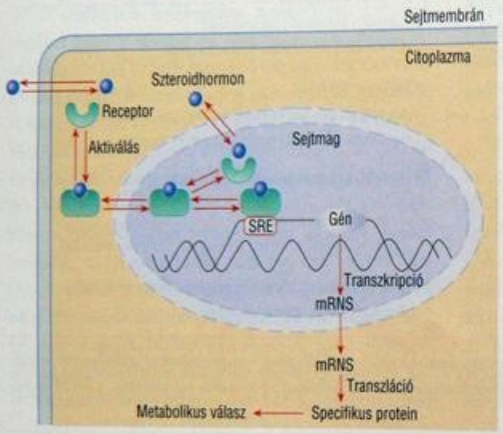
Figure 7.4 Categories of cellular receptors. Membrane-impermeant signaling molecules can bind to and activate either channel-linked receptors (A), enzyme-linked receptors (B), or G-protein-coupled receptors (C). Membrane permeant signaling molecules activate intracellular receptors (D).

[Receptor típusok:](#)

-Ion csatornák

- Enzimhez direkt módon kapcsolt receptorok
- G-proteinez kapcsolt receptorok
- Intracelluláris receptorok

- Foszforiláció, monomer G-protein



kifejtette pozitív vagy negatív hatását, a szteroid leválik a receptorról. A receptor visszanyeri eredeti („üres") konformációját, és új ciklusba léphet. A receptorról levált szteroid a sejten belül átalakul, inaktiválódik.

5-1. ábra

Az intracelluláris receptoron ható hormonok hatásának lépései

Hunyady L. „A hormonok és celluláris hatásaik" in *A klinikai endokrinológia és anyagcsere-betegségek kézikönyve*. Medicina 2001.

5-1. táblázat

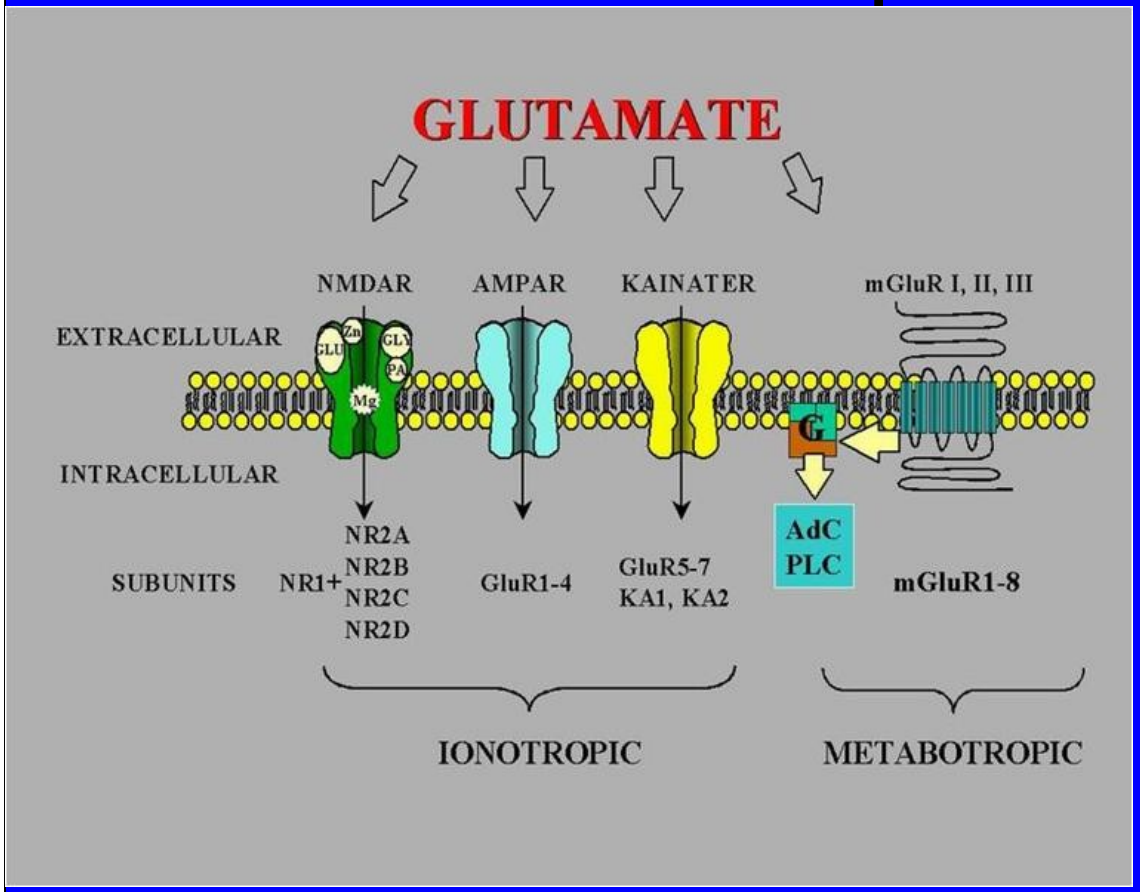
A receptorfehérjék osztályozása

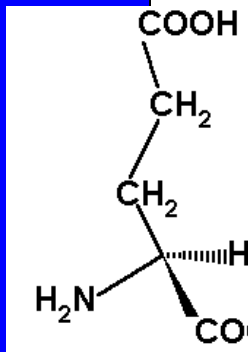
Barnard E. A. (1996): Receptor classes and the transmitter-gated ion channels, Trends Pharmacol. Sci. 17. 306. alapján

Receptortípus	Jellemző tulajdonságok
Mediátortól függő intracelluláris transzkripciós regulátorok	Nukleáris receptor szupercsalád: DNS-kötő doménnel rendelkeznek
Transzmitterrel szabályozott ioncsatornák*	Oligomer fehérjék, az alegységek két vagy több transzmembrán szakasza fog körül egy központi csatornát
7-TM-fehérjék*	G-fehérjéhez kapcsolódó receptorok
Egyetlen transzmembránszakasszal rendelkező receptorok	Enzimaktivitásuk van (guanilát-cikláz, tirozinkináz, szerin/treoninkináz)
	Nincs enzimaktivitásuk, közvetlenül kapcsolódnak intracelluláris tirozinkinázhoz

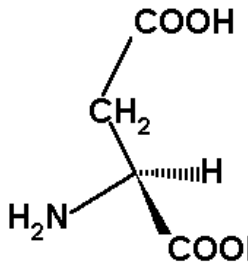
* Több olyan mediátor van (pl. acetil-kolin, GABA, glutamát), amelyek – célsejttől függően – transzmitterrel szabályozott ioncsatornához és 7-TM-fehérjéhez is képesek kötődni, és a jelátvitelt megindítani. A szabályozott ioncsatornát ionotrop, a 7-TM-receptort metabotrop receptorként említjük (l. a 6. fejezetet)

Glutamát receptorok



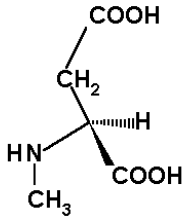


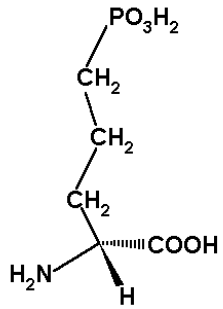
L-Glutamic Acid



L-Aspartic Acid

N-Methyl-D-Aspartic Acid
(NMDA)





(AP5)

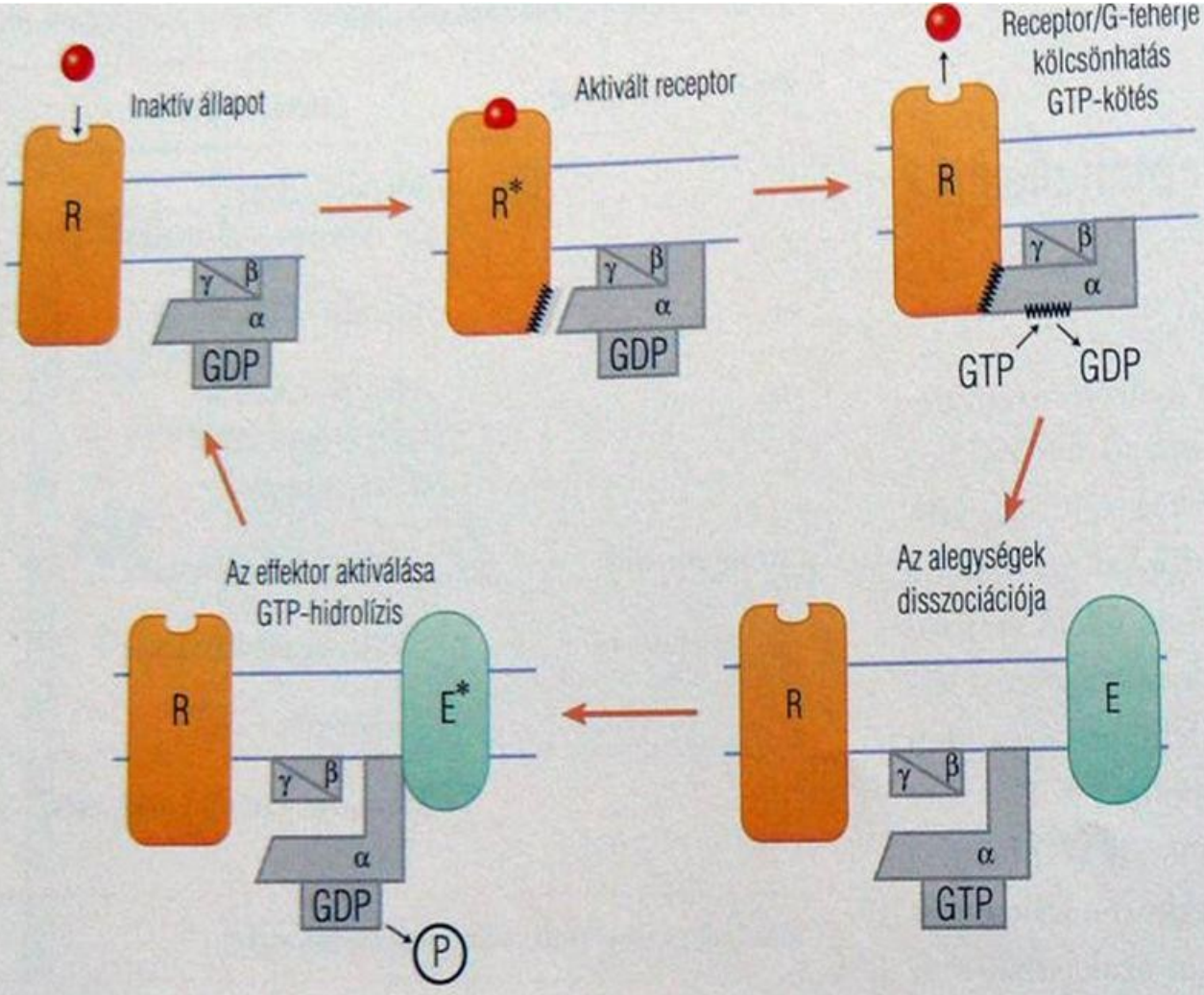
D-2-Amino-Phosphonopentanoic Acid

Receptorok csoportosítása:

Agonisták és antagonisták valamint gén szekvencia alapján

http://www.ucl.ac.uk/~smgxt01/frameh.htm?page=glutamat.htm

közvetített szabályozással, amelyben a G-fehérjék csak közvetett szerepet játszanak!)



5-2. ábra

Receptorhoz kapcsolódó heterotrimer G-fehérjék aktiválásának modellje

R: receptor, E: hatást közvetítő enzim, GDP: guanozin-5"-difoszfát, GTP: guanozin-5"-trifoszfát, az α, β és γ görög betűk a heterotrimer G-fehérje három alegységét jelentik

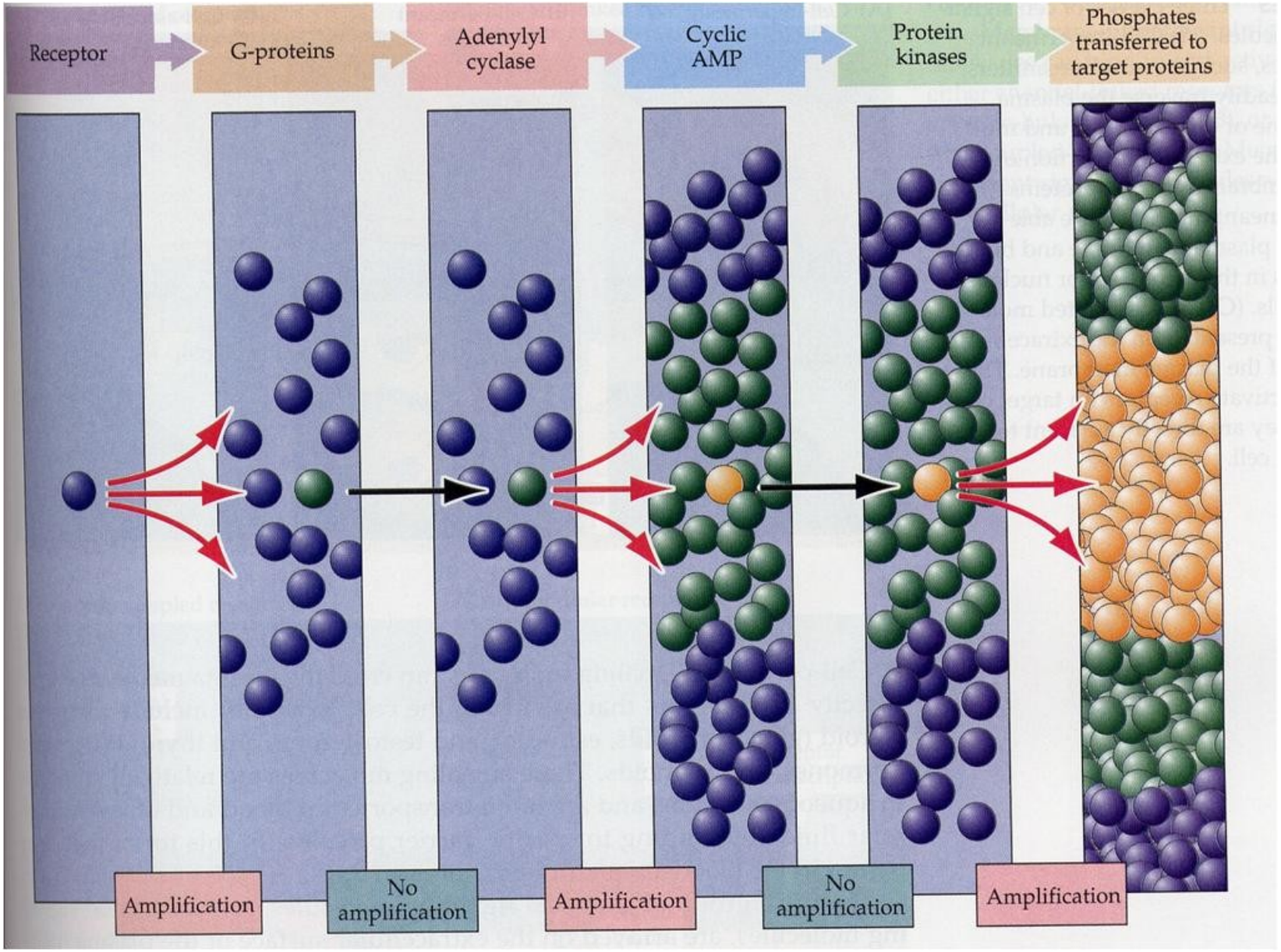
5-2. táblázat

A heterotrimer G-fehérjék osztályozása α-alegységeik szerkezete alapján

G-fehérje α-alegység	Hatás(ok)
G_s	Adenilát-cikláz ↑ Ca-csatorna szabályozás
G_{olf}	Adenilát-cikláz ↑
$G_{i/o}$	Adenilát-cikláz ↓ Ca^{2+}-csatornák ↓ K^+-csatornák ↑
G_t (transzducin)	cGMP-foszfodiészteráz ↑
G_{gust} (gustducin)	cGMP-foszfodiészteráz ↑
G_q	Foszfolipáz Cβ ↑
$G_{12/13}$	Monomer („kis") G-fehérjék aktiválása

A táblázat csak a főbb családokat tünteti fel

Jel erősítési funkció



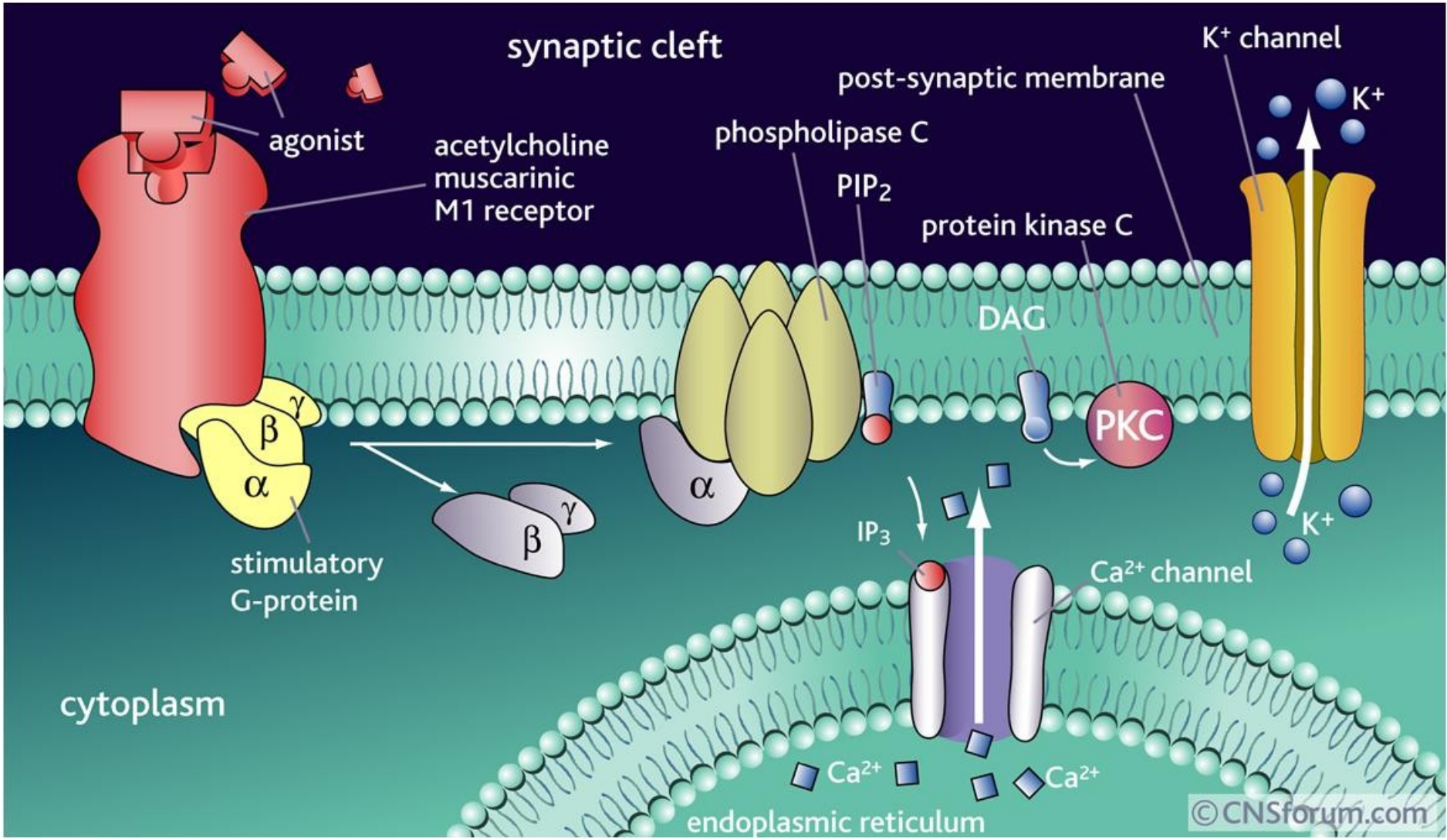
5-3. táblázat

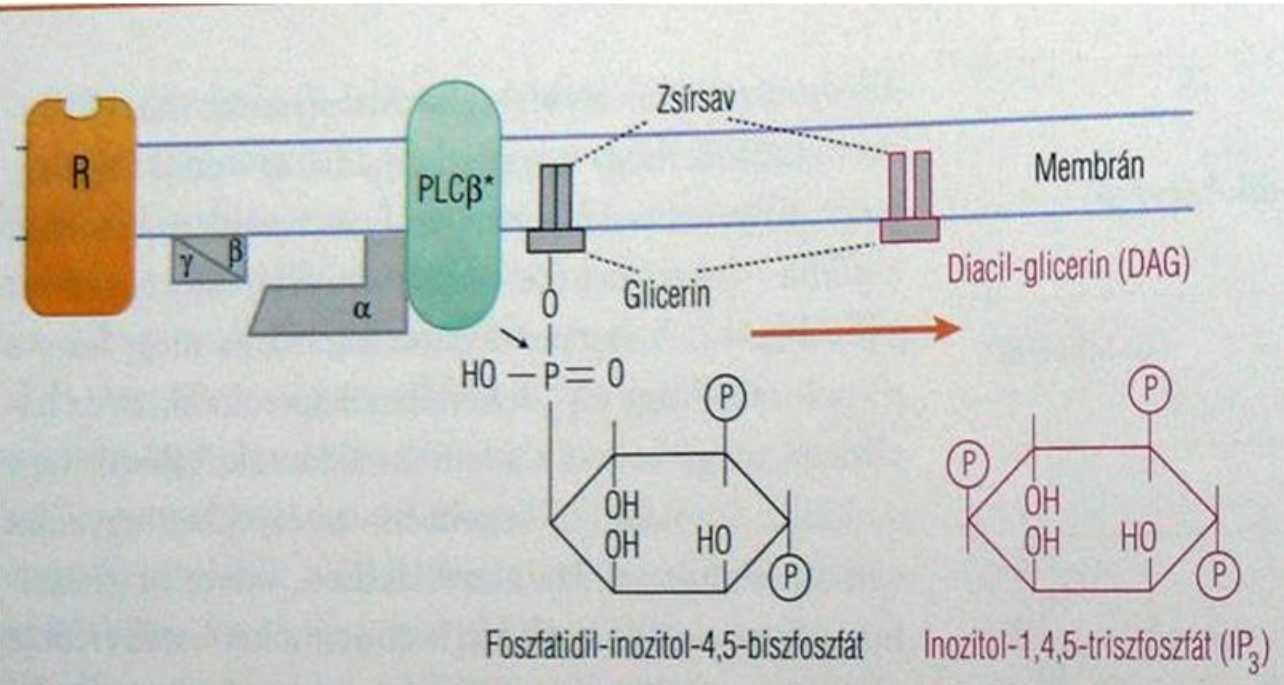
Néhány 7-TM-receptor, amelyek második hírvivő mechanizmushoz kapcsolódnak

Receptor	Agonista jelölése	G-fehérjék
	Acetil-kolin	
M_1, M_3 és M_5	ACh	G_q
M_2 és M_4	ACh	$G_{i/o}$
	Katecholaminok	
α_1	Noradrenalin, adrenalin	G_q
α_2	Noradrenalin, adrenalin	$G_{i/o}$
β_1, β_2 és β_3	Adrenalin, noradrenalin	G_s
D_1 és D_5	Dopamin	G_s
D_2 és D_4	Dopamin	$G_{i/o}$
	Nukleotidok és nukleozidok	
P_{2Y}	Adenin nukleotidok	G_q
A_1	Adenozin	$G_{i/o}$
A_2	Adenozin	G_s
	Aminosavszármazékok	
$GABA_B$	GABA	$G_{i/o}$
H_1	Hisztamin	G_q
H_2	Hisztamin	G_s
	Eikozanoidok	
TP	Tromboxán A_2 (TXA_2)	G_q
FP	Prosztaglandin F_{2a}	G_q
IP	Prosztaciklin (PGI_2)	G_s
	Peptidek	
V_1	Vazopresszin	G_q
V_2	Vazopresszin	G_s
AT_1	Angiotenzin II	G_q
VIP	Vazoaktív intestinalis peptid	G_s
MC_2	ACTH	G_s
SST_{1-5}	Szomatosztatin	G_i

A táblázatban nem tüntettük fel a G-fehérjék közvetlen hatását a plazmamembrán ioncsatornáira. Az M_2-, M_4-, α_2-, A_1- és D_2-receptorokhoz kapcsolódó aktivált G-fehérjék megnövelik a K^+-csatornák nyitási valószínűségét.

Inositol trifoszfát (IP3) jelátviteli mechanizmus (Intracelluláris kalcium reguláció)

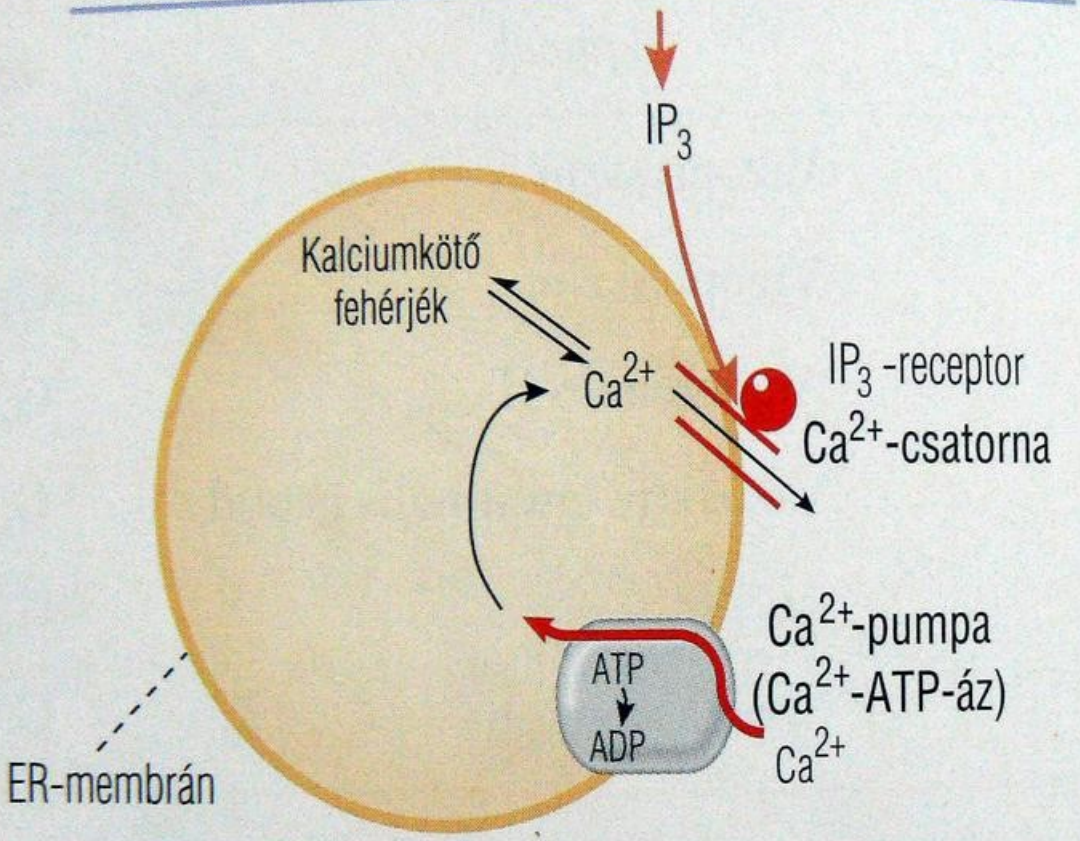




5-3. ábra

Az inozitol foszfolipidekből kiinduló jelátvitel két ága: két második hírvivő (DAG és IP_3) kialakulása

R: receptor, PLCβ: β-típusú foszfolipáz C, glic: a lipid glicerin oldallánca, α, β és γ a heterotrimer G-fehérje alegységei



5-4. ábra

Az IP_3 hatásának vázlata

ER: endoplasma-reticulum; IP_3: inozitol-1,4,5-triszfoszfát

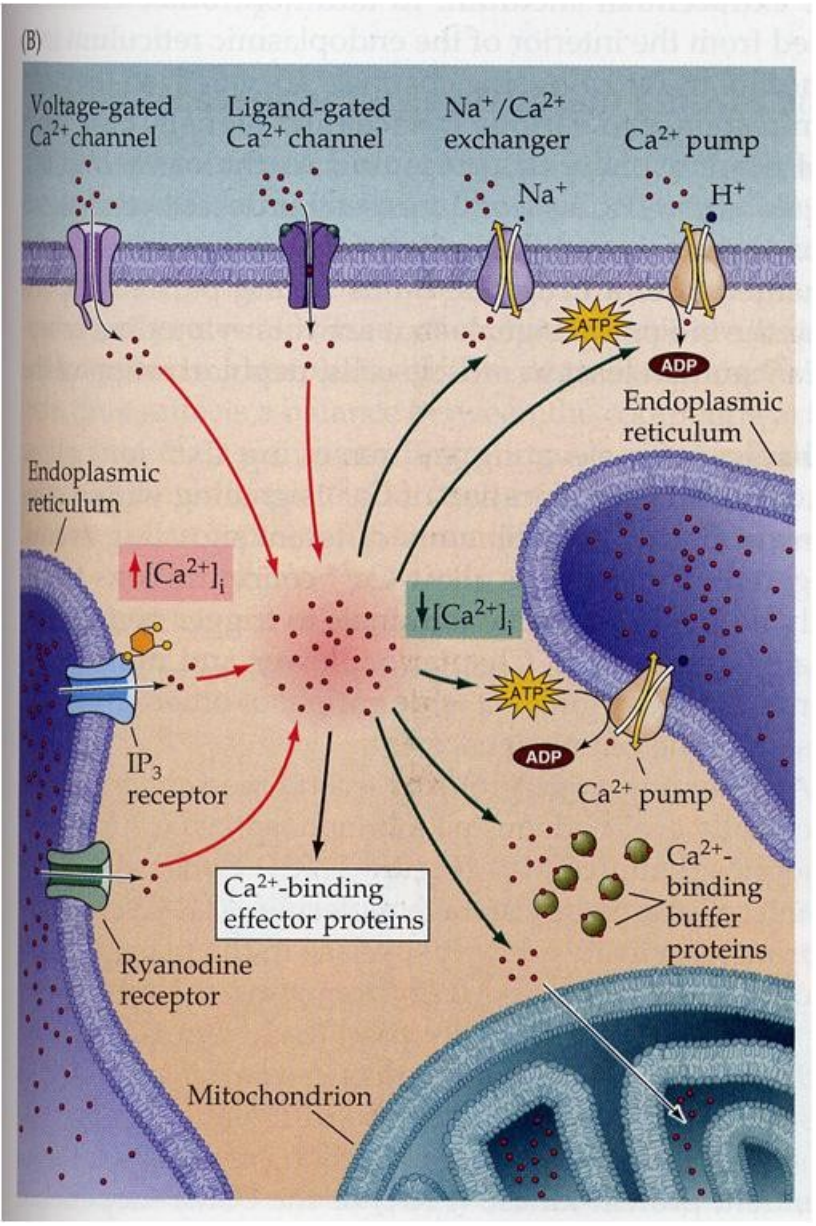
Másodlagos hírvivők

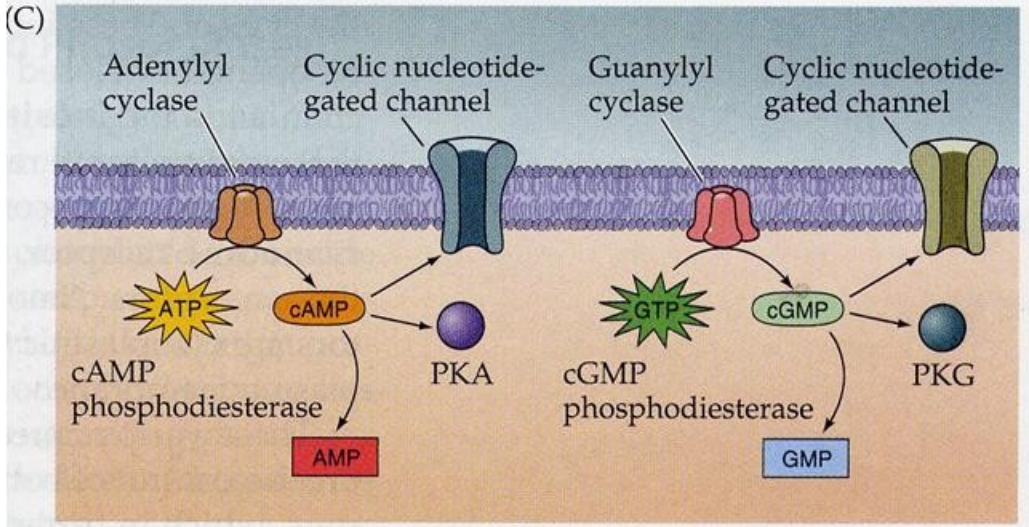
(A)

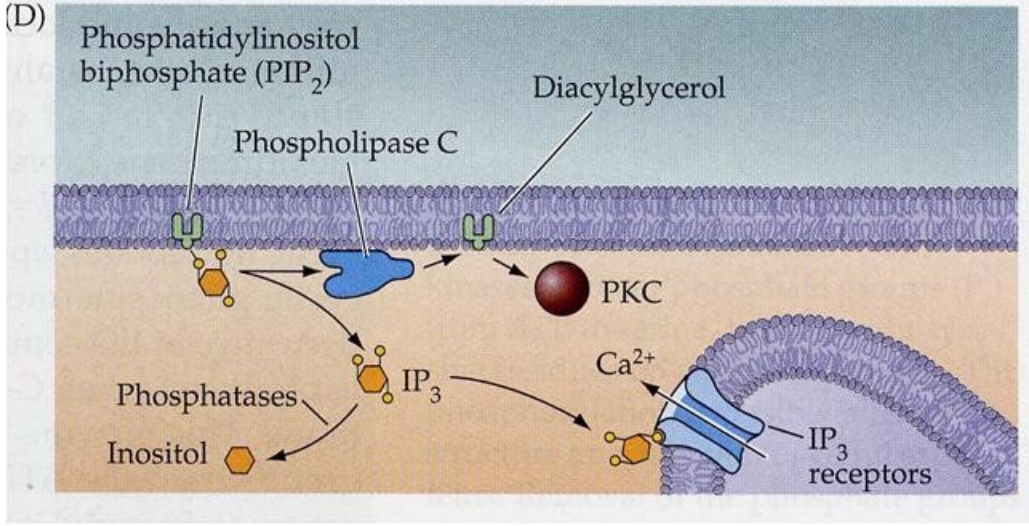
Second messenger	Sources	Intracellular targets	Removal mechanisms
Ca^{2+}	Plasma membrane: Voltage-gated Ca^{2+} channels Various ligand-gated channels Endoplasmic reticulum: IP_3 receptors Ryanodine receptors	Calmodulin Protein kinases Protein phosphatases Ion channels Synaptotagmin Many other Ca^{2+}-binding proteins	Plasma membrane: Na^+/Ca^{2+} exchanger Ca^{2+} pump Endoplasmic reticulum: Ca^{2+} pump Mitochondria
Cyclic AMP	Adenylyl cyclase acts on ATP	Protein kinase A Cyclic nucleotide-gated channels	cAMP phosphodiesterase
Cyclic GMP	Guanylyl cyclase acts on GTP	Protein kinase G Cyclic nucleotide-gated channels	cGMP phosphodiesterase
IP_3	Phospholipase C acts on PIP_2	IP_3 receptors on endoplasmic reticulum	Phosphatases
Diacylglycerol	Phospholipase C acts on PIP_2	Protein kinase C	Various enzymes

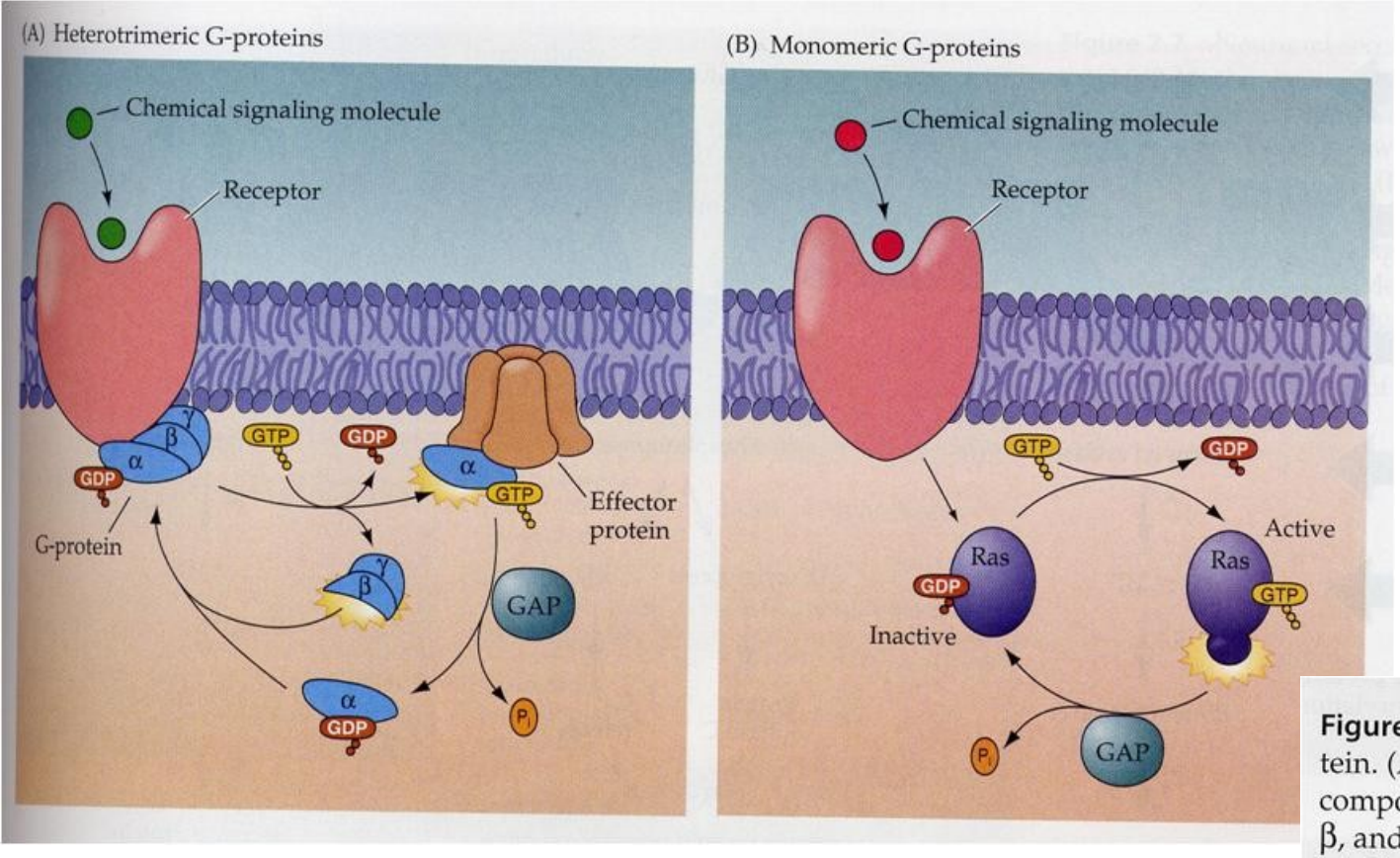
Figure 7.7 Neuronal second messengers. (A) Mechanisms responsible for producing and removing second messengers, as well as the downstream targets of these messengers. (B) Proteins involved in delivering calcium to the cytoplasm and in removing calcium from the cytoplasm. (C) Mechanisms of production and degradation of cyclic nucleotides. (D) Pathways involved in production and removal of diacylglycerol (DAG) and IP_3.

PIP2: Phosphatidylinositol bisphosphate


(B)
Voltage-gated Ca^{2+} channel
Ligand-gated Ca^{2+} channel
Na^+/Ca^{2+} exchanger
Ca^{2+} pump
Na^+
H^+
ATP
ADP
Endoplasmic reticulum
Endoplasmic reticulum
$\uparrow[Ca^{2+}]_i$
$\downarrow[Ca^{2+}]_i$
ATP
ADP
IP_3 receptor
Ca^{2+} pump
Ca^{2+}-binding effector proteins
Ca^{2+}-binding buffer proteins
Ryanodine receptor
Mitochondrion


(C)
Adenylyl cyclase
Cyclic nucleotide-gated channel
Guanylyl cyclase
Cyclic nucleotide-gated channel
ATP
cAMP
PKA
GTP
cGMP
PKG
cAMP phosphodiesterase
AMP
cGMP phosphodiesterase
GMP


(D)
Phosphatidylinositol biphosphate (PIP_2)
Diacylglycerol
Phospholipase C
PKC
IP_3
Ca^{2+}
Phosphatases
Inositol
IP_3 receptors



Monomeric G Proteins (small GTPases) homologous to the alpha (α) subunit

Figure 7.5 Types of GTP-binding protein. (A) Heterotrimeric G-proteins are composed of three distinct subunits (α, β, and γ). Receptor activation causes the binding of the G-protein and the α subunit to exchange GDP for GTP, leading to a dissociation of the α and βγ subunits. The biological actions of these G-proteins are terminated by hydrolysis of GTP, which is enhanced by GTPase-activating (GAP) proteins. (B) Monomeric G-proteins use similar mechanisms to relay signals from activated cell surface receptors to intracellular targets. Binding of GTP stimulates the biological actions of these G-proteins, and their activity is terminated by hydrolysis of GTP, which is also regulated by GAP proteins.

Proteins in the Ras family are very important molecular switches for a wide variety of signal pathways that control such processes as cytoskeletal integrity, proliferation, cell adhesion, apoptosis, and cell migration. Ras and ras related proteins are often deregulated in cancers, leading to increased invasion and metastasis, and decreased apoptosis. The Ras superfamily includes the Ras, Rho, and Rab families.

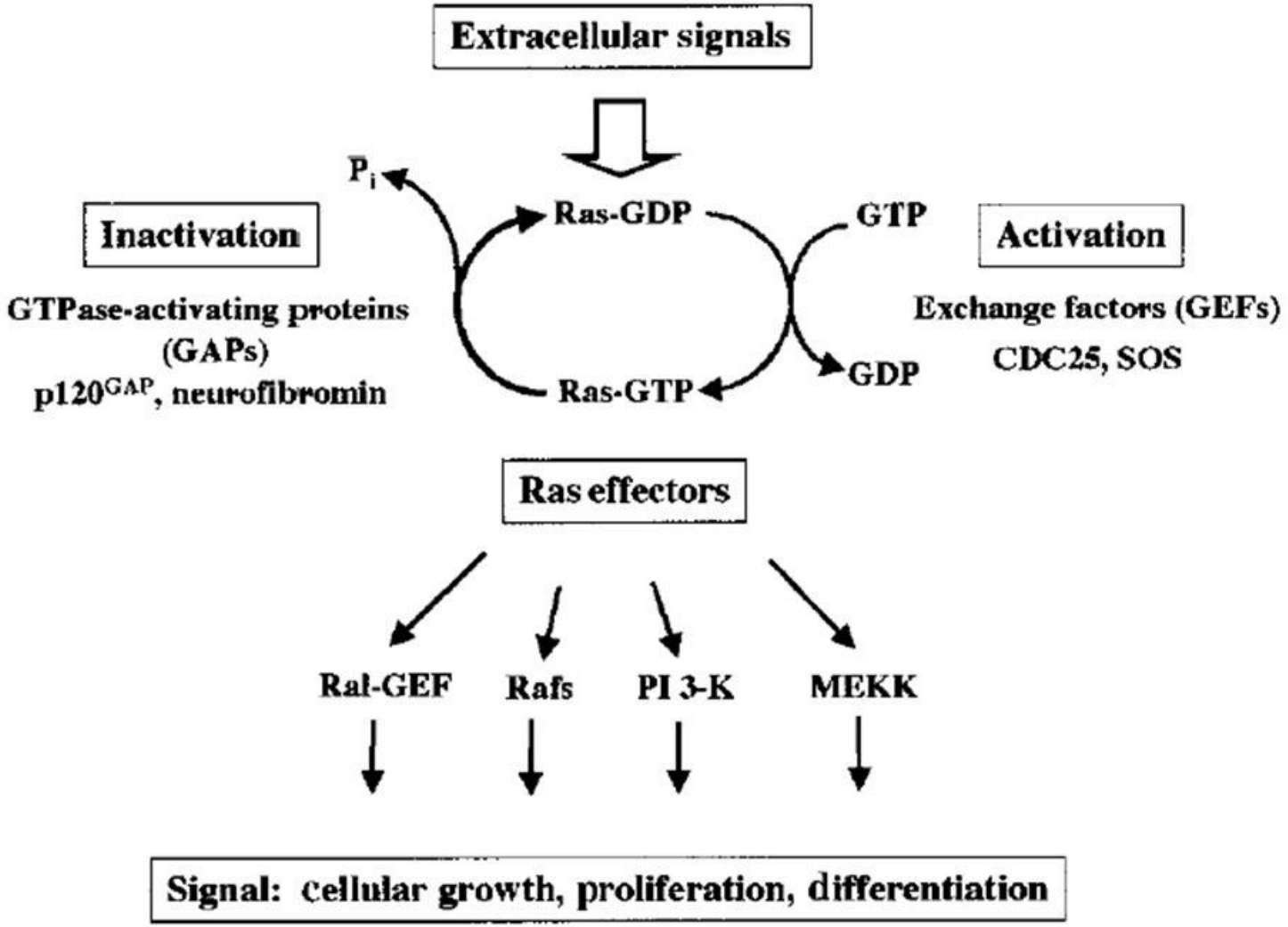
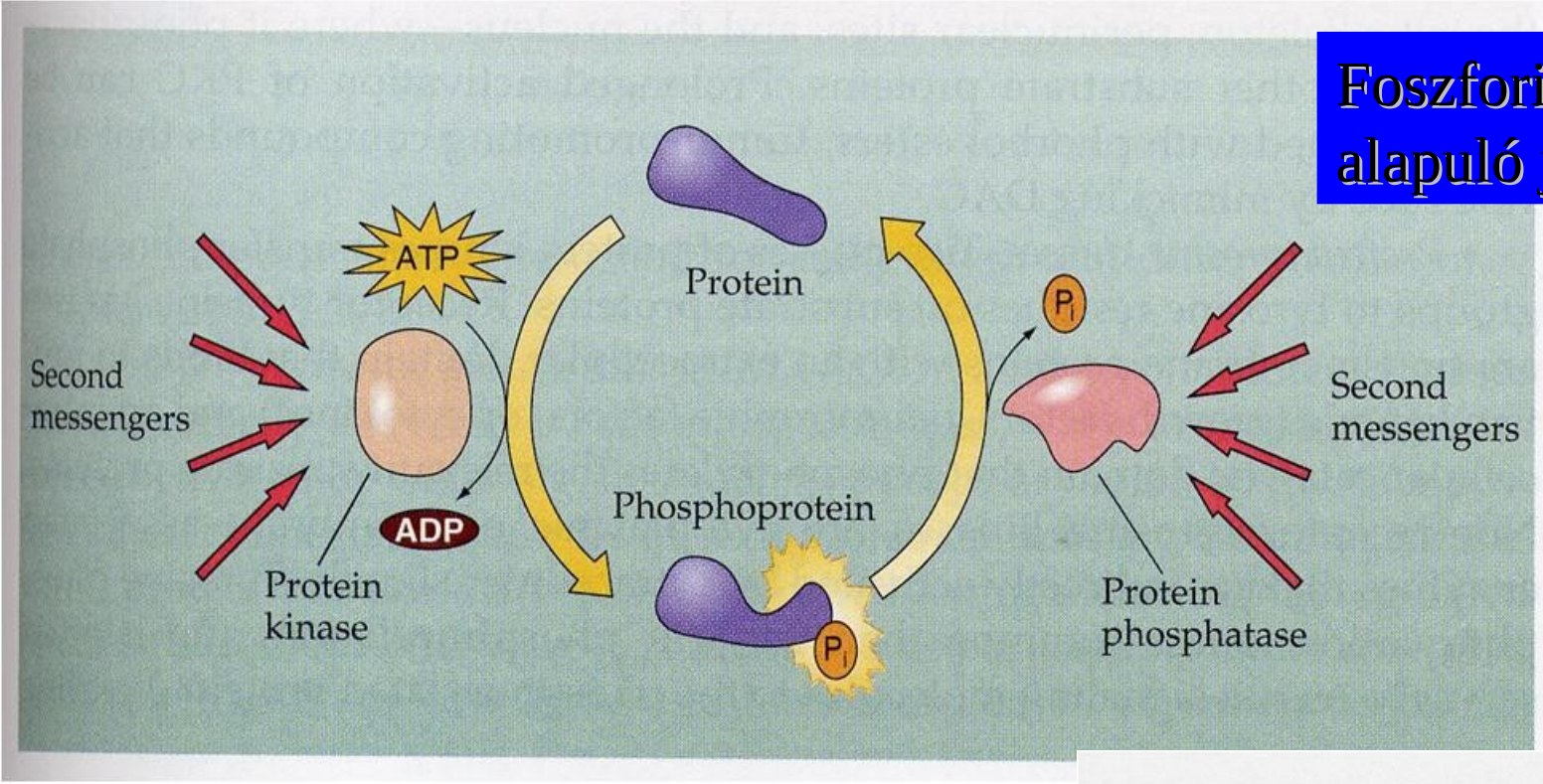


Figure 1. The switch function of Ras. Ras cycles between the active GTP-bound and the inactive GDP-bound state. Mitogenic signals activate guanine GEFs such as SOS and CDC25. GEFs increase the rate of dissociation of GDP and stabilize the nucleotide-free form of Ras, leading to binding of GTP to Ras proteins. Ras can also be activated by the inhibition of the GAPs.

Foszforiláción alapuló jelátvitel



PKA (cAMP)

CaMKII (Ca)

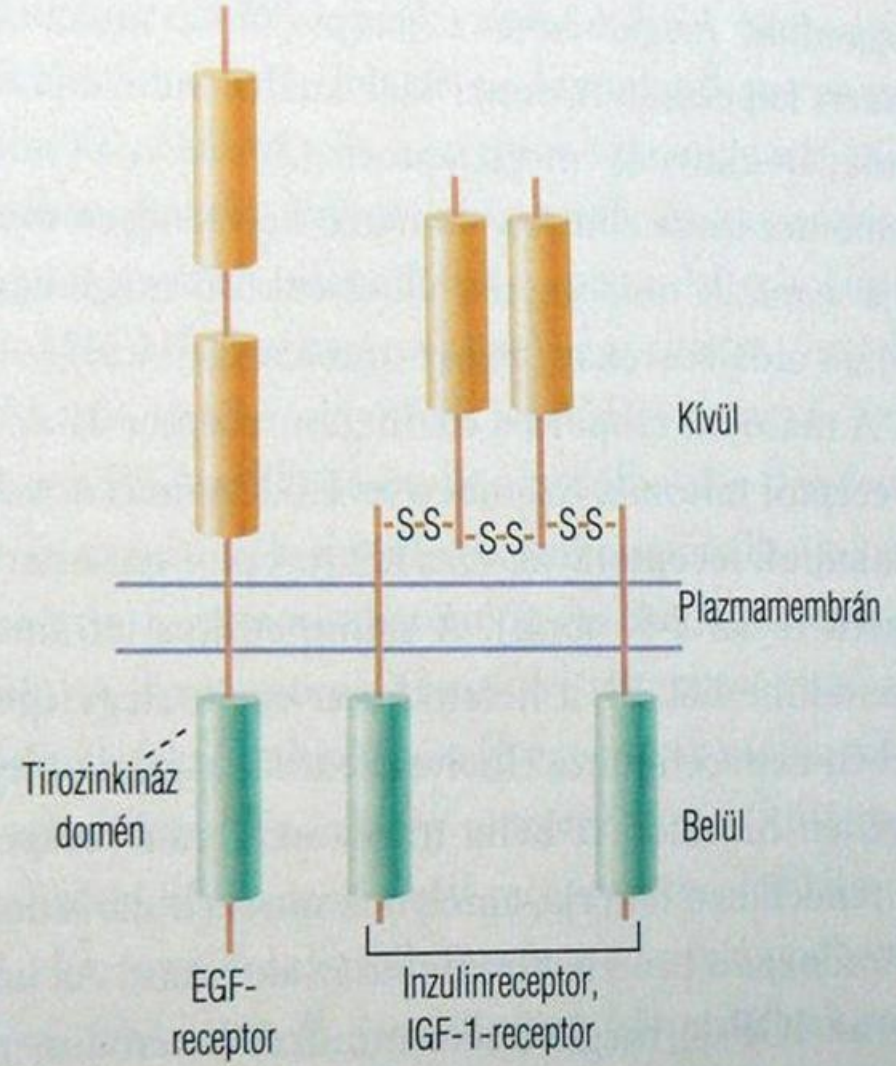
PKC (DAG, Ca)

Protein tyrosine kinases

Mitogen-activated protein kinase /MAPK/ = extracellular signal regulated kinase /ERK/

Phosphates PP1, PP2A PP2B /calcineurin/

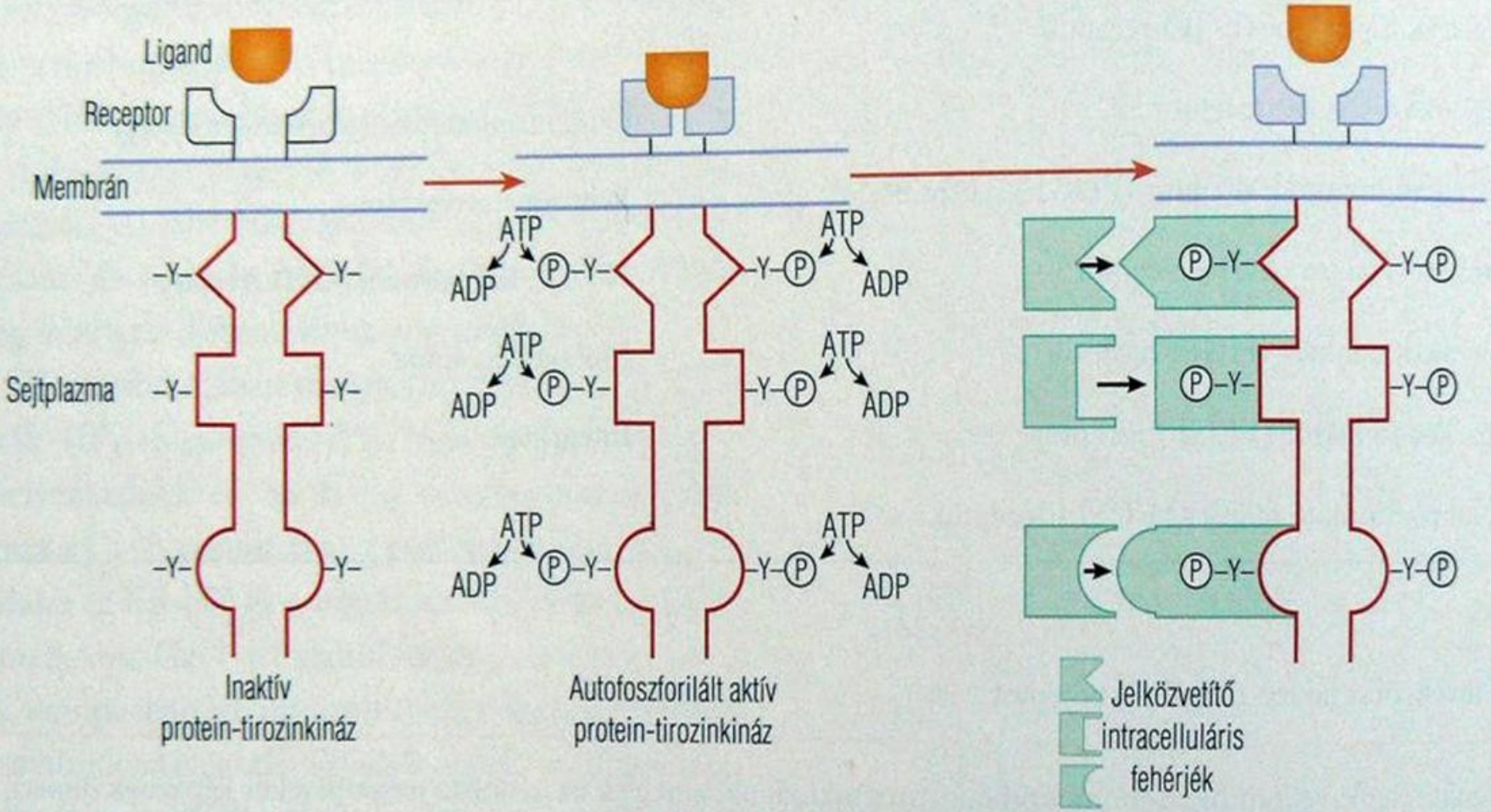
Figure 7.8 Regulation of cellular proteins by phosphorylation. Protein kinases transfer phosphate groups (P_i) from ATP to serine, threonine, or tyrosine residues on substrate proteins. This phosphorylation reversibly alters the structure and function of cellular proteins. Removal of the phosphate groups is catalyzed by protein phosphatases. Both kinases and phosphatases are regulated by a variety of intracellular second messengers.



5-5. ábra

A receptor protein-tirozinkinázok felépítésének vázlata

EGF: epidermalis növekedési faktor; IGF: inzulinszerű növekedési faktor



5-6. ábra

Receptor protein-tirozinkináz (EGF-receptor) jelközvetítő működésének vázlata

5-4. táblázat

Receptor protein-tirozinkinázok és protein-tirozinkinázhoz közvetlenül kapcsolt receptorok

Receptor protein-tirozinkinázok	Protein-tirozinkinázhoz közvetlenül kapcsolt receptorok
Epidermalis növekedési faktor (EGF) receptor	
Idegnövekedési faktor (NGF) receptor	Citokin/interleukinreceptorok többsége
Thrombocytaeredetű növekedési faktor (PDGF) receptor	Eritropoetinreceptor
Fibroblast növekedési faktor (FGF) receptor	Növekedési hormon (GH) receptor
Hepatocyta növekedési faktor (HGF) receptor	Prolaktinreceptor
Érendothel növekedési faktor (VEGF) receptor	Integrinek
Macrophag kolóniastimuláló faktor (M-CSF) receptor	
Inzulinreceptor	
Inzulinszerű növekedési faktor 1 (IGF-1) receptor	

A vízszintes vonal feletti receptorok monomer protein-tirozinkinázok, amelyek az agonista megkötésekor képeznek dimert; a vízszintes vonal alatti két receptorban heterodimerek tetramert képeznek (l. az 5-5. ábrát)

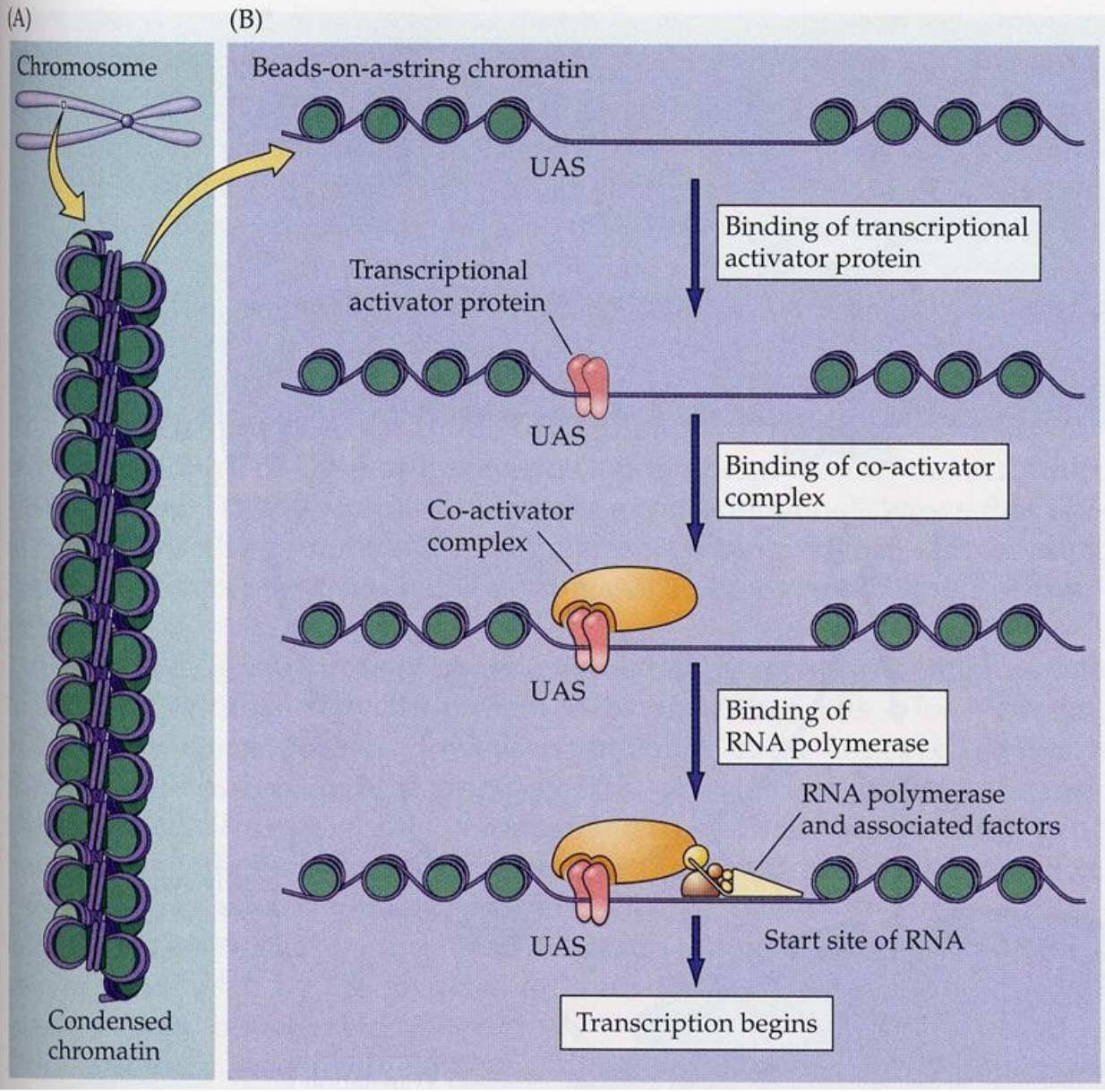
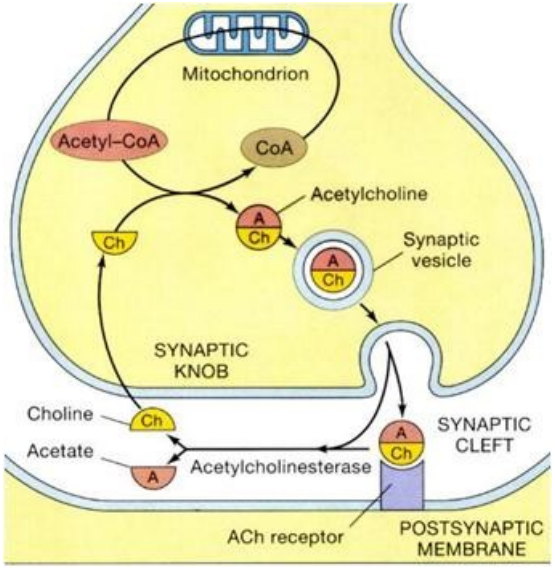


Figure 7.10 Steps involved in transcription of DNA into RNA. Condensed chromatin (A) is decondensed into a beads-on-a-DNA-string array (B) in which an upstream activator site (UAS) is free of proteins and is bound by a sequence-specific transcriptional activator protein (transcription factor). The transcriptional activator protein then binds co-activator complexes that enable the RNA polymerase with its associated factors to bind at the start site of transcription and initiate RNA synthesis.

Regulation of gene expression

Szinapszis: Specializált struktúra, mely két sejt közötti funkcionális kölcsönhatást biztosítja. Alkotórészei: preszinaptikus terminál, posztszinaptikus célterület és köztük a szinaptikus rés (Biochimica et Biophysica Acta 1662 (2004) 113–137)



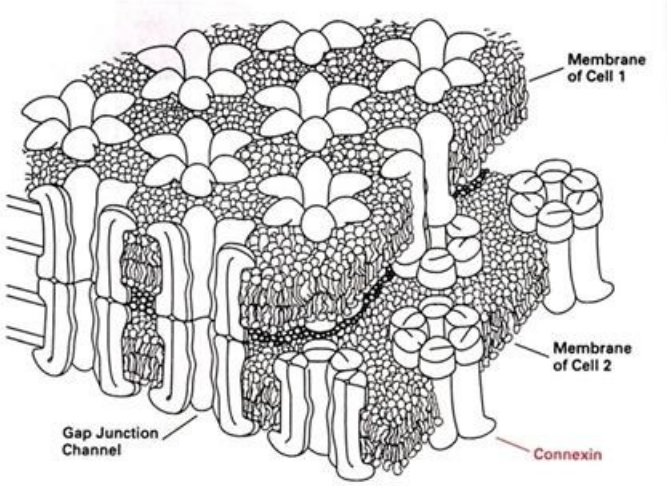


Figure 7-1. Gap junctions. Pores spanning two cell membranes are made of connexin proteins. This picture evolved from the X-ray diffraction work of Makowski et al. (1977).

Kémiai szinapszis

- Neurotranszmitter mediálja a transzmissziót (szinaptikus késés)
- Szinaptikus rés: 20 – 40 nm
- Szinaptikus vezikulák, kalciumfüggő transzmitter kibocsátás, pre és posztszinaptikus receptorok, diffúzió, transzmitter bontó enzimek, felvétel

Elektromos szinapszis (gap junction)

- Közvetlen kapcsolat a sejtek között csatornákon keresztül (nincs késés, kis molekulák cseréje)
- 2 nm rés a membránok között
- Connexinek
- Kétirányú (de lehet aszimmetrikus)

http://cla.calpoly.edu/~cslem/Wizdemo/3-ChapterSplash.html

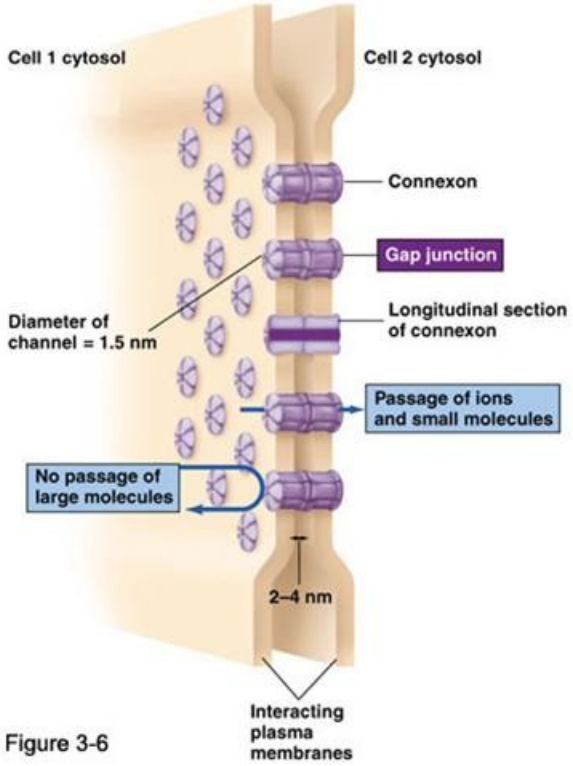
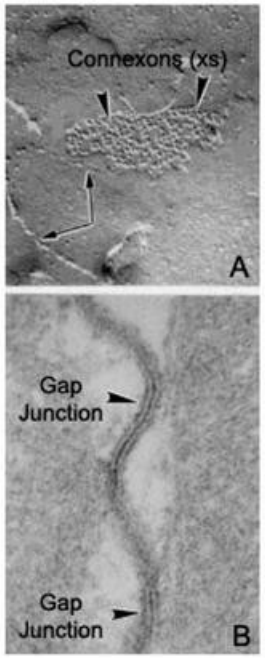
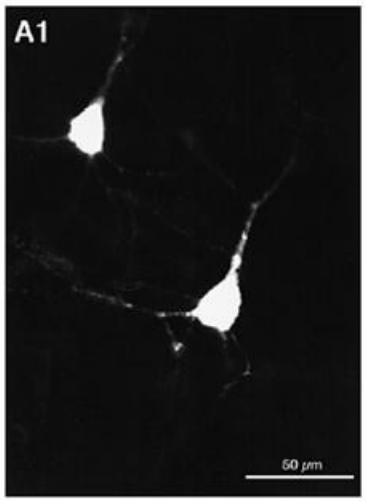
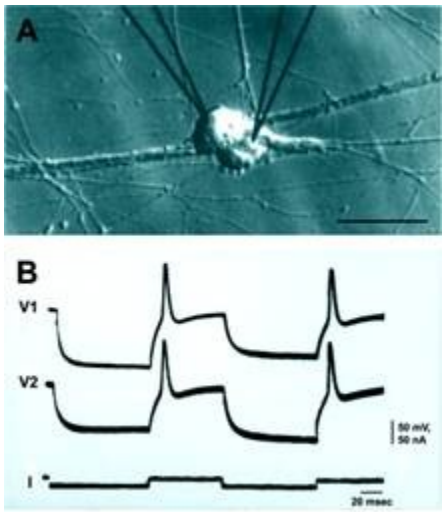


Figure 3-6







'NON-SYNAPTIC' MECHANISMS IN SEIZURES AND EPILEPTOGENESIS*
F. EDWARD DUDEK*, THOMAS YASUMURA and JOHN E. RASH

http://www.sci.saitama-u.ac.jp/~ohnishi/Lec/Gap_junction.htm

http://www.colorado.edu/kines/Class/IPHY3430-200/04neuron.html

Hogyan tanulmányozzák az elektromos szinapszisokat :

- Festék átvitel
- Elektromos kapcsolat (nincs szinaptikus késés,farmakológia)
- Transzgén állatok

Role of Gap Junctions in Synchronized Neuronal Oscillations in the Inferior Olive
Elena Leznik and Rodolfo Llina´s

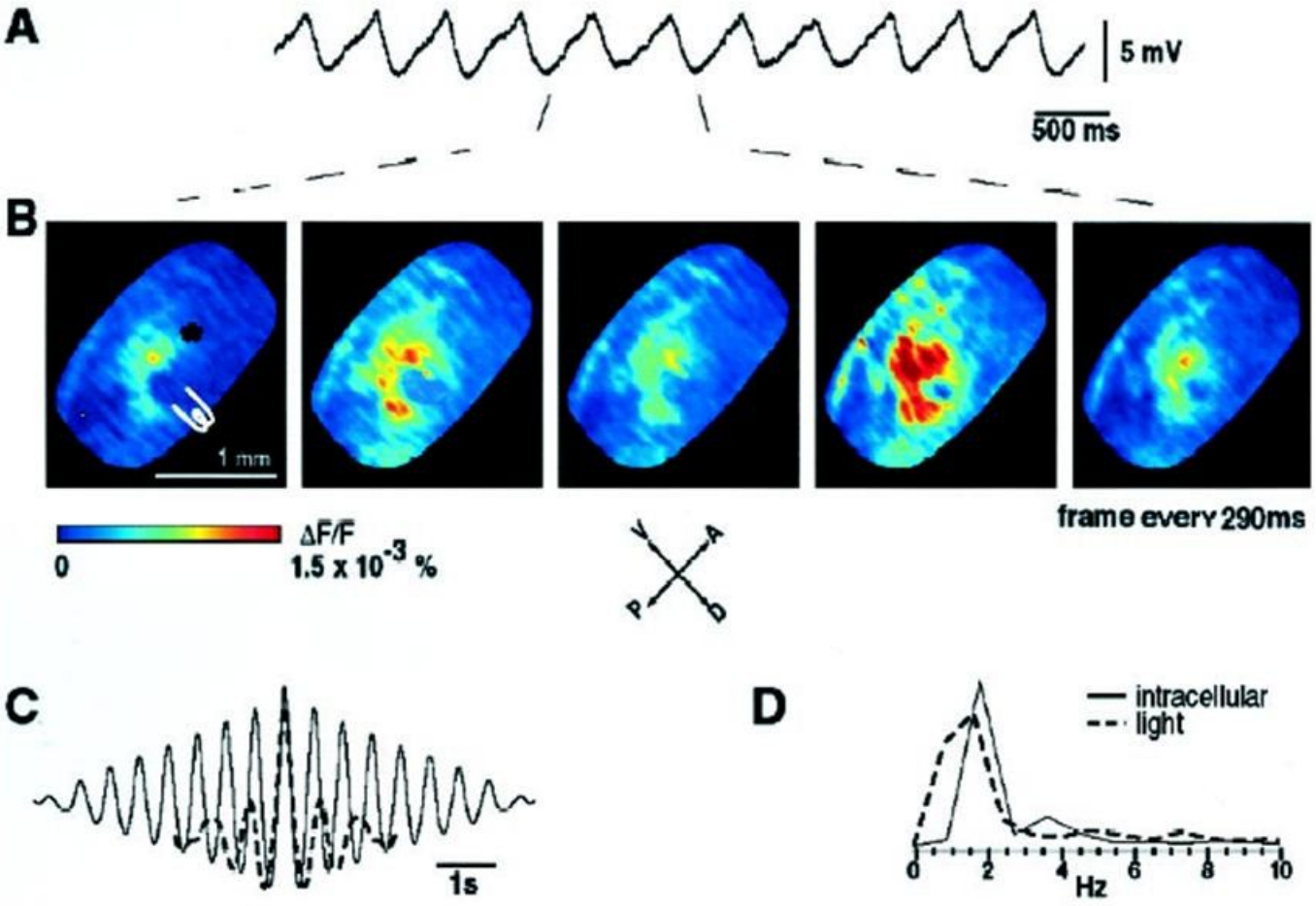


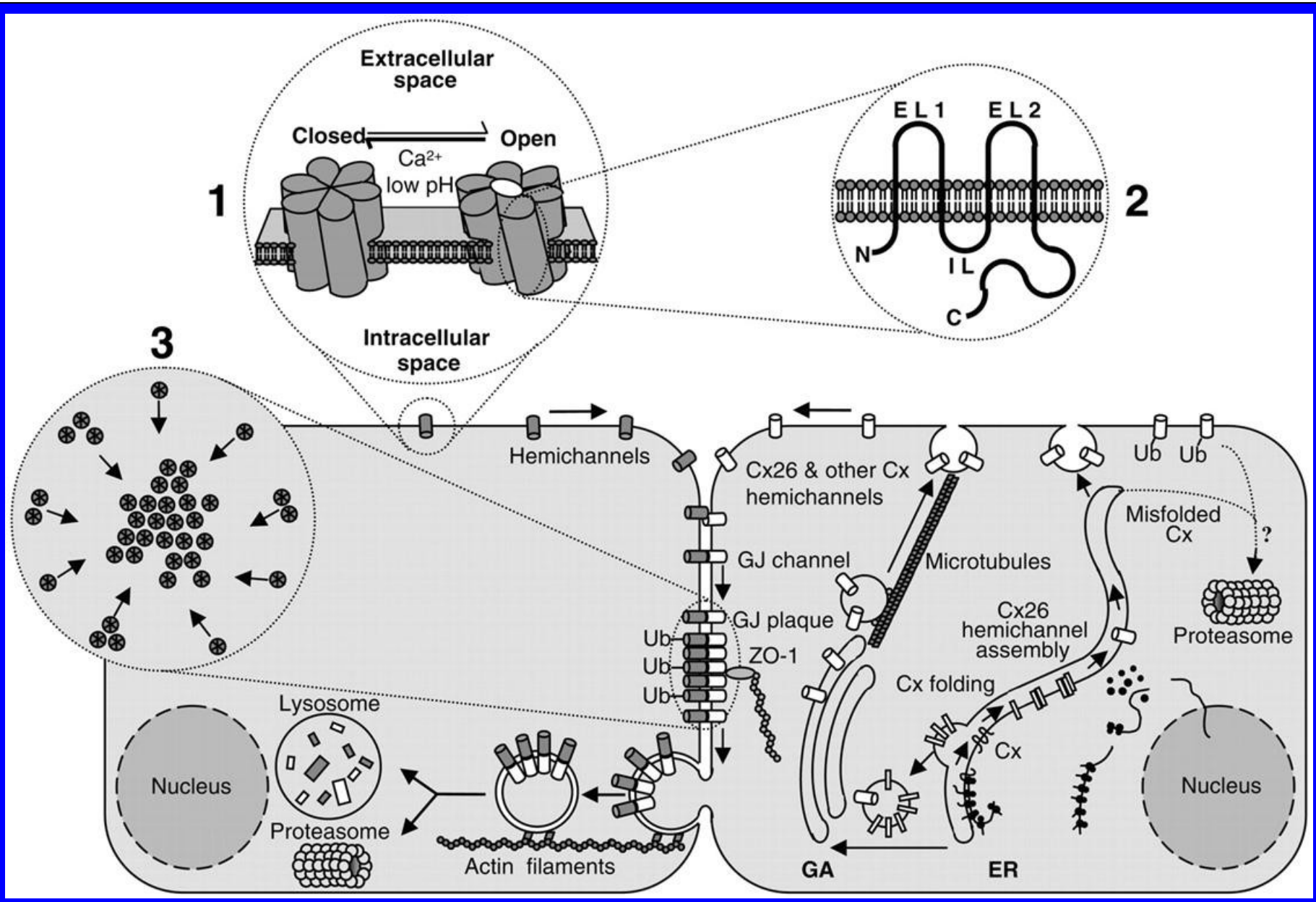
Figure 5. Comparison between optically recorded and intracellularly recorded IO oscillations. *A*, Subthreshold oscillations recorded intracellularly from an IO cell in the presence of dye (RH-414). Position of the recording electrode is marked with an *asterisk* in *B*. *B*, Frames from optically recorded oscillations from the same slice as in *A*. Two cycles of oscillations are shown. The position of the stimulating electrode is indicated. *C*, Autocorrelograms and power spectra of the optically recorded ensemble oscillations (*dashed black line*) and intracellular recorded oscillations (*solid black line*). Note that the clusters, seen as spots of fluorescence in the image panel, have oscillatory voltage profiles at frequencies similar to those observed intracellularly.

The Journal of Neuroscience, April 1, 2002, 22(7):2804–2815

Electrotonically Mediated Oscillatory Patterns in Neuronal Ensembles: An *In Vitro* Voltage-Dependent Dye-Imaging Study in the Inferior Olive

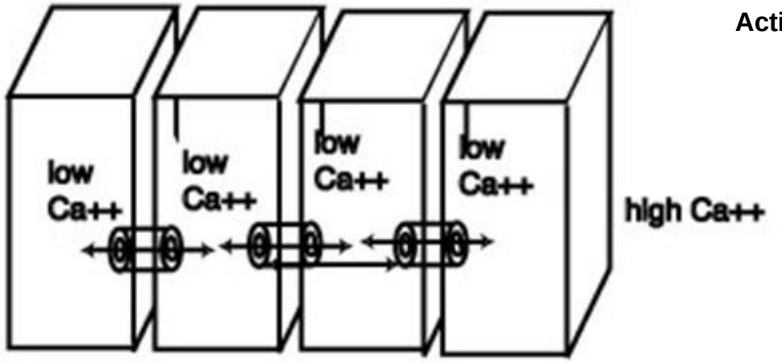
Elena Leznik, Vladimir Makarenko, and Rodolfo Llinás

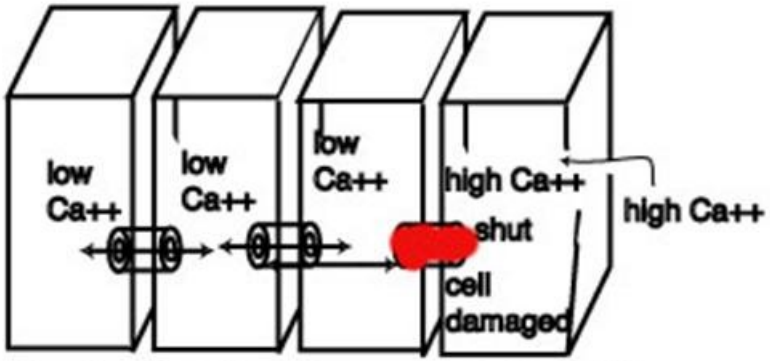
Department of Physiology and Neuroscience, New York University School of Medicine, New York, New York 10016



http://www.sci.saitama-u.ac.jp/~ohnishi/Lec/Gap_junction.htm

When intracellular Ca++ concentration is low the gap junctions are open





When the intracellular Ca++ concentration is high the gap junctions close.

Activity-dependent Neuronal Control of Gap-junctional Communication in Astrocytes
Nathalie Rouach, Jacques Glowinski, and Christian Giaume

Nature. 1993 Mar 25;362(6418):318-24

Am J Physiol Lung Cell Mol Physiol 283: L665–L670, 2002;
10.1152/ajplung.00142.2002.

EB2002 featured topic

Role of gap junctions in CO_2 chemoreception and respiratory control

Anticonvulsant Actions of Gap Junctional Blockers in an In Vitro Seizure Model

SHOKROLLAH S. JAHROMI,[1,2] KIRSTEN WENTLANDT,[1,2] SANAZ PIRAN,[2] AND PETER L. CARLEN[1,2,3]
[1]*Toronto Western Research Institute, Division of Cellular and Molecular Biology, University Health Network,*
[2]*Departments of Physiology and* [3]*Medicine, University of Toronto, Toronto, Ontario M5T 2S8, Canada*

Received 1 October 2001; accepted in final form 3 June 2002

http://academic.brooklyn.cuny.edu/biology/bio4fv/page/gap-junctions.html

Magas intracelluláris kalcium (sejt sérülése) zárja a csatornákat

Szabályozás: Foszforizációval

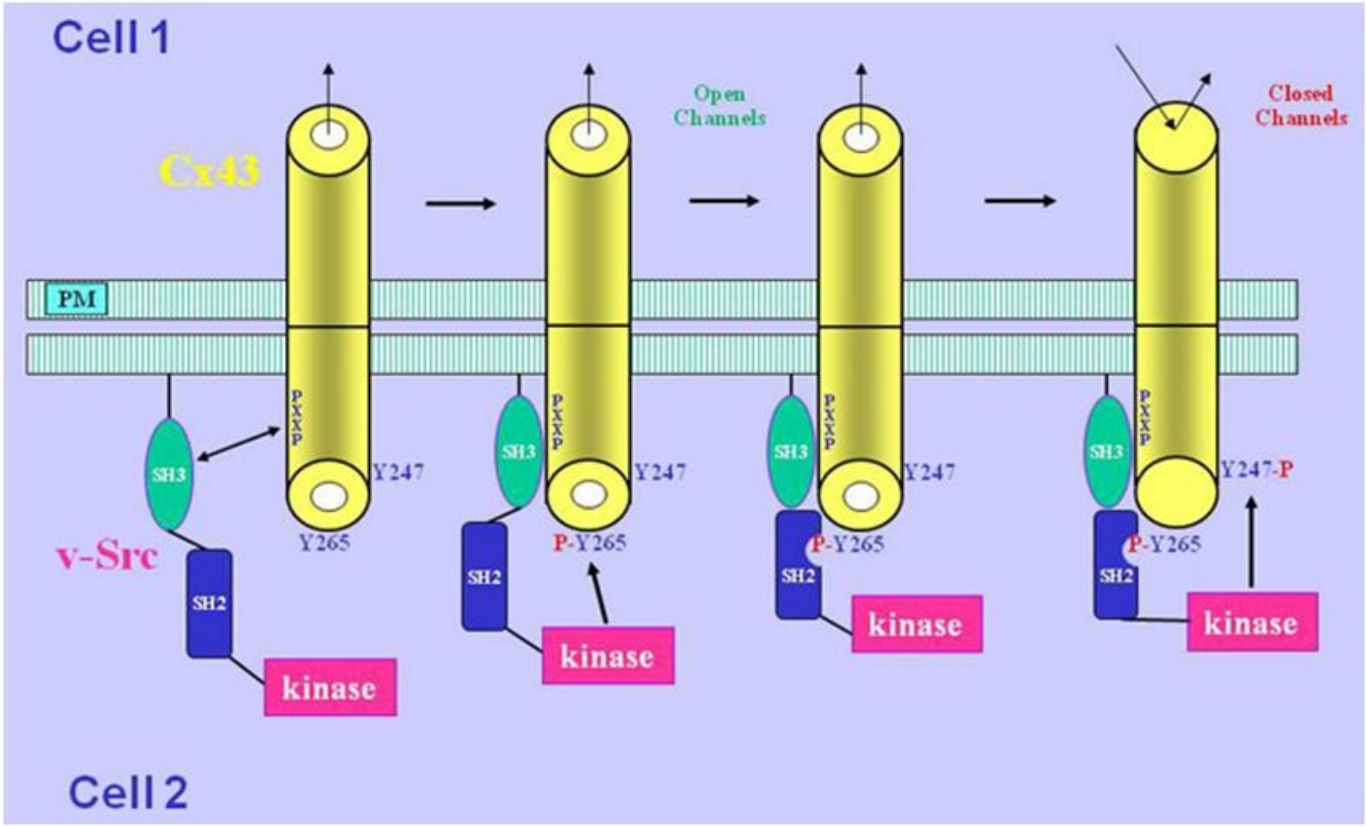


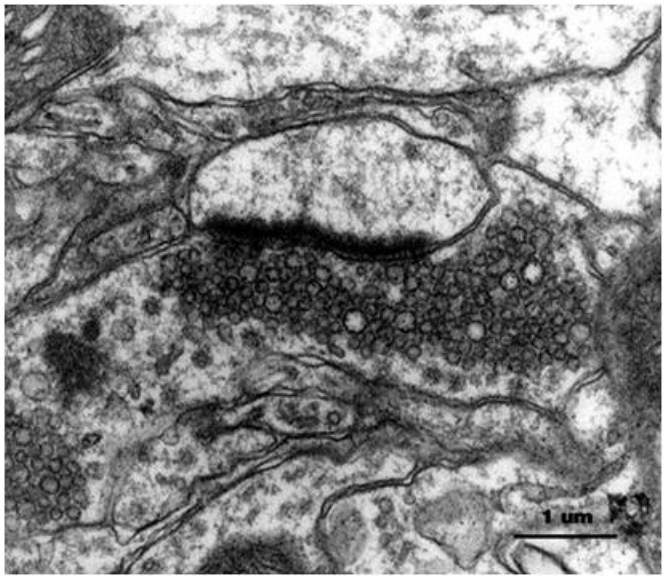
Figure 1. A model for the interaction of v-Src with Cx43.
In this model, the binding of Cx43 to v-Src is dependent initially upon a SH3 domain interaction followed by SH2 domain interactions, which are important for v-Src–induced phosphorylation of Cx43 at the Y265 site and the subsequent phosphorylation at the Y247 site, leading to closure of the Cx43 channel. PXXP denotes the P274–P284 proline-rich sequence of Cx43 that interacts with the SH3 domain of v-Src. For simplicity, gap junction channels are depicted as cylinders. PM denotes the plasma membrane. http://www.crch.org/ProfileLau.htm

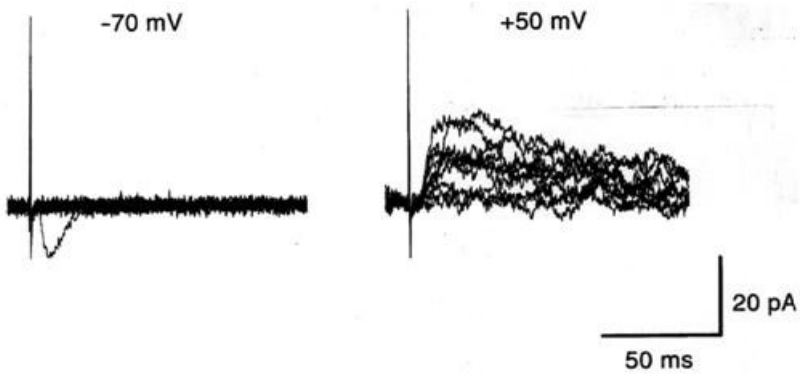
Table 1
Distribution of connexins in neurons of the central nervous system

Connexin	mRNA	Protein	Reporter gene
Cx36	Inferior olive, olfactory bulb, cerebral cortex, CA3 region of the hippocampus, hilus of the dentate gyrus, parvalbumin containing GABAergic neurons in the strata radiatum and oriens of the hippocampus, cerebellum, striatum, pineal gland, principal accessory nuclei, inner nuclear layer of the retina, cerebellar cortex, spinal cord gray matter [25,26,33,42,172,174–176,342]; lumbar spinal motor neurons [157]; forebrain, midbrain, sympathetic and spinal ganglia, spinal cord (E9.5–E12.5) [343]; suprachiasmatic nucleus [344]; olfactory epithelium, ventral and lateral regions of turbinates [345].	Inferior olive [110,175,177]; retinal inner and outer plexiform layers, AII amacrine cells [110,112,175,177,178,266,270,271]; cerebral cortex [178]; hippocampus, cerebellum [177]; anterior pituitary, pineal gland [175]; spinal cord [110]; olfactory nerve bundles underlying the olfactory epithelium, olfactory nerve layer and glomerular layer of the olfactory bulb, glomerular layer of the accessory olfactory bulb, vomeronasal nerve [175,345].	Retinal photoreceptors, cone bipolar cells, AII amacrine cells [272]; reticular thalamus [179]; inferior olive [180]; cortex, co-localization with somatostatin and parvalbumin neurons [112]; olfactory epithelium and olfactory bulb [345].
Cx43	Olfactory epithelium (sustentacular cells, mature and immature olfactory receptor neurons, basal cells) [181].	Mature olfactory receptor neurons [181].	Olfactory epithelium (sustentacular cells, mature and immature olfactory receptor neurons, basal cells) [181]; olfactory bulb [183].
Cx45	Motor neurons [157]; retina [267,269]; dopaminergic neurons of the midbrain floor [346]; cerebral cortex, granular and molecular layers of the cerebellum [172]; olfactory epithelium and mature olfactory neurons (co-localization with olfactory marker protein) [185].	Inner and outer plexiform layers of the retina [267]; motor neurons [157]; dopaminergic neurons of the midbrain floor [346]; neurons of the olfactory epithelium, proximal processes of mitral cells in the olfactory bulb [185].	Ganglion cells and the inner nuclear layers of the retina [267,278]; widespread expression during embryogenesis and up to P15, CA3–CA4 region of hippocampus, thalamus and cerebellum (basket and stellate cells) in the adult [184].

The identity of gap junction proteins expressed in neurons remains controversial and discrepancies persist concerning the distribution of several candidate neuronal connexins. A selected compilation of the expression profiles of three connexins, for which standard molecular biology and immunocytochemistry techniques have been combined with genetic approaches based on the expression of a reporter gene to trace their cellular distribution, is presented here. E=embryonic day; P=postnatal day.

A (kémiai) szinapszis



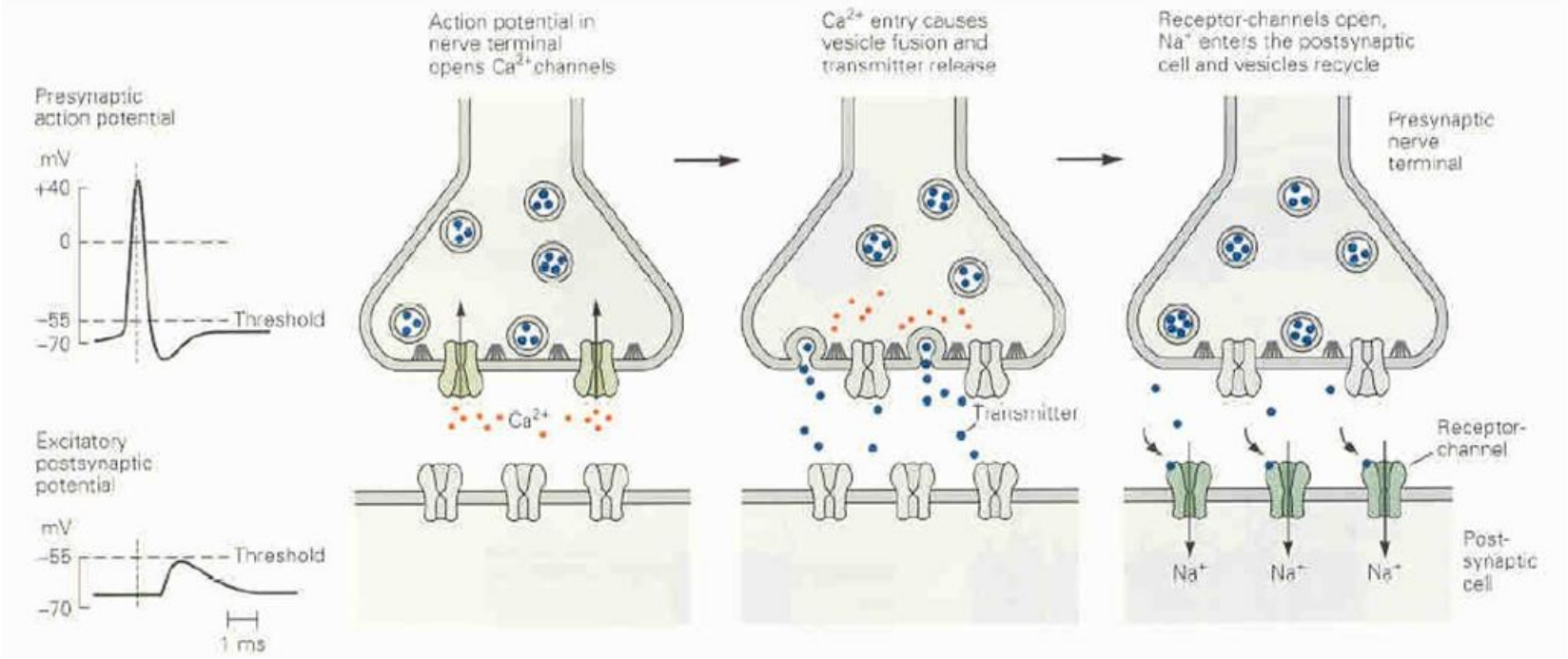


http://www.meddean.luc.edu/lumen/meded/neuro%20/lectures/Transmission.pdf

http://www.itg.uiuc.edu/exhibits/gallery/pages/image-51.htm

Hogyan tanulmányozzák:

- Electron mikroszkóp
- Preszinaptikus stimuláció posztszinaptikus áramot vált ki, amely antagonistákkal gátolható
- Visszafordítási potenciál
- Spontán transzmitter kibocsátás (mEPSPs, mIPSPs)
- Quantal analízis

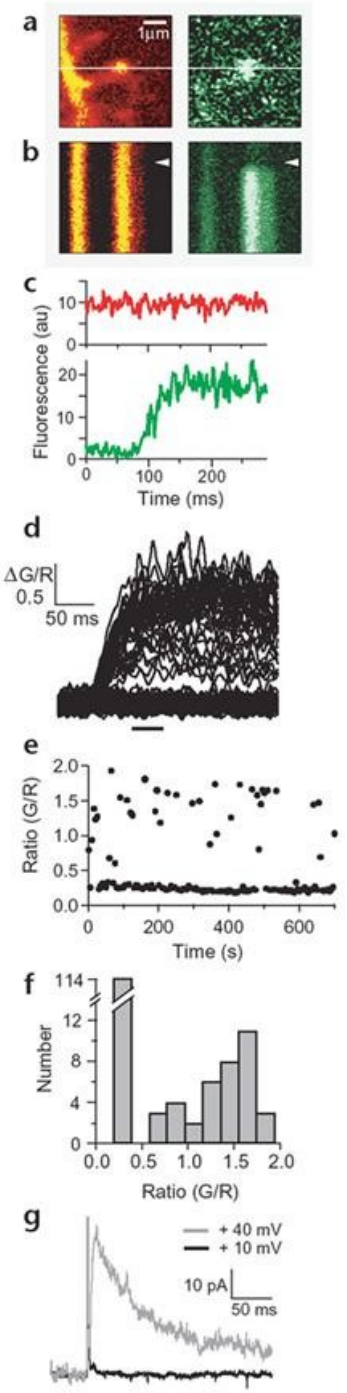


Az akciós potenciál eléri a preszinaptikus terminált → feszültségfüggő kalcium csatornák nyílnak → kalcium beáramlás↑→ A magas [Ca2+]i neurotranszmittert tartalmazó vezikulák sejtmembránnal történő fúzióját okozza → A neurotranszmitter a szinaptikus résbe ürül, diffúzióval eljut a posztszinaptikus membránhoz és a posztszinaptikus receptorokhoz → Hozzákapcsolódik a posztszinaptikus (és közben a preszinaptikus) receptotokhoz → Posztszinaptikus depolarizáció (ion csatorna), metabolikus receptorok aktivációja → posztszinaptikus sejtválasz (akciós potenciál) → A transzmitter eltávolítása a szinaptikus résből (lebontás, felvétel)

Quantal Analysis

Figure 1. Measurement of NMDAR-mediated [Ca^{2+}] transients in single spines.

(**a**) Left, dendrite with several spines (red fluorescence) and right, [Ca^{2+}] transient after synaptic stimulation (green fluorescence, G). White line indicates position of the line scan. (**b**) Line scans across spine head (total duration, 450 ms). White triangles indicate time of synaptic stimulation. Red fluorescence did not change (left), whereas green fluorescence increased rapidly in the spine after synaptic stimulation (right). A weak and delayed increase in [Ca^{2+}] due to Ca^{2+} diffusion is apparent in the dendrite. (**c**) Time course of fluorescence intensity in the spine head in the [Ca^{2+}]-insensitive (red) and [Ca^{2+}]-sensitive (green) fluorescence channels (single trial, same data as in **b**). (**d**) Multiple responses to synaptic stimulation with single pulses (130 trials). Failures of neurotransmitter release can be clearly distinguished from successes. (**e**) Response amplitudes over time. Response amplitudes, failure rates, and resting fluorescence (corresponding to resting $[Ca^{2+}]_i$) were stable (same data as in **d**); response amplitudes were averaged in a 40 ms window starting 50 ms after stimulation (horizontal bar at bottom of **d**). (**f**) Histogram of response amplitudes. (**g**) EPSC measured in the soma at nominal holding potentials of +10 mV (black) and +40 mV (gray). The initial fast transient is the stimulus artifact.



Nature Neuroscience **5**, 657 - 664 (2002)
Published online: 10 June 2002; | doi:10.1038/nn867

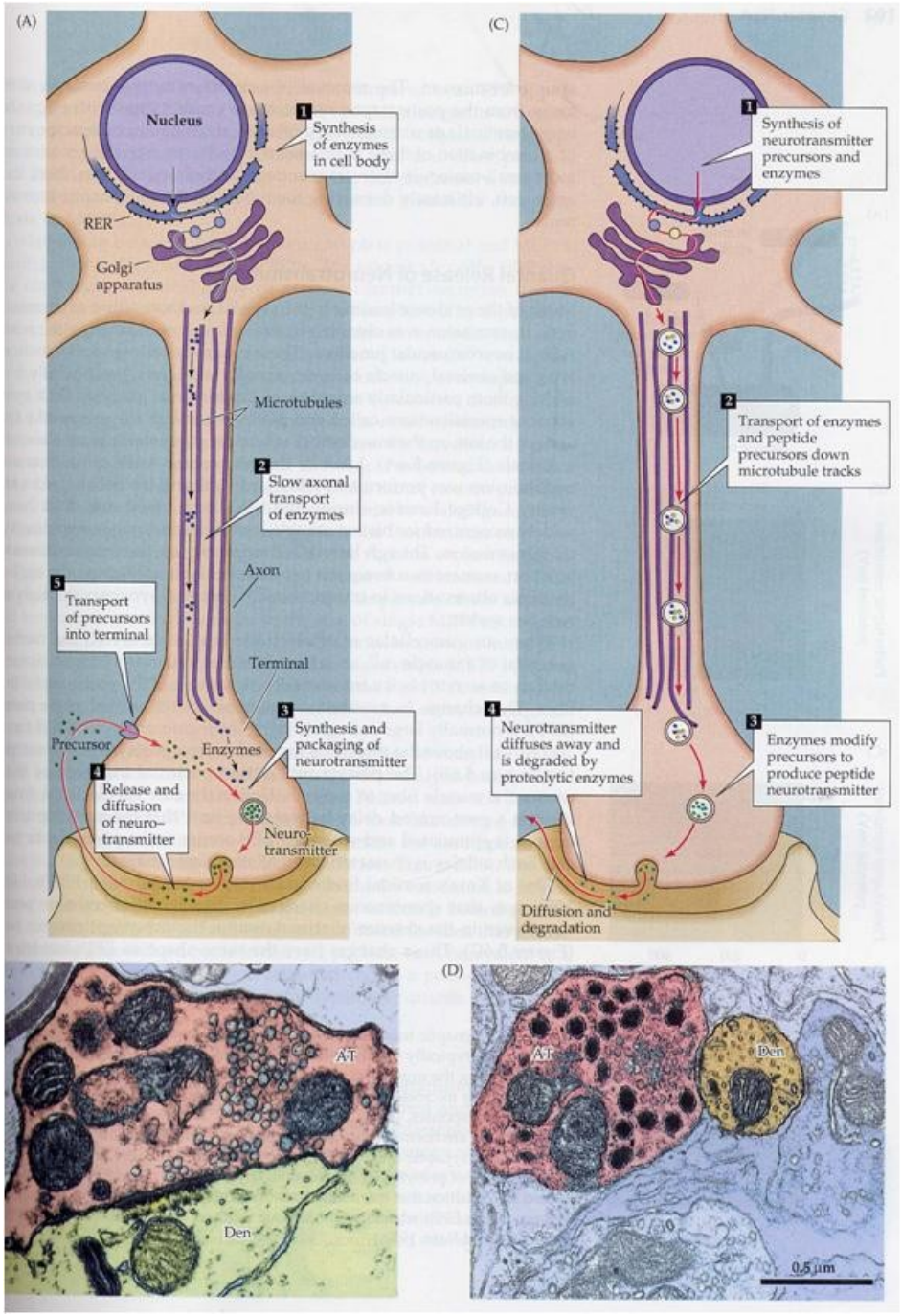
Facilitation at single synapses probed with optical quantal analysis

Thomas G. Oertner, Bernardo L. Sabatini, Esther A. Nimchinsky & Karel Svoboda

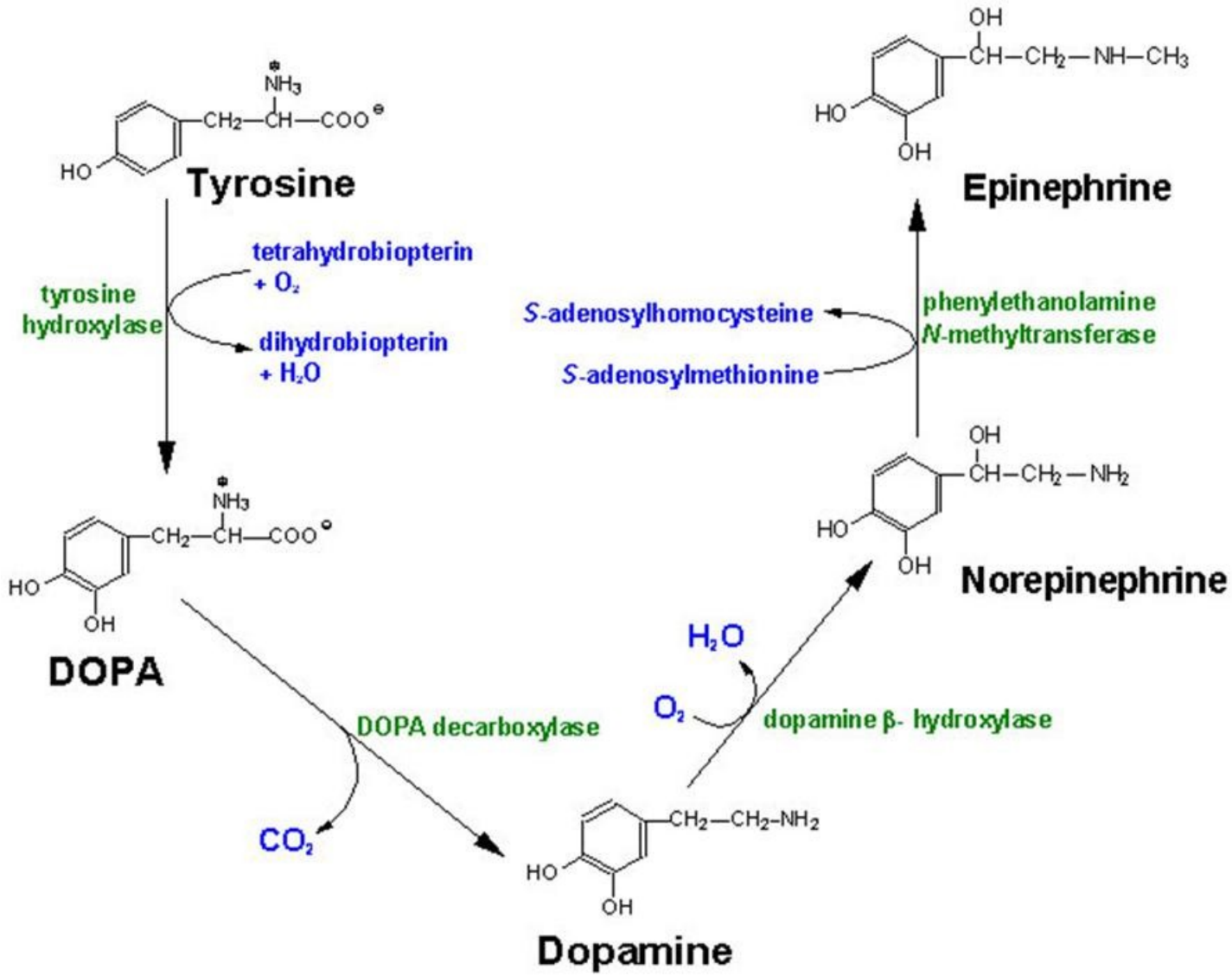
Mi az a neurotransmitter ?

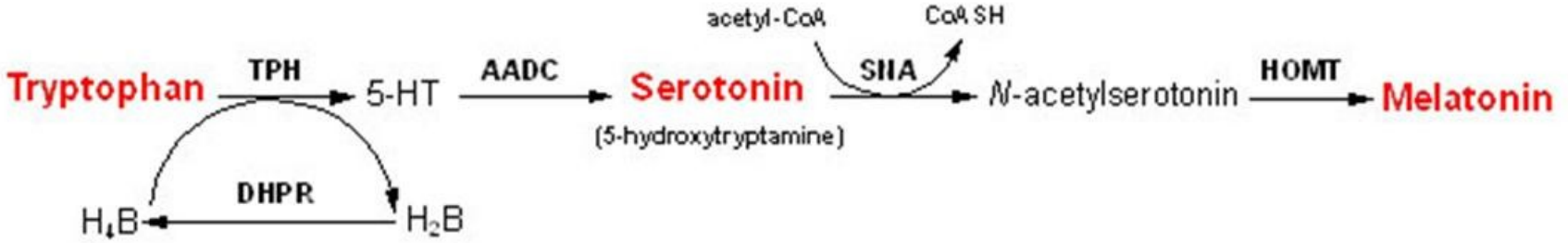
- A neuronban szintetizálódik
- Jelen van a preszinaptikus terminálban és abból elég nagy mennyiségben ürül ahhoz, hogy kiváltsa a mért posztszinaptikus választ.
- Kibocsátása kalciumfüggő
- Ha kívülről juttatjuk a szinapszisba, ugyanolyan posztszinaptikus választ vált ki, mint az eredeti
- Lebontására, a szinatikus résből való eltávolítására létezik mechanizmus.

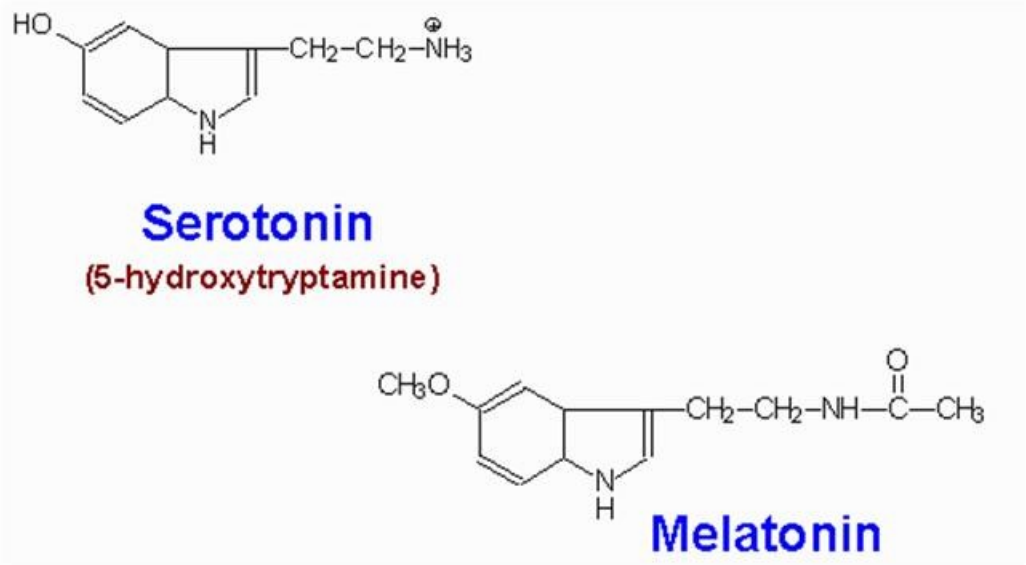
Synthesis of Neurotransmitters



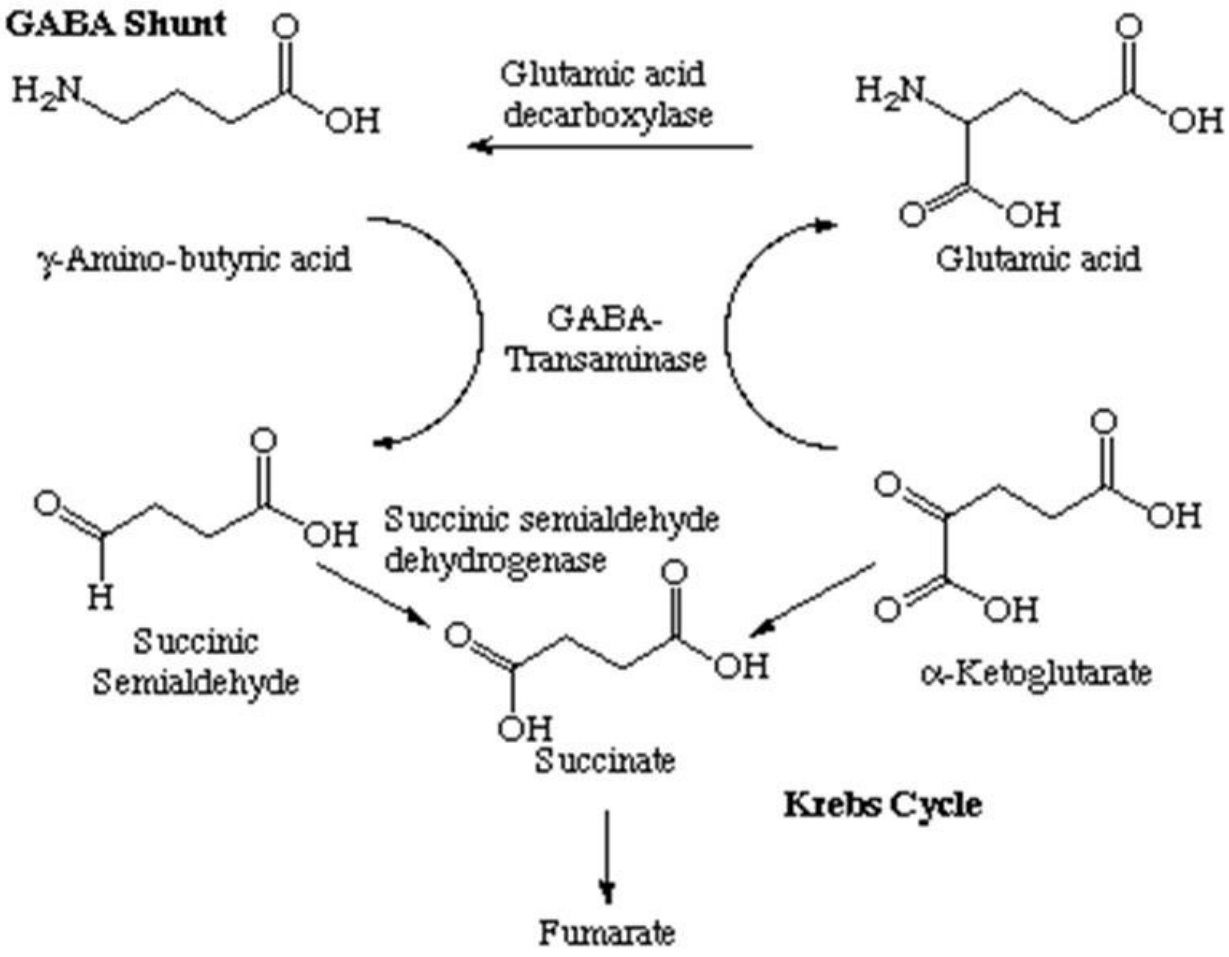
http://www.indstate.edu/thcme/mwking/aminoacidderivatives.html







Pathway for serotonin and melatonin synthesis from tryptophan. Abbreviations: THP = tryptophan hydroxylase, DHPR = dihydropteridine reductase, H2B = dihydrobiopterin, H4B = tetrahyrobiopterin, 5-HT = 5-hydroxytryptophan, AADC = aromatic L-amino acid decarboxylase, SNA = serotonin *N*-acetylase, HOMT = hydroxyindole-*O*-methyltransferase.


GABA Shunt
Glutamic acid decarboxylase
γ-Amino-butyric acid
Glutamic acid
GABA-Transaminase
Succinic semialdehyde dehydrogenase
Succinic Semialdehyde
α-Ketoglutarate
Succinate
Krebs Cycle
Fumarate

Transmitter release

SNARE: soluble NSF attachment receptor

NSF: N-ethylmaleimide sensitive fusion protein

SNARE proteins on two joining membranes (usually a vesicle and a target membrane such as the plasma membrane) form a tight complex. The role of NSF is to undo these SNARE complexes once membrane fusion has occurred. The dissociated SNAREs can then be recycled for reuse in further rounds of membrane fusion.

SNAP-25 (synaptosome-associated protein of 25,000 daltons)

Soluble NSF attachment protein (-SNAP) are thought to be soluble factors that transiently bind and

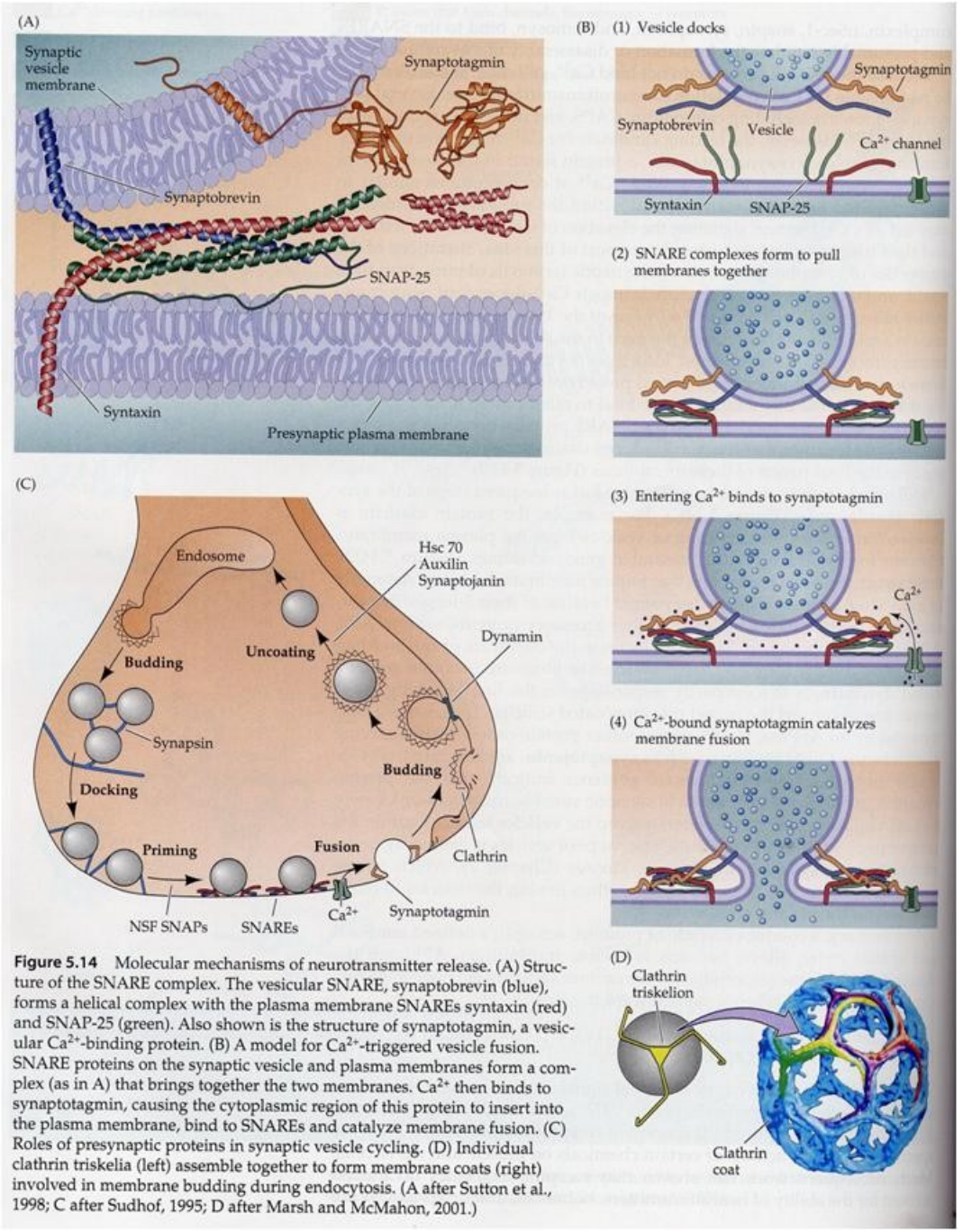
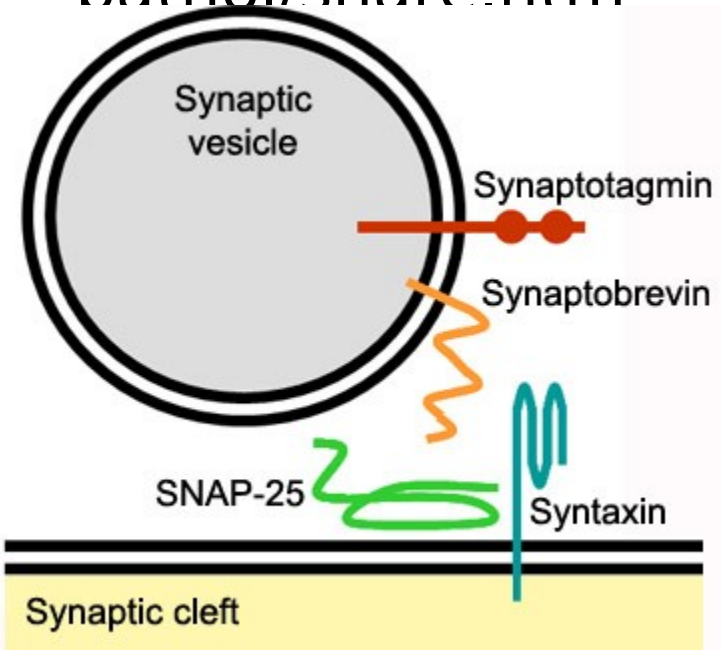


Figure 5.14 Molecular mechanisms of neurotransmitter release. (A) Structure of the SNARE complex. The vesicular SNARE, synaptobrevin (blue), forms a helical complex with the plasma membrane SNAREs syntaxin (red) and SNAP-25 (green). Also shown is the structure of synaptotagmin, a vesicular Ca^{2+}-binding protein. (B) A model for Ca^{2+}-triggered vesicle fusion. SNARE proteins on the synaptic vesicle and plasma membranes form a complex (as in A) that brings together the two membranes. Ca^{2+} then binds to synaptotagmin, causing the cytoplasmic region of this protein to insert into the plasma membrane, bind to SNAREs and catalyze membrane fusion. (C) Roles of presynaptic proteins in synaptic vesicle cycling. (D) Individual clathrin triskelia (left) assemble together to form membrane coats (right) involved in membrane budding during endocytosis. (A after Sutton et al., 1998; C after Sudhof, 1995; D after Marsh and McMahon, 2001.)

http://
www.neuro.wustl.edu
/neuromuscular/
pathol/snare.htm

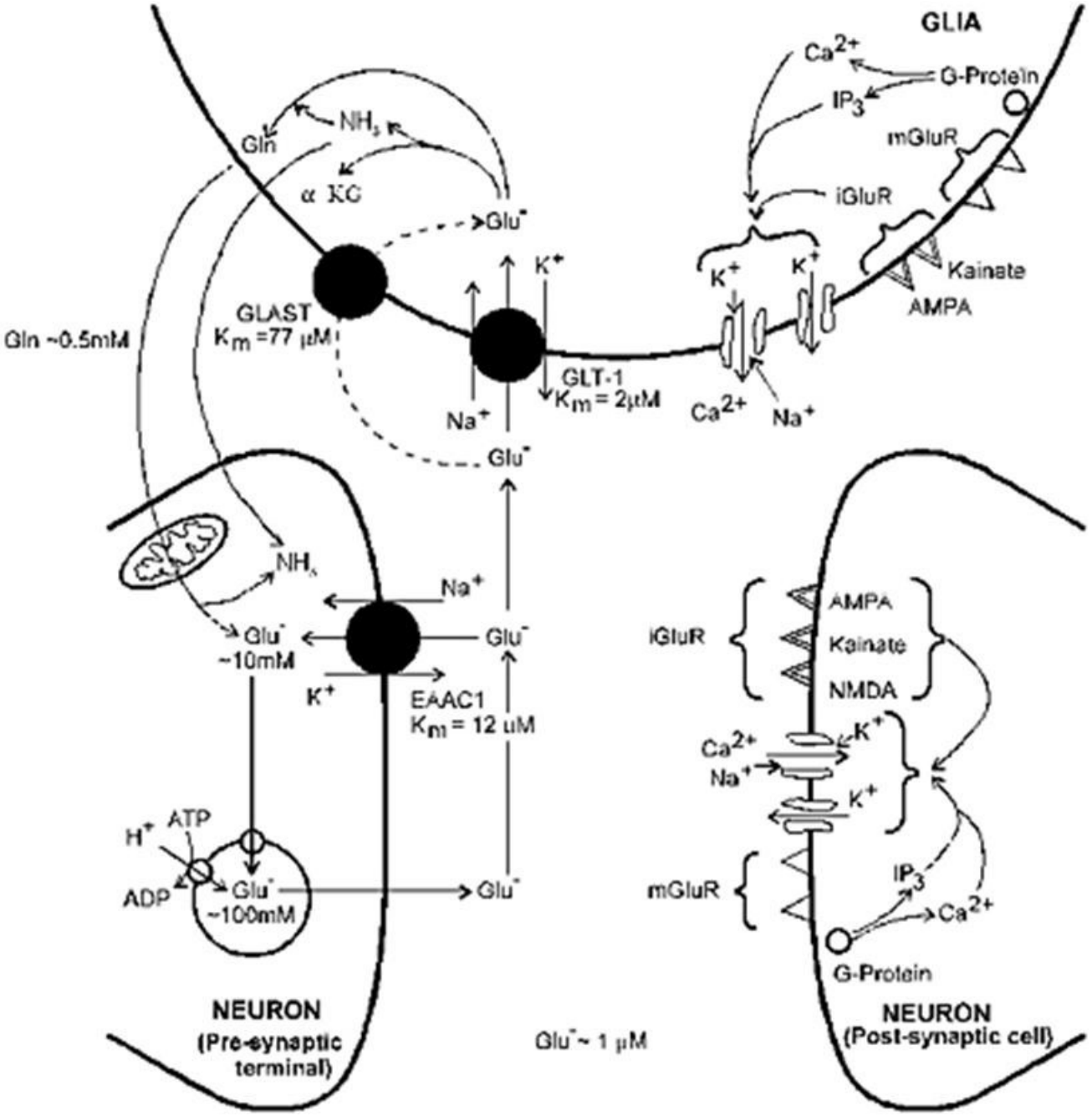


Synaptobrevin: v-SNARE
Synaptotagmin: Calcium sensor
Syntaxin: t-SNARE

SNAP receptors implicated in vesicle targeting and fusion.

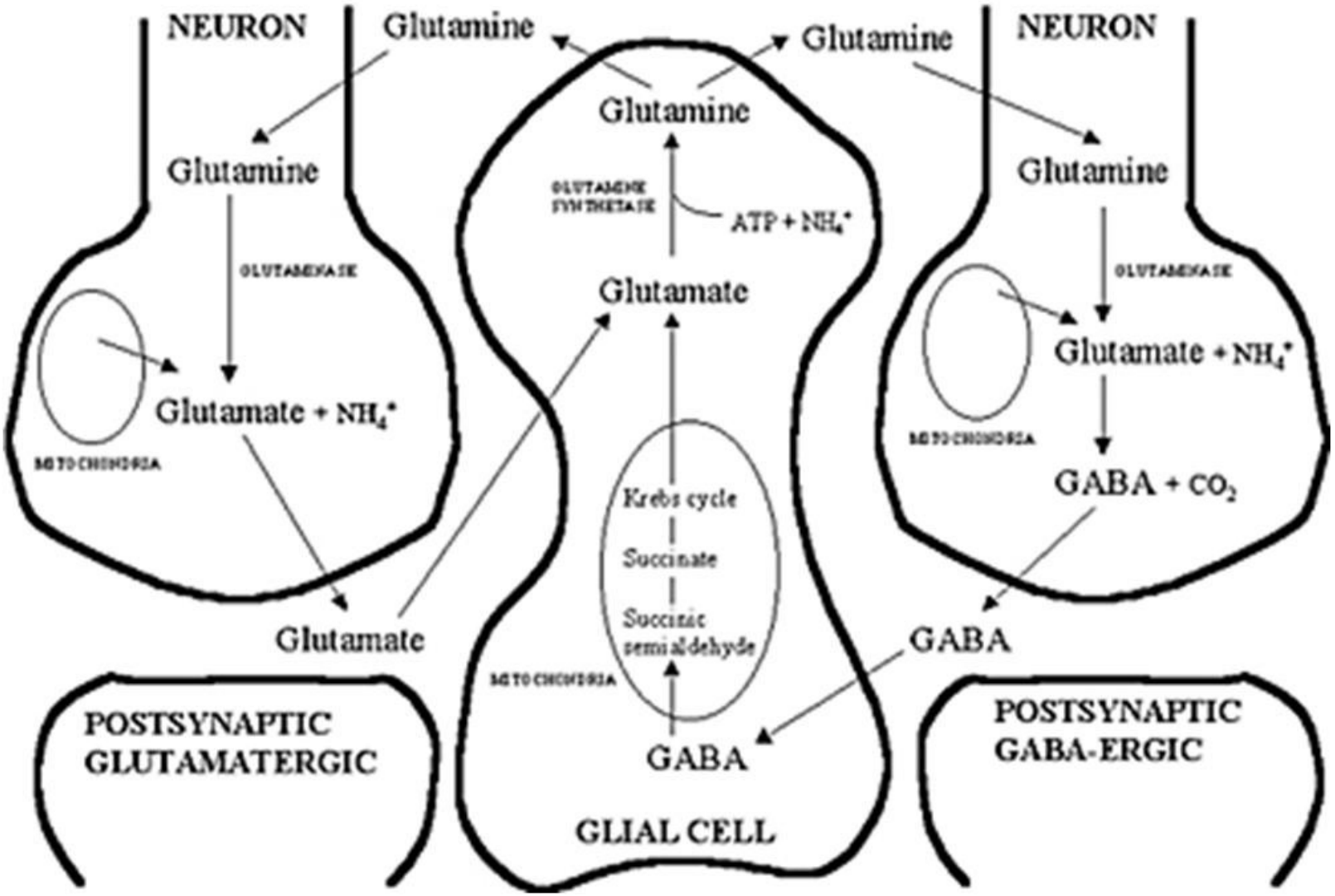
Sollner T, Whiteheart SW, Brunner M, **Erdjument-Bromage H**, **Geromanos S**, **Tempst P**, **Rothman JE**.

The **N-ethylmaleimide-sensitive fusion protein** (NSF) and the **soluble NSF attachment proteins** (SNAPs) appear to be essential components of the intracellular membrane fusion apparatus. An affinity purification procedure based on the natural binding of these proteins to their targets was used to isolate **SNAP receptors** (SNAREs) from bovine brain. Remarkably, the four principal proteins isolated were all proteins associated with the synapse, with one type located in the synaptic vesicle and another in the plasma membrane, suggesting a simple mechanism for vesicle docking. The existence of numerous SNARE-related proteins, each apparently specific for a single kind of vesicle or target membrane, indicates that NSF and SNAPs may be universal components of a vesicle fusion apparatus common to both constitutive and regulated fusion (including neurotransmitter release), in which the SNAREs may help to ensure vesicle-to-target specificity.

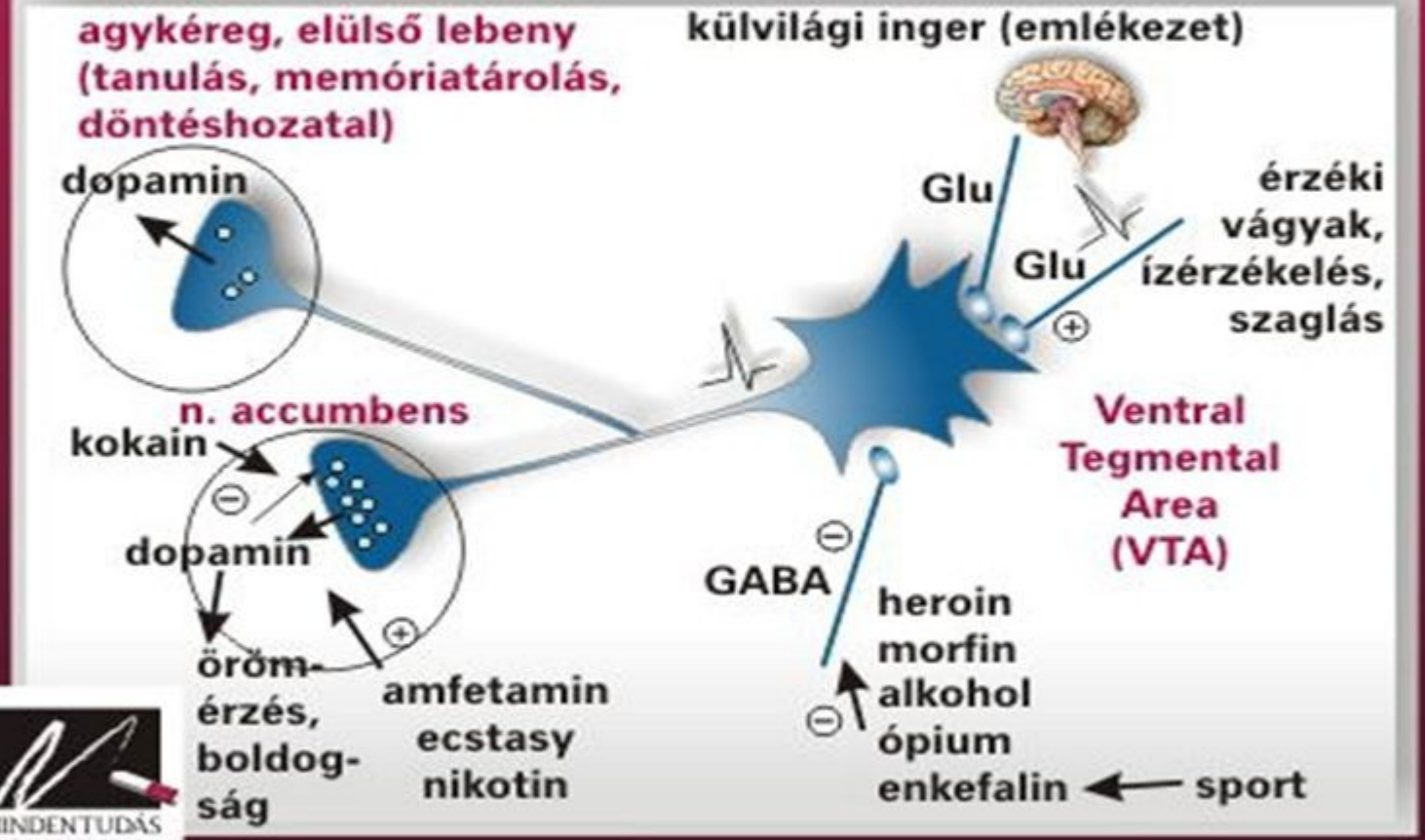


http://bioscience.org/1998/v3/d/palmada/fig1.jpg

http://bioscience.org/1998/v3/d/palmada/d701-718.htm



„A jutalmazási hálózat”: mezolimbikus dopaminerg idegpálya



MINDENTUDÁS EGYETEME

https://slideplayer.hu/slide/1950580/

Therapeutic class	Examples	Pharmacological effects	Comments
Analgesics	Acetylsalicylic acid Paracetamol Non-steroidal anti-inflammatory drugs	Anti-inflammatory; analgesia; antipyretic	Aspirin and paracetamol have been shown to be relatively safe for use in hyperbaric conditions. Narcotic-related analgesics have sedative effects. They may decrease mental performance and may combine with inert gas narcosis to produce CNS depression.[12]
Anxiolytics	Benzodiazepines	Relieve anxiety; depress CNS	Diazepam has been used to depths of 50m without any side effects. However, anxiolytics generally cause drowsiness, lethargy, and confusion and hypotension, that could be fatal in the water. A short-acting benzodiazepine might be considered for insomnia after a long saturation dive. [13]
Hypnotics	Barbiturates	Depress CNS and induce sleep	Safe diving requires an alert, responsive individual, therefore, these drugs are generally contraindicated for divers. [15]
Antipsychotics	Phenothiazines Butyrophenones	Relieve anxiety and thought disturbances	These drugs cause sedation, hypothermia, hypotension, reduction of seizure threshold, cardiac arrythmias and are an absolute contra-indication to diving. [15]
Antidepressants	Tricyclic Antidepressants Monoamine-Oxidase Inhibitors	Psychostimulants; CNS stimulants; Anticholinergic	Tricyclics can cause dry mouth, blurred vision, tachycardia and cardiac arrythmias. Monamine-oxidase inhibitors have been shown to interact synergistically with high nitrogen pressures. [16]
CNS Stimulants	Amphetamines	Increase alertness; inhibit fatigue; suppress appetite; mood elevation	These cause dizziness, excessive sweating, euphoria, anxiety and panic. Amphetamines have been shown to interact synergistically with increased pressure of air at sea pressures of 2 bar. These drugs are contraindicated in diving. [12]
Antiemetics	Phenothiazines Anticholinergics Antihistamines	Relieve nausea and vomiting	Antihistamines are the only indicated drugs for divers for treating motion sickness, although drowsiness may cause decreased cognitive abilities. No significant effects using transdermal scopolamine have been noted. [19]