Computational Neuroscience

Lecture 7: Neurotransmitters and receptors

| Dmitry Bozhko | Georgy Galumov | Sofia Kolchanova | Vladislav Myrov |

Agenda

- Information exchange in living systems
- Signaling pathway
- Membrane receptor
- Neurotransmission and Where to Find it
- What is vesicle?
- Neurotransmitters overview
- Neurotransmitter recycling
- Reuptake
- Retrograde signaling
- More than “one more thing”

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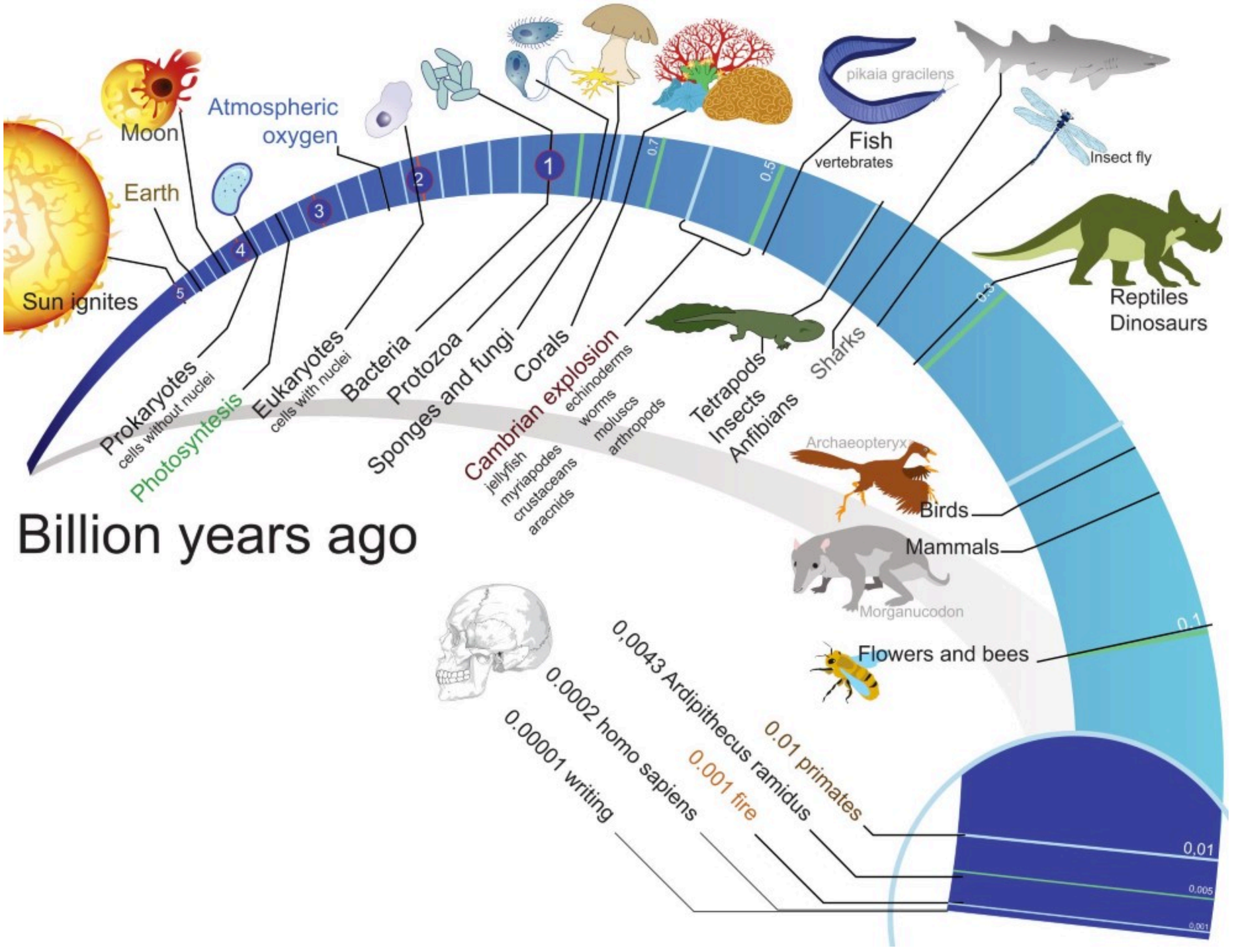
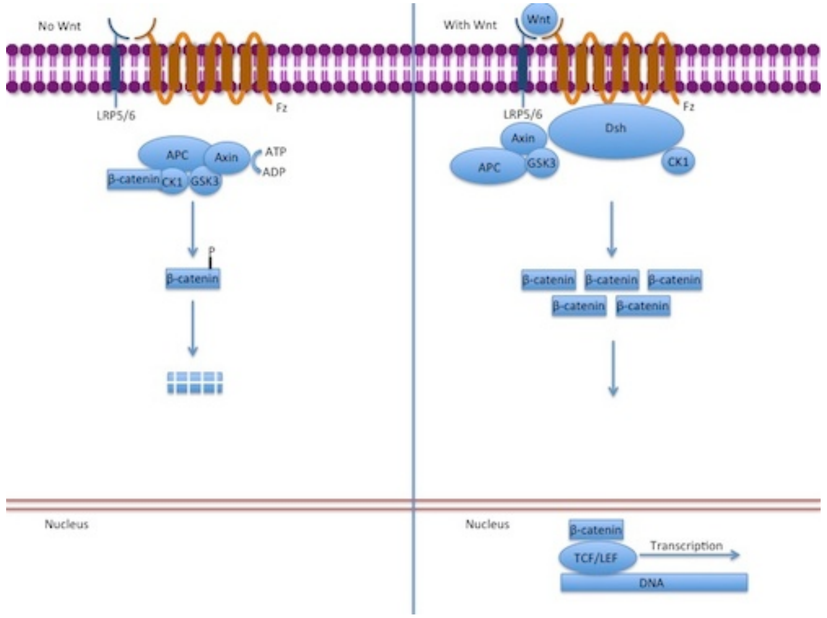
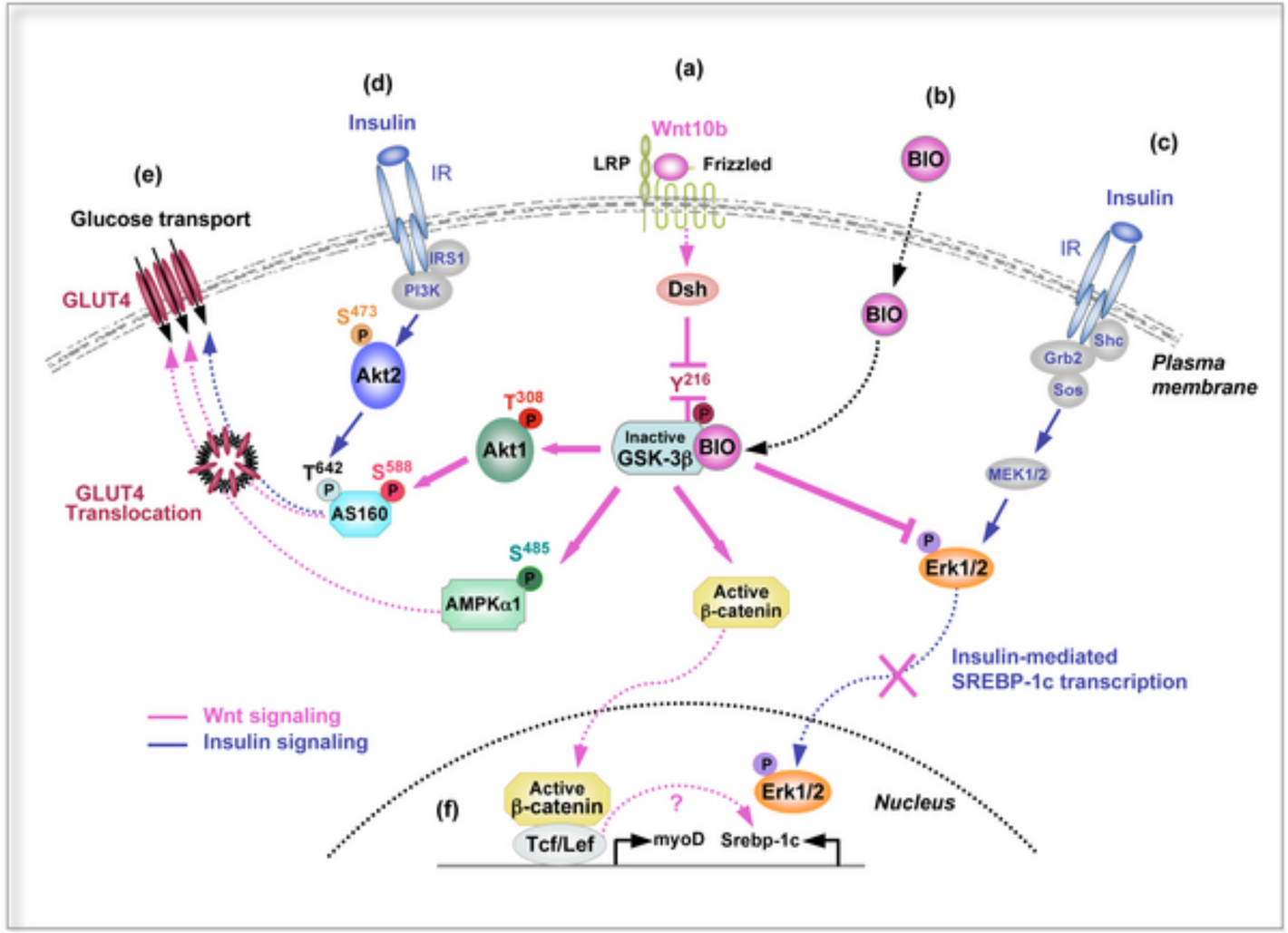

Sun ignites
Earth
Moon
Atmospheric oxygen
Prokaryotes
cells without nuclei
Photosyntesis
Eukaryotes
cells with nuclei
Bacteria
Protozoa
Sponges and fungi
Corals
Cambrian explosion
echinoderms
worms
moluscs
arthropods
jellyfish
myriapodes
crustaceans
aracnids
Tetrapods
Insects
Anfibians
Sharks
Fish
vertebrates
pikaia gracilens
Insect fly
Reptiles
Dinosaurs
Archaeopteryx
Birds
Mammals
Morganucodon
Flowers and bees
Billion years ago
0,0043 Ardipithecus ramidus
0.0002 homo sapiens
0.00001 writing
0.01 primates
0.001 fire
0,01
0,005
0,001

Information exchange in living systems

Signaling pathway (signal transmission chain)

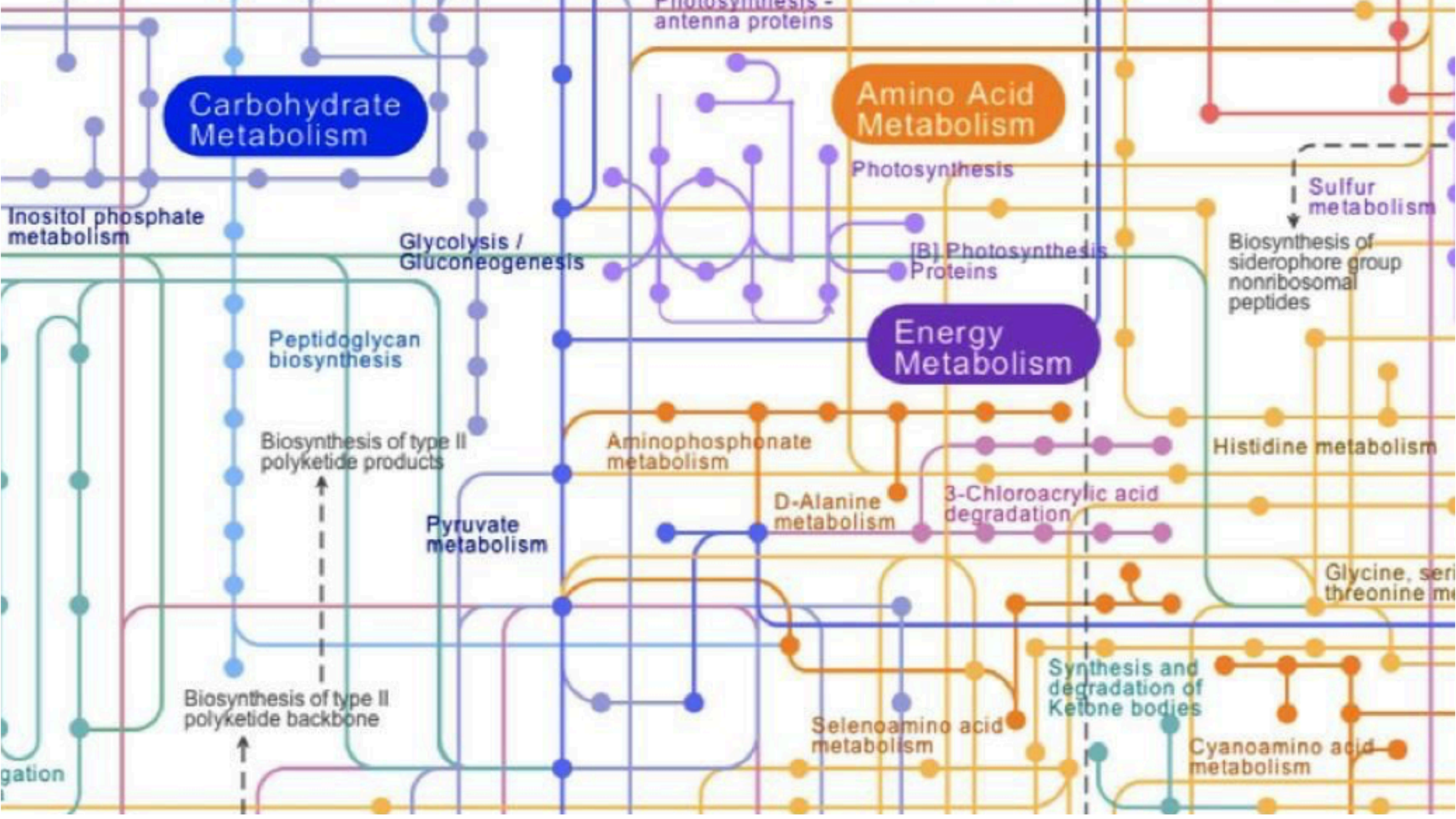
- Set of sequential reactions
- The probability of interruption at any stage of execution
- Possibility to loop the reaction cycle
- Providing a fast and delayed response
  - milliseconds to activate ion channels
  - minutes to activate secondary and tertiary intermediaries
  - hours or days to change gene expression
- Amplification or reduction of a signal





(L) Scheme of the canonical Wnt path

(R) Scheme of changes in the sensitivity of the insulin signaling pathway from the Wnt pathway¶


Photosynthesis - antenna proteins
Carbohydrate Metabolism
Amino Acid Metabolism
Photosynthesis
Sulfur metabolism
Inositol phosphate metabolism
Glycolysis / Gluconeogenesis
[B] Photosynthesis Proteins
Biosynthesis of siderophore group nonribosomal peptides
Energy Metabolism
Peptidoglycan biosynthesis
Biosynthesis of type II polyketide products
Aminophosphonate metabolism
Histidine metabolism
D-Alanine metabolism
3-Chloroacrylic acid degradation
Pyruvate metabolism
Glycine, seri threonine me
Synthesis and degradation of Ketone bodies
Biosynthesis of type II polyketide backbone
Selenoamino acid metabolism
Cyanoamino acid metabolism
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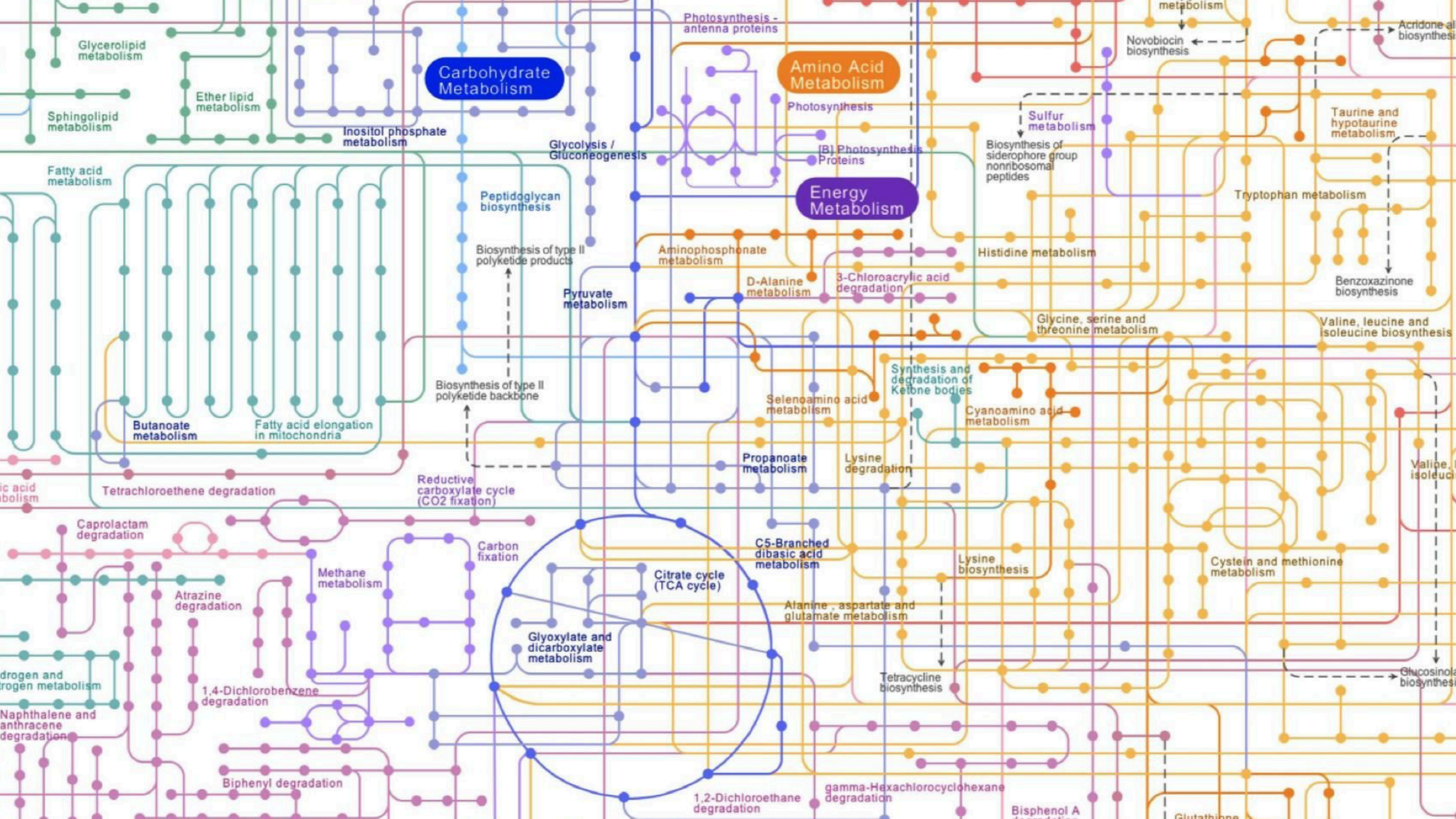
Carbohydrate Metabolism
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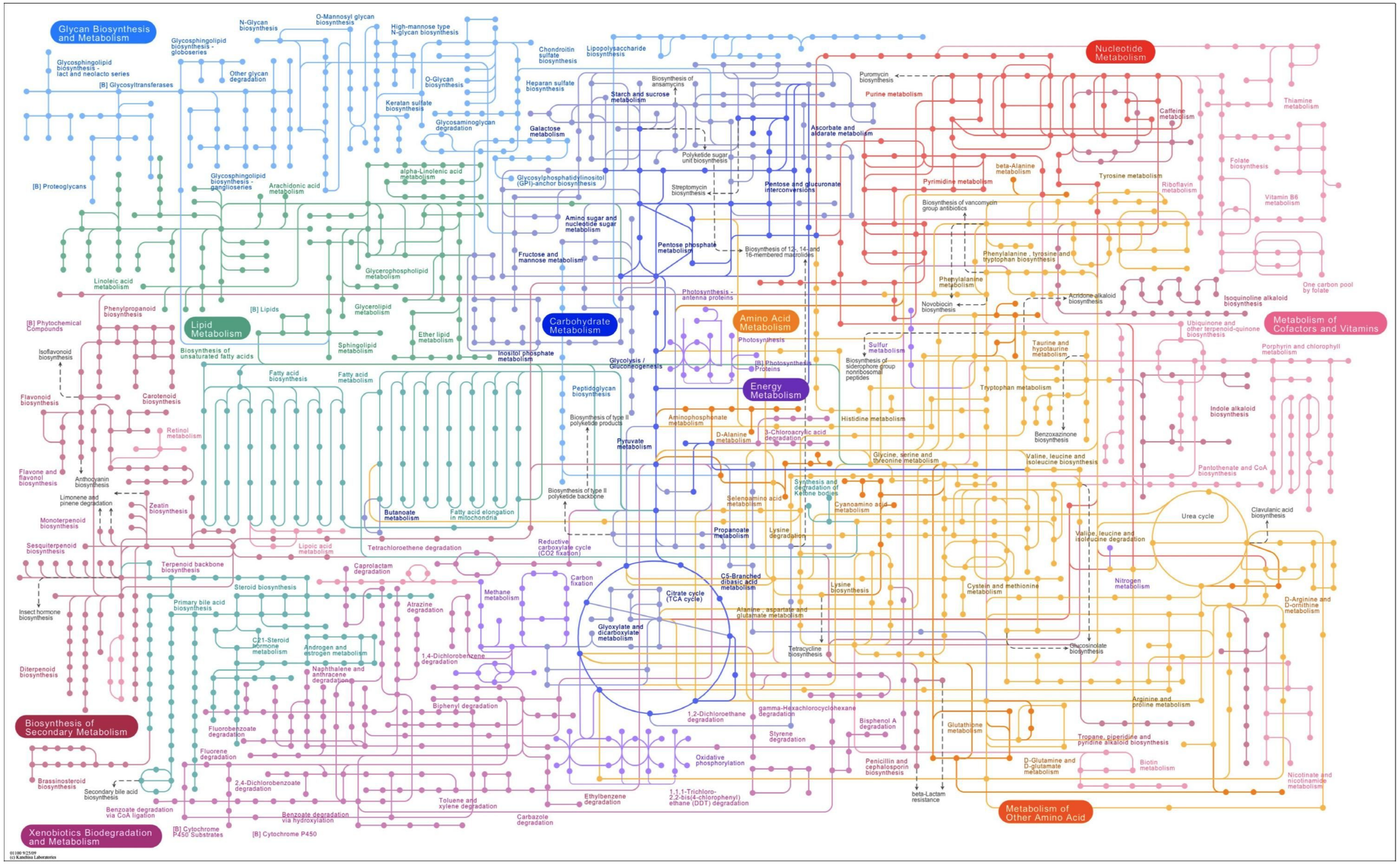
Taurine and hypotaurine metabolism
Tryptophan metabolism
Benzoxazinone biosynthesis
Glycine, serine and threonine metabolism
Valine, leucine and isoleucine biosynthesis
Synthesis and degradation of Ketone bodies
Selenoamino acid metabolism
Cyanoamino acid metabolism
Butanoate metabolism
Fatty acid elongation in mitochondria
Propanoate metabolism
Lysine degradation
Tetrachloroethene degradation
Reductive carboxylate cycle (CO2 fixation)
Caprolactam degradation
Carbon fixation
Methane metabolism
Atrazine degradation
Citrate cycle (TCA cycle)
C5-Branched dibasic acid metabolism
Lysine biosynthesis
Cystein and methionine metabolism
Alanine , aspartate and glutamate metabolism
Glyoxylate and dicarboxylate metabolism
Tetracycline biosynthesis
1,4-Dichlorobenzene degradation
Naphthalene and anthracene degradation
Biphenyl degradation
1,2-Dichloroethane degradation
gamma-Hexachlorocyclohexane degradation
Bisphenol A


Glycan Biosynthesis and Metabolism
Lipid Metabolism
Carbohydrate Metabolism
Amino Acid Metabolism
Energy Metabolism
Nucleotide Metabolism
Metabolism of Cofactors and Vitamins
Metabolism of Other Amino Acid
Biosynthesis of Secondary Metabolism
Xenobiotics Biodegradation and Metabolism
N-Glycan biosynthesis
O-Mannosyl glycan biosynthesis
High-mannose type N-glycan biosynthesis
Glycosphingolipid biosynthesis - globoseries
Glycosphingolipid biosynthesis - lact and neolacto series
[B] Glycosyltransferases
Other glycan degradation
O-Glycan biosynthesis
Keratan sulfate biosynthesis
Glycosaminoglycan degradation
Chondroitin sulfate biosynthesis
Lipopolysaccharide biosynthesis
Heparan sulfate biosynthesis
Biosynthesis of ansamycins
Starch and sucrose metabolism
Galactose metabolism
Ascorbate and aldarate metabolism
Polyketide sugar unit biosynthesis
Streptomycin biosynthesis
Pentose and glucuronate interconversions
Pentose phosphate metabolism
Biosynthesis of 12-, 14- and 16-membered macrolides
Amino sugar and nucleotide sugar metabolism
Fructose and mannose metabolism
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis
alpha-Linolenic acid metabolism
Arachidonic acid metabolism
Glycosphingolipid biosynthesis - ganglioseries
[B] Proteoglycans
Glycerophospholipid metabolism
Linoleic acid metabolism
Glycerolipid metabolism
[B] Lipids
Phenylpropanoid biosynthesis
[B] Phytochemical Compounds
Isoflavonoid biosynthesis
Biosynthesis of unsaturated fatty acids
Sphingolipid metabolism
Ether lipid metabolism
Inositol phosphate metabolism
Fatty acid biosynthesis
Fatty acid metabolism
Flavonoid biosynthesis
Carotenoid biosynthesis
Retinol metabolism
Flavone and flavonol biosynthesis
Anthocyanin biosynthesis
Limonene and pinene degradation
Zeatin biosynthesis
Monoterpenoid biosynthesis
Sesquiterpenoid biosynthesis
Terpenoid backbone biosynthesis
Steroid biosynthesis
Primary bile acid biosynthesis
Insect hormone biosynthesis
C21-Steroid hormone metabolism
Androgen and estrogen metabolism
Diterpenoid biosynthesis
Naphthalene and anthracene degradation
Brassinosteroid biosynthesis
Secondary bile acid biosynthesis
Benzoate degradation via CoA ligation
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Benzoate degradation via hydroxylation
[B] Cytochrome P450
Toluene and xylene degradation
Carbazole degradation
Ethylbenzene degradation
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1,2-Dichloroethane degradation
gamma-Hexachlorocyclohexane degradation
Styrene degradation
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Lysine biosynthesis
Tetracycline biosynthesis
Bisphenol A degradation
Penicillin and cephalosporin biosynthesis
beta-Lactam resistance
Puromycin biosynthesis
Purine metabolism
Caffeine metabolism
Thiamine metabolism
beta-Alanine metabolism
Pyrimidine metabolism
Tyrosine metabolism
Folate biosynthesis
Riboflavin metabolism
Vitamin B6 metabolism
Biosynthesis of vancomycin group antibiotics
Phenylalanine, tyrosine and tryptophan biosynthesis
Phenylalanine metabolism
One carbon pool by folate
Novobiocin biosynthesis
Acridone alkaloid biosynthesis
Isoquinoline alkaloid biosynthesis
Ubiquinone and other terpenoid-quinone biosynthesis
Porphyrin and chlorophyll metabolism
Sulfur metabolism
Taurine and hypotaurine metabolism
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Tryptophan metabolism
Indole alkaloid biosynthesis
Benzoxazinone biosynthesis
Glycine, serine and threonine metabolism
Valine, leucine and isoleucine biosynthesis
Pantothenate and CoA biosynthesis
Urea cycle
Clavulanic acid biosynthesis
Valine, leucine and isoleucine degradation
Nitrogen metabolism
Cystein and methionine metabolism
D-Arginine and D-ornithine metabolism
Glucosinolate biosynthesis
Arginine and proline metabolism
Glutathione metabolism
Tropane, piperidine and pyridine alkaloid biosynthesis
D-Glutamine and D-glutamate metabolism
Biotin metabolism
Nicotinate and nicotinamide metabolism
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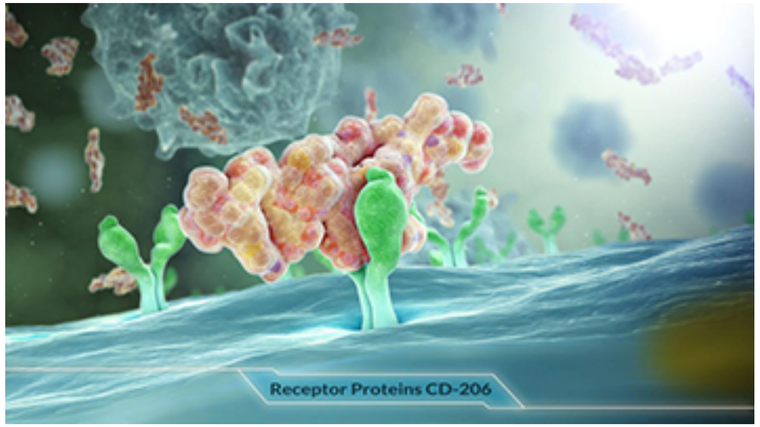
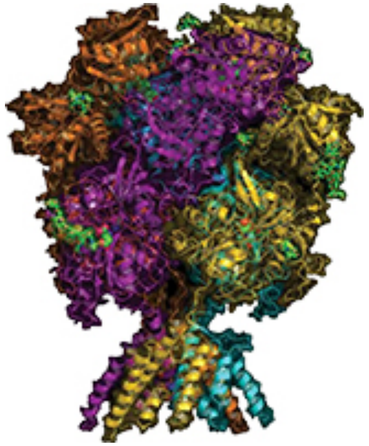
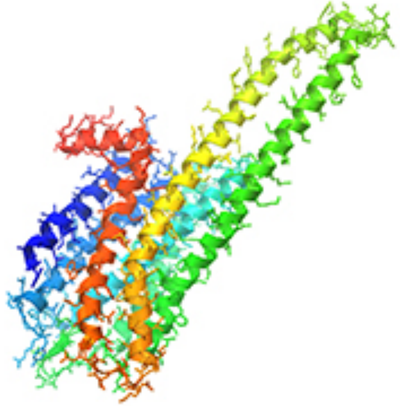
(c) Kanehisa Laboratories

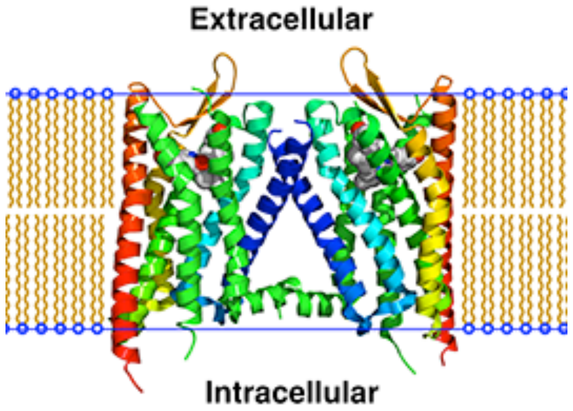
Receptor - effector

- The membrane is an insurmountable obstacle for most molecules
- The membrane receptor is a mechanism for transferring information "outside" →"inside" (your cell's API)
- The receptor supports "authentication" and "authorisation"



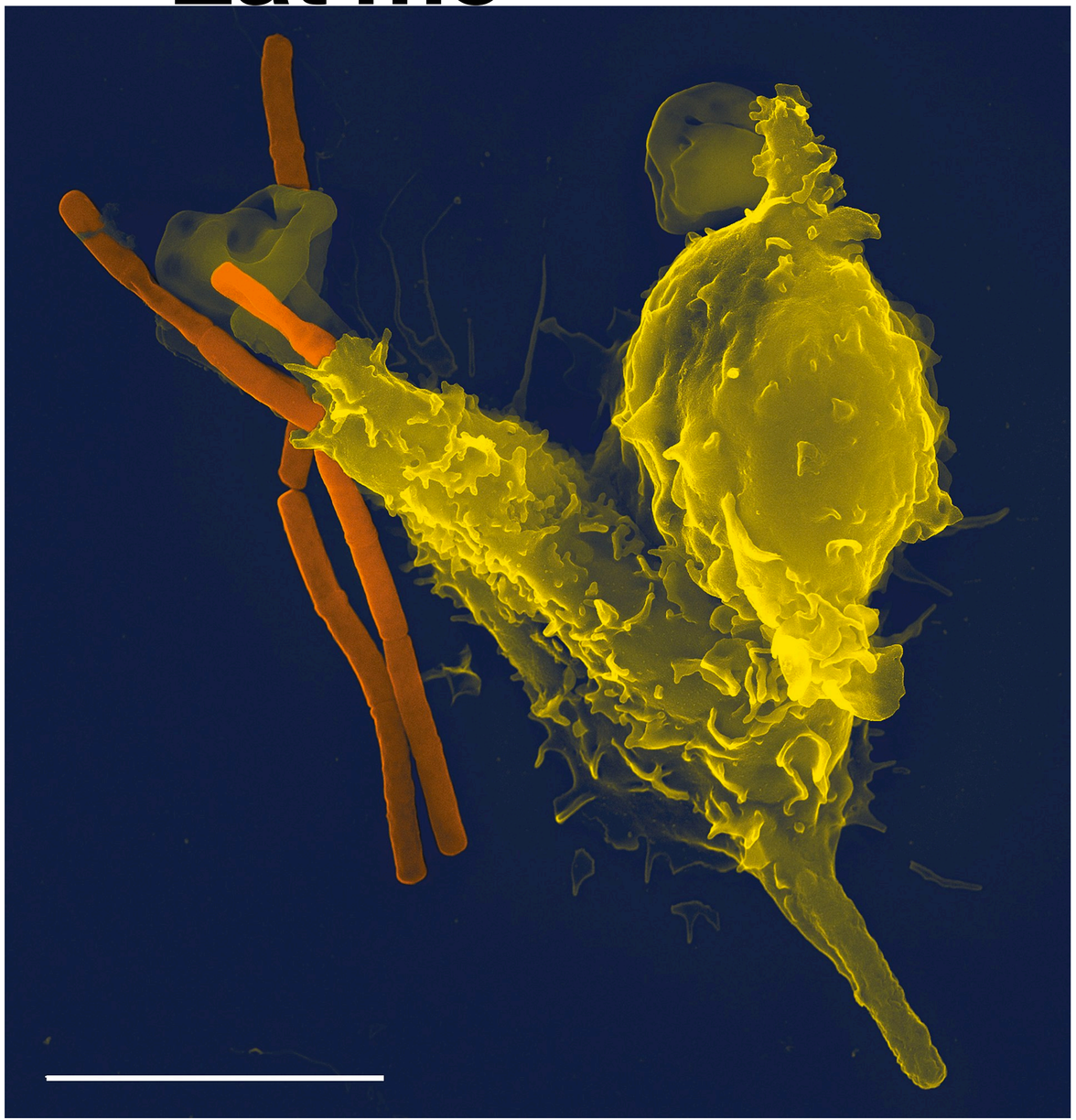


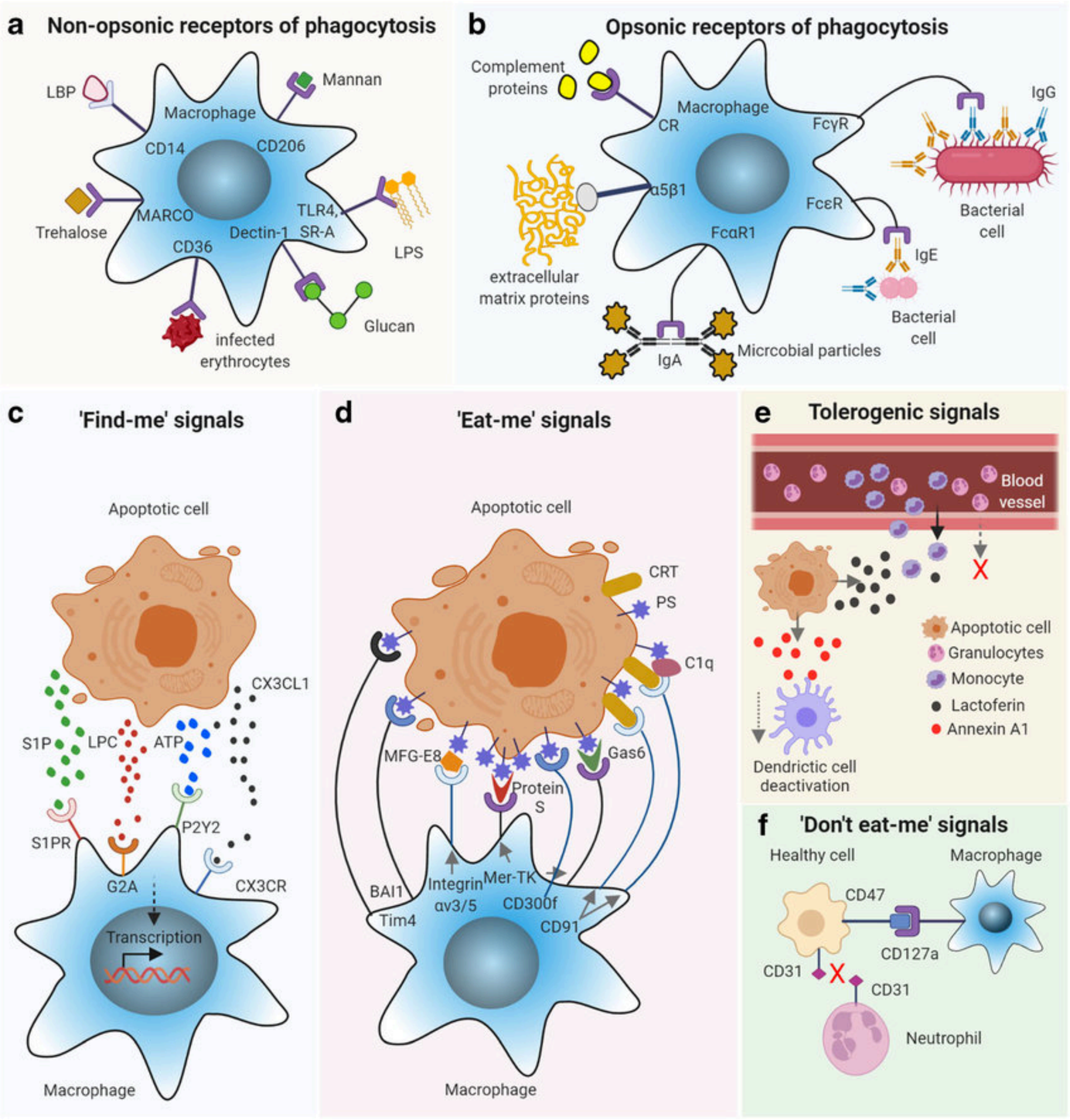




🖼️ (1) Mannose receptor on the surface of macrophages and dendritic cells
(2) NMDA receptor (3) 5HT2A receptor (4) k-opioid receptor

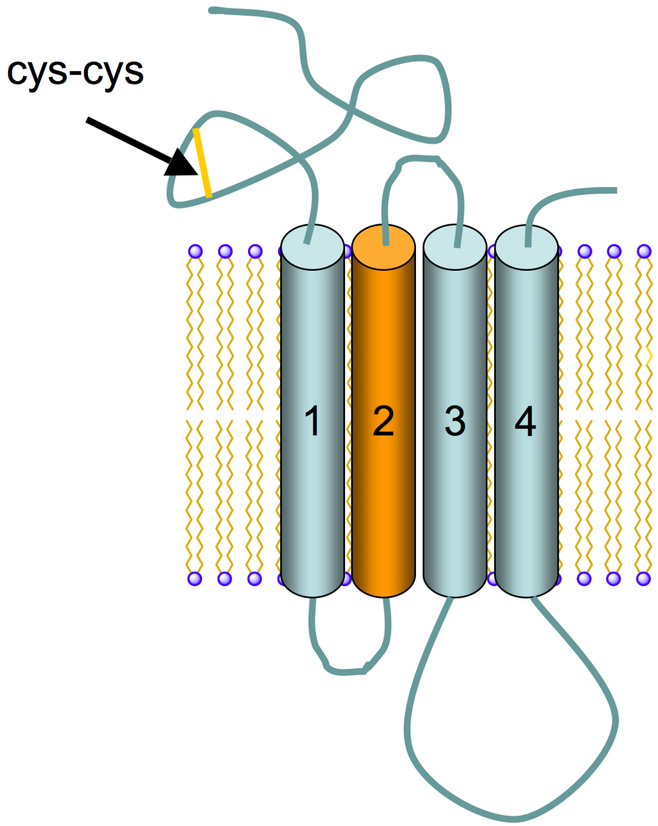
“Eat me”

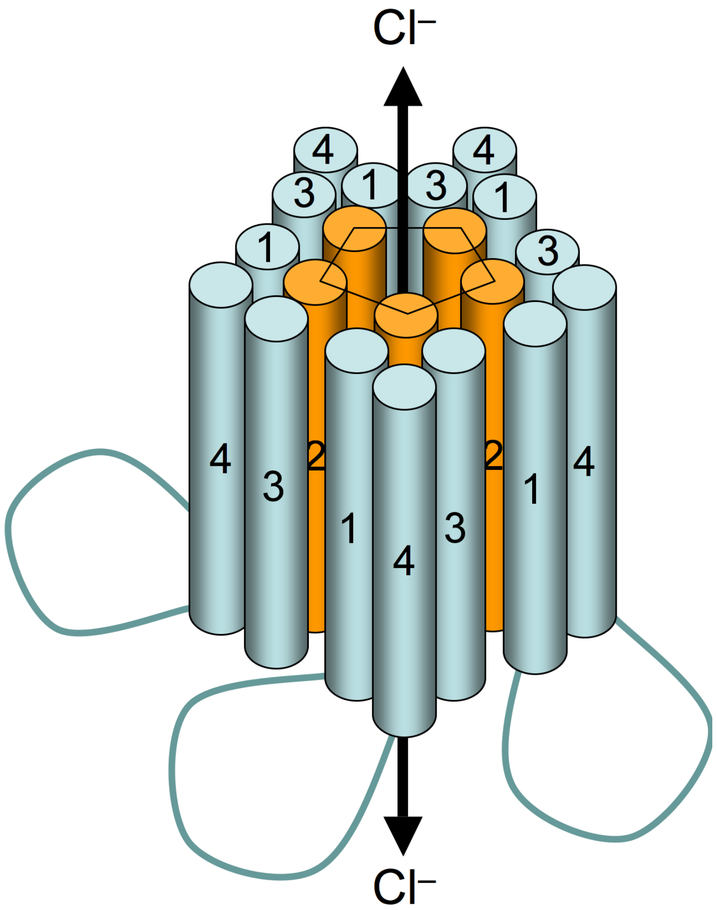



a Non-opsonic receptors of phagocytosis
LBP
Mannan
Macrophage
CD14
CD206
Trehalose
MARCO
TLR4, SR-A
Dectin-1
CD36
LPS
Glucan
infected erythrocytes
b Opsonic receptors of phagocytosis
Complement proteins
Macrophage
CR
FcγR
IgG
α5β1
FcεR
FcαR1
Bacterial cell
extracellular matrix proteins
IgE
Bacterial cell
IgA
Micrcobial particles
c 'Find-me' signals
Apoptotic cell
CX3CL1
S1P
LPC
ATP
S1PR
P2Y2
G2A
CX3CR
Transcription
Macrophage
d 'Eat-me' signals
Apoptotic cell
CRT
PS
C1q
MFG-E8
Gas6
Protein S
BAI1
Integrin αv3/5
Mer-TK
CD300f
Tim4
CD91
Macrophage
e Tolerogenic signals
Blood vessel
Apoptotic cell
Granulocytes
Monocyte
Lactoferin
Annexin A1
Dendrictic cell deactivation
f 'Don't eat-me' signals
Healthy cell
Macrophage
CD47
CD127a
CD31
CD31
Neutrophil

Membrane receptor

- The membrane receptor is a protein complex
- Consists of transmembrane domains
- Complexes of transmembrane domains form ligand binding sites
- There are endogenous and exogenous receptor ligands
- The attached ligand can cause reversible or irreversible changes in the receptor conformation
- Receptors have their own activity
- Can be blocked by inverse agonists (blockers)
- Are subject to allosteric modifications (reversible or irreversible)
- Can break, internalize, desensitize
- Receptors interface with: ion channel (ionotropic); G protein (metabotropic); enzyme (enzyme-coupled)

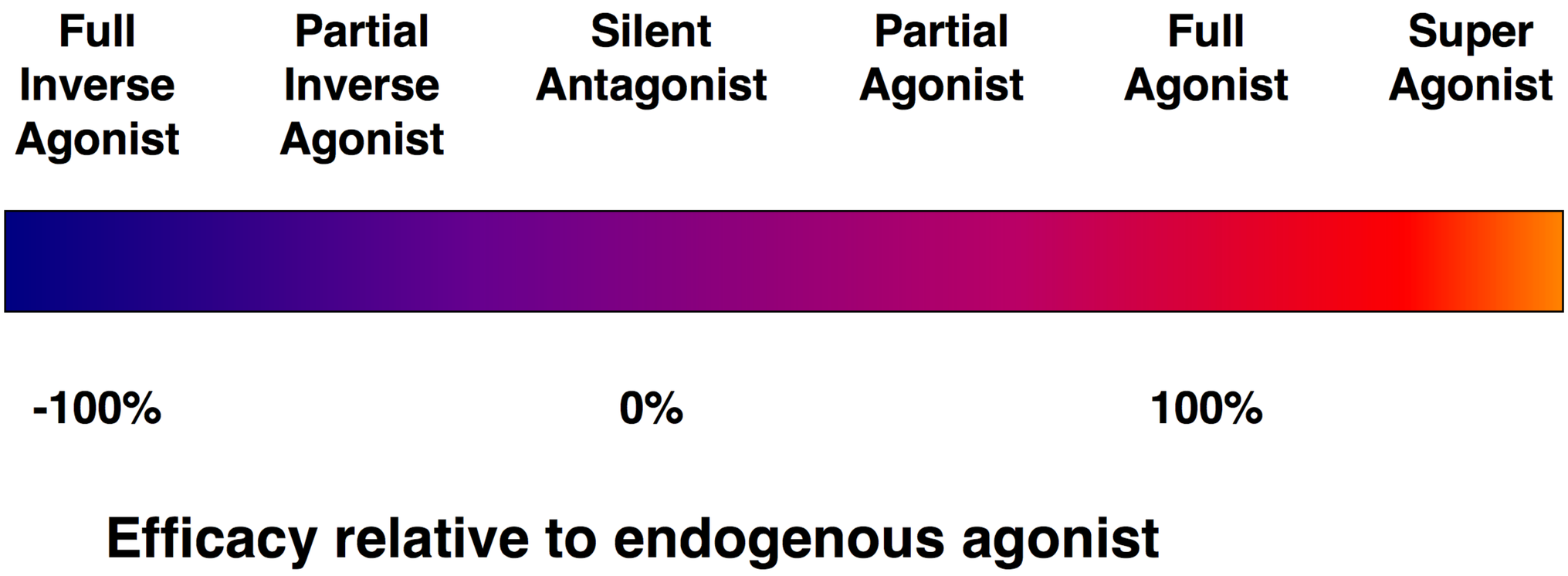




Ionotropic $GABA_A$-receptor

Membrane receptor → Agonism

- Agonist is a substance that, when interacting with a receptor, changes its state, leading to a biological response
- The activity of the agonist towards the receptor determines the end result
- In the absence of a ligand, the receptor has its own neutral activity

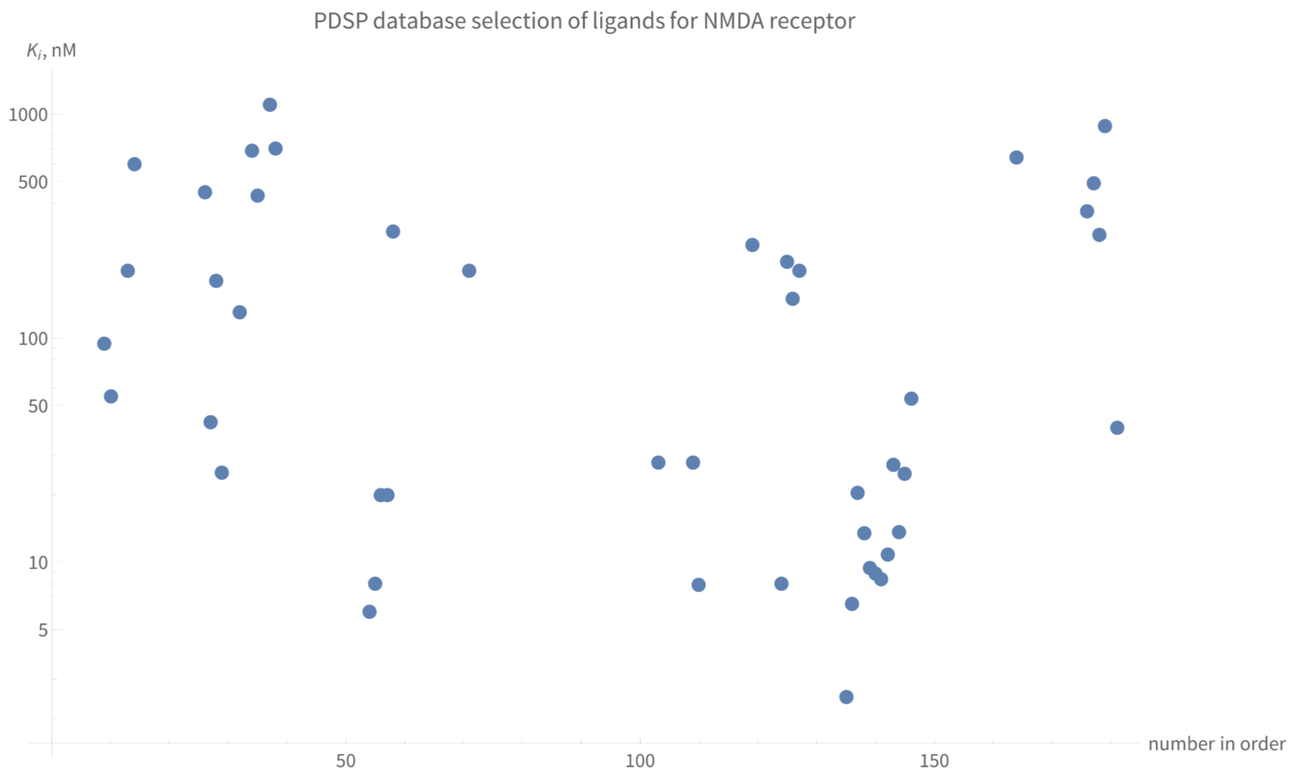


Membrane receptor → Affinity

- K_i is inhibition constant, coefficient characterizing the affinity of a ligand for a cell receptor or another protein or DNA
- K_i is expressed in moles and characterizes the concentration of the ligand if it is connected to half of the available receptors in the equilibrium state of the system
- The lower the K_i - the greater the affinity for the receptor this ligand has
- K_i characterizes the strength of the action (including the time during which the receptor will be occupied by the ligand), but does not characterize the modality of this strength (inhibition or activation of the receptor)
- K_d is dissociation constant, measures equilibrium between the ligand-protein complex and the dissociated components
- K_d is an inverse of K_i

$$\mathrm{L} + \mathrm{P} \rightleftharpoons \mathrm{LP}$$

$$K_d = \frac{[\mathrm{L}]\,[\mathrm{P}]}{[\mathrm{LP}]}$$



Receptor states

- Many receptors function as ligand-dependent channels for Na^+, K^+, Ca^{2+} ions
- In the absence of a ligand, a relatively small amount of ions is passed (neutral activity)
- A certain number of ligand molecules are required to transfer the receptor to an activated state
- Ligand can both attach and detach from the receptor
- When the ligand is bound to the desired binding sites, there is a possibility of both the activation of the receptor and the transition to a state of insensitivity (does not allow ions to pass)

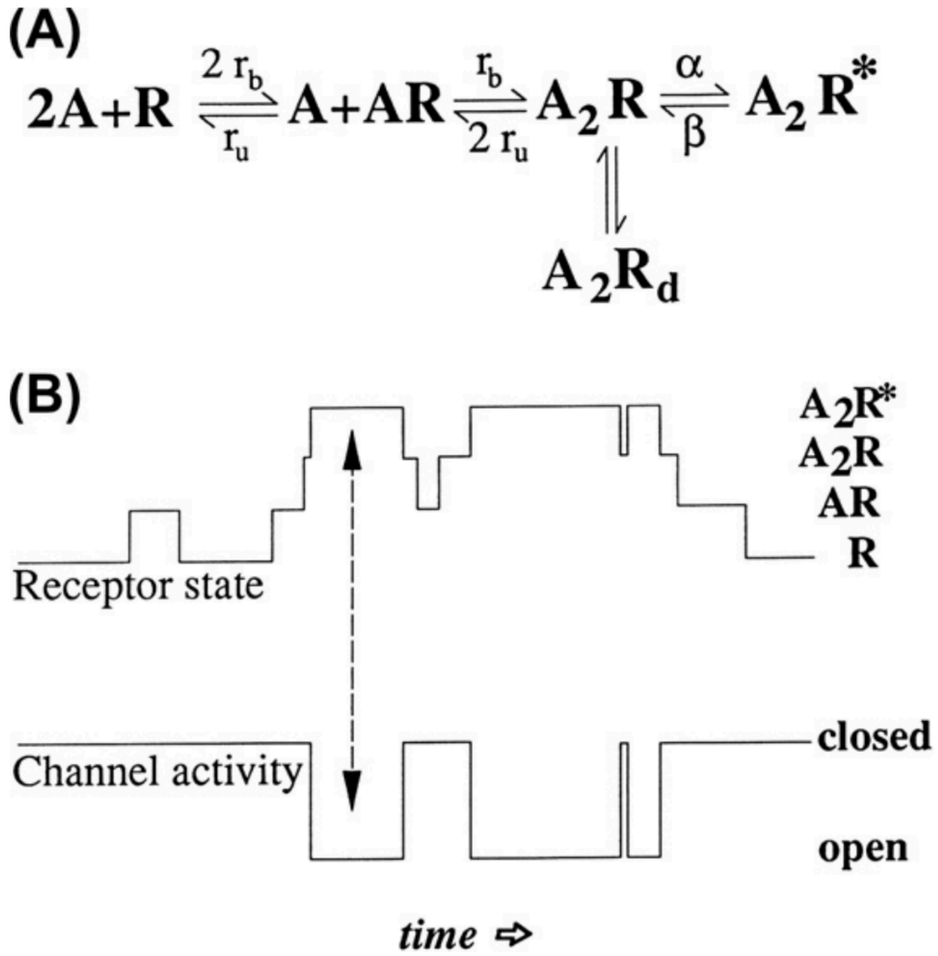
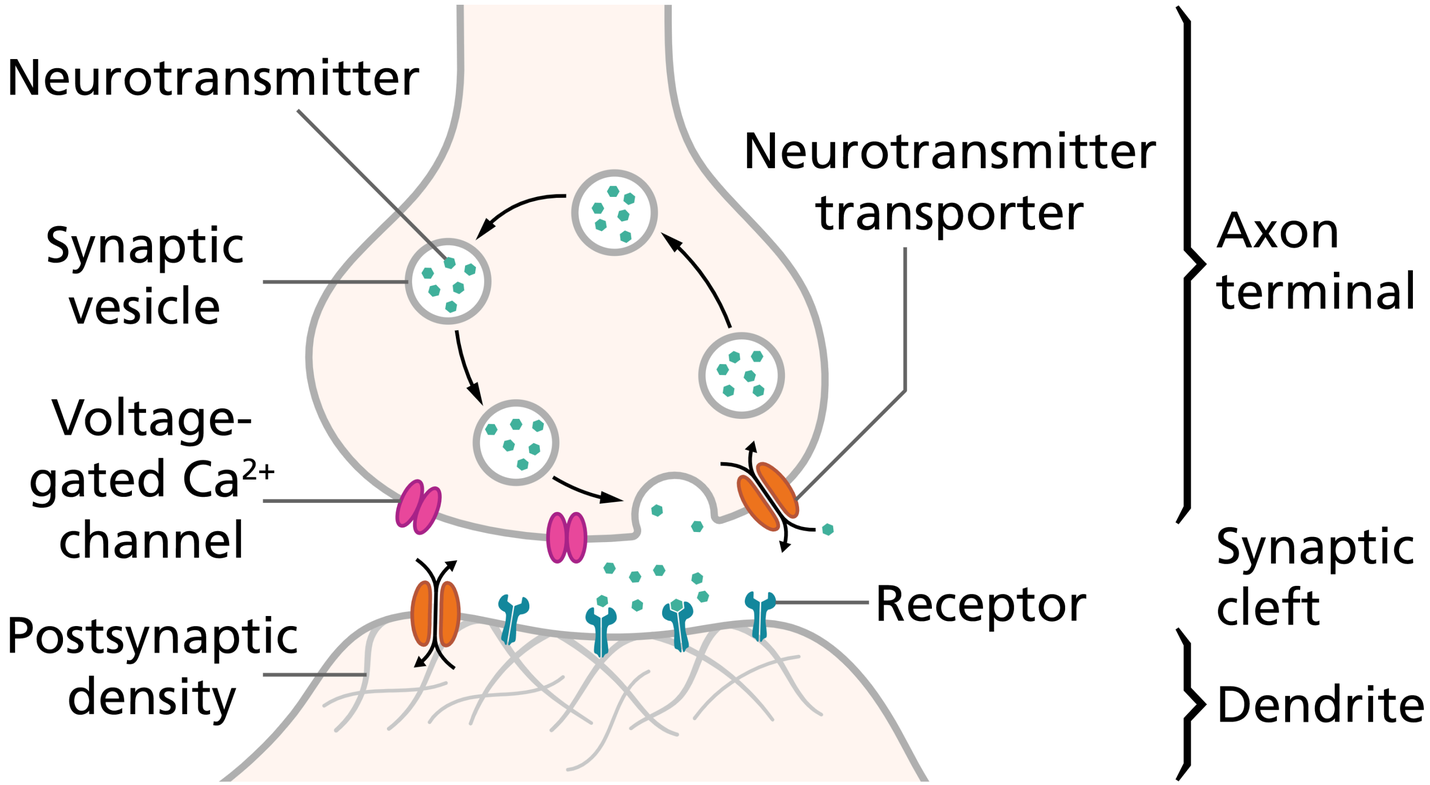


FIGURE 31.2 Kinetics of ligand-gated channels. (A) Example of a four-state kinetic scheme used to describe the behavior of ligand-gated ion channels. In this example, two agonist molecules (A) must bind before the channel can open (A_2R^*) or enter a non-conducting desensitized state (A_2R_d). The rate constants for agonist binding and unbinding are designated r_b and r_u, and the rate constants for channel opening and closing are designated as β and α. (B) Relationship of the state of the receptor to the open and closing of the channel. The channel opens only when the receptor is in the A_2R^* state as indicated by the arrows.

Neurotransmission

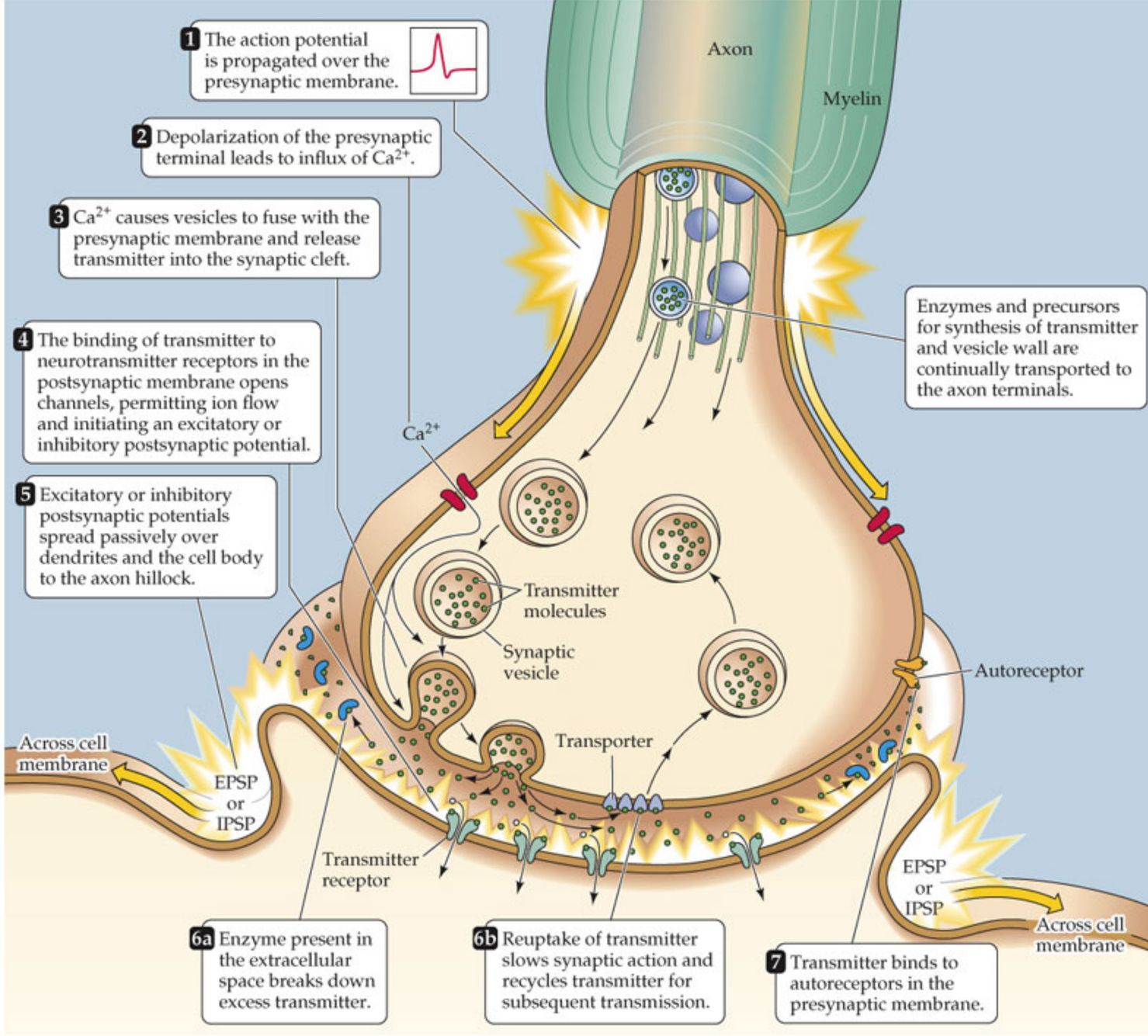
Neurotransmission

Neurotransmission is the process by which signaling molecules called neurotransmitters are released by the axon terminal of a neuron (the presynaptic neuron), and bind to and react with the receptors on the dendrites of another neuron (the postsynaptic neuron) a short distance away.



Chemical synapse

- Chemical synapse - the junction of the axon of a nerve cell with other cells
- The following types of CS are usually distinguished: axodendritic, axosomatic, axoaxonal
- Distance between neurons in CS ~ 20nm
- The small volume of the synaptic cleft allows you to rapidly increase or decrease the concentration of mediators
- The spatial configuration of the synapse is responsible for the "strength" of the connection between neurons
- The synapse is not an isolated space, leaks are possible
- The escape neurotransmitter will act on the bodies and synapses of the surrounding cells (volumetric neurotransmission)
- The receiving cell within one synapse can perceive several different signals, the transmitting cell emits only one signal (specialization of the presynaptic neuron)
- Chemical synapse provides delayed information transmission
- A chemical synapse is much more functional and flexible than an electrical synapse



***THE MIND'S MACHINE 2e*, Figure 3.11**

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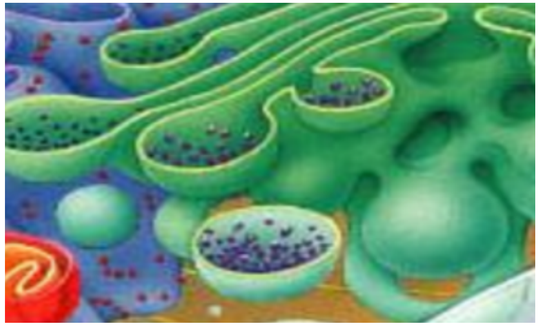
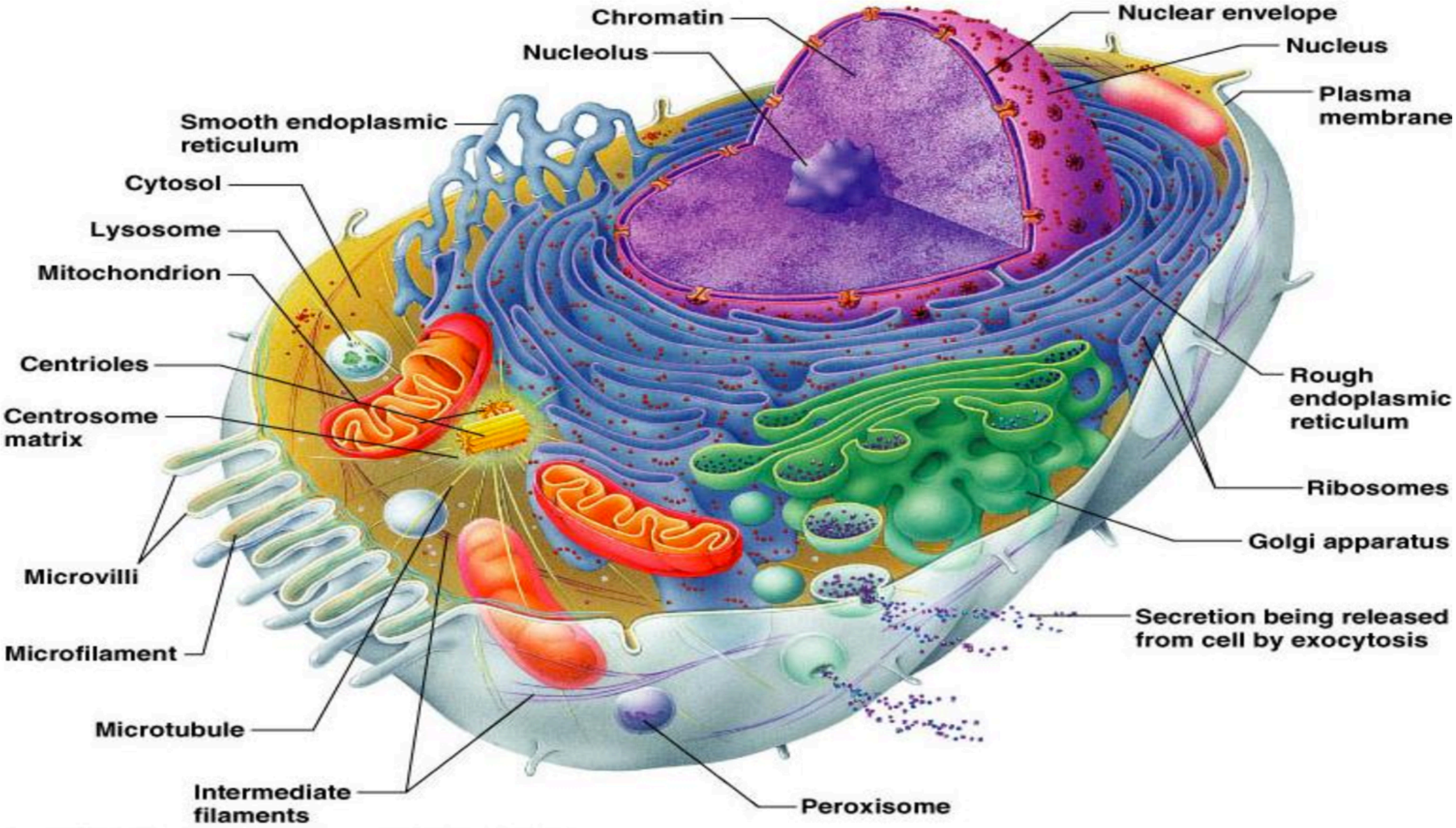
Vesicles and neurotransmitter release

- The cell is a highly organized structural unit of the body
- Vesicle - membrane-protected organelle, storage of nutrients inside the cell
- The cell has an enterprise-level transport system
  - Cytoskeleton
  - Vesicular transport

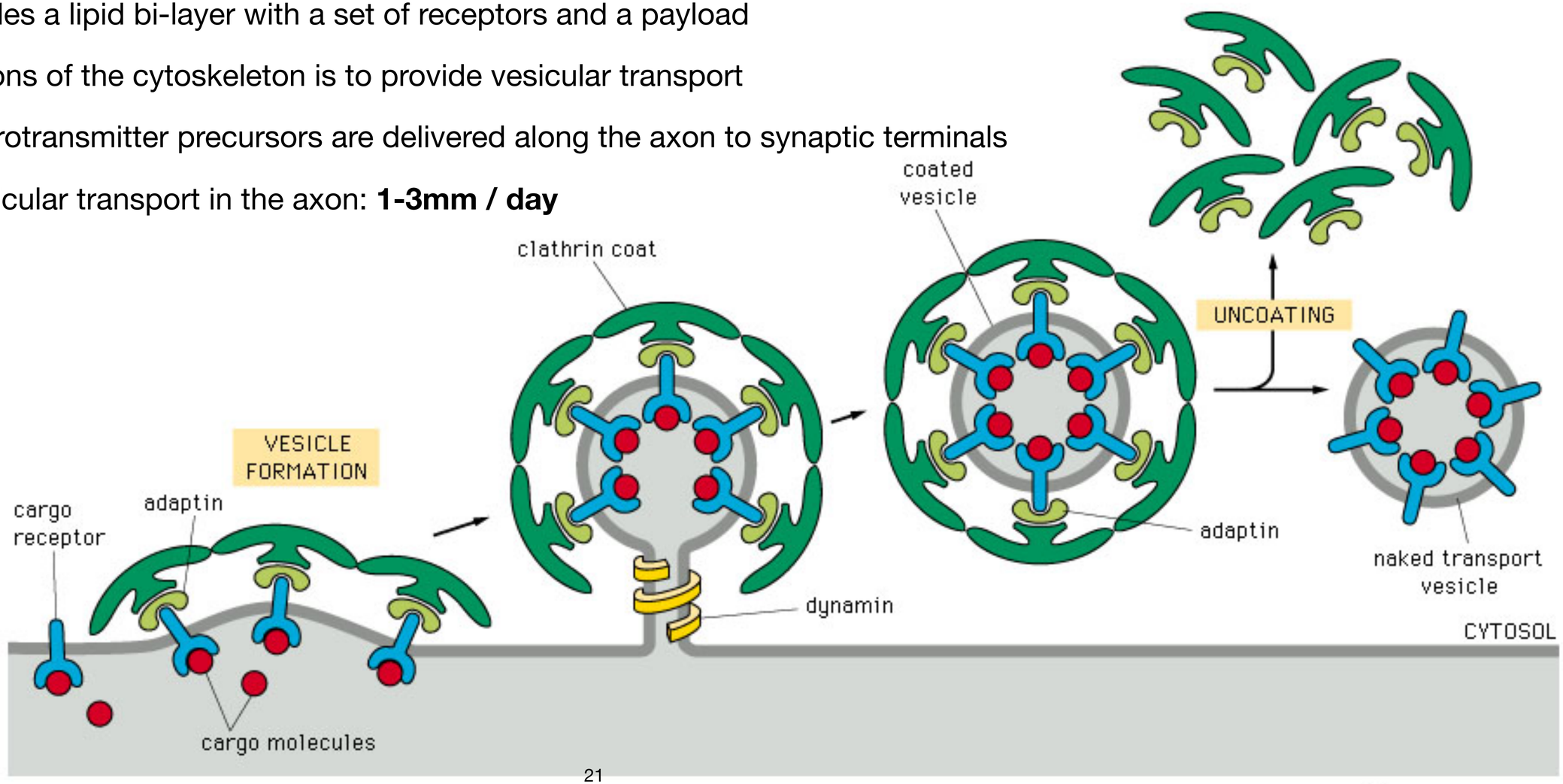


Structure of a Generalized Cell



Vesicular transport

- Vesicle - membrane-protected organelle, storage and carrier of nutrients inside the cell
- The vesicle includes a lipid bi-layer with a set of receptors and a payload
- One of the functions of the cytoskeleton is to provide vesicular transport
- Vesicles with neurotransmitter precursors are delivered along the axon to synaptic terminals
- The speed of vesicular transport in the axon: **1-3mm / day**



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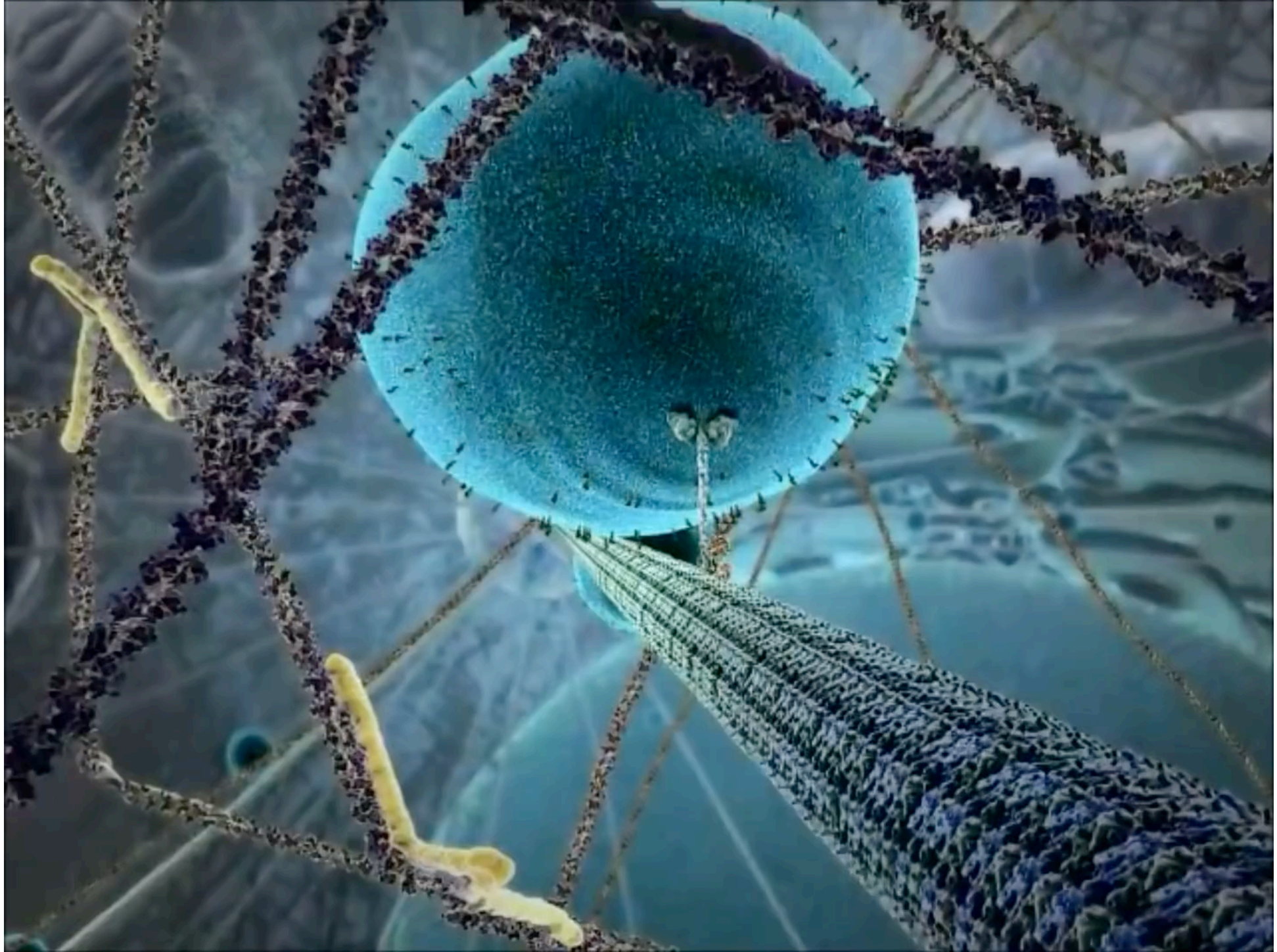
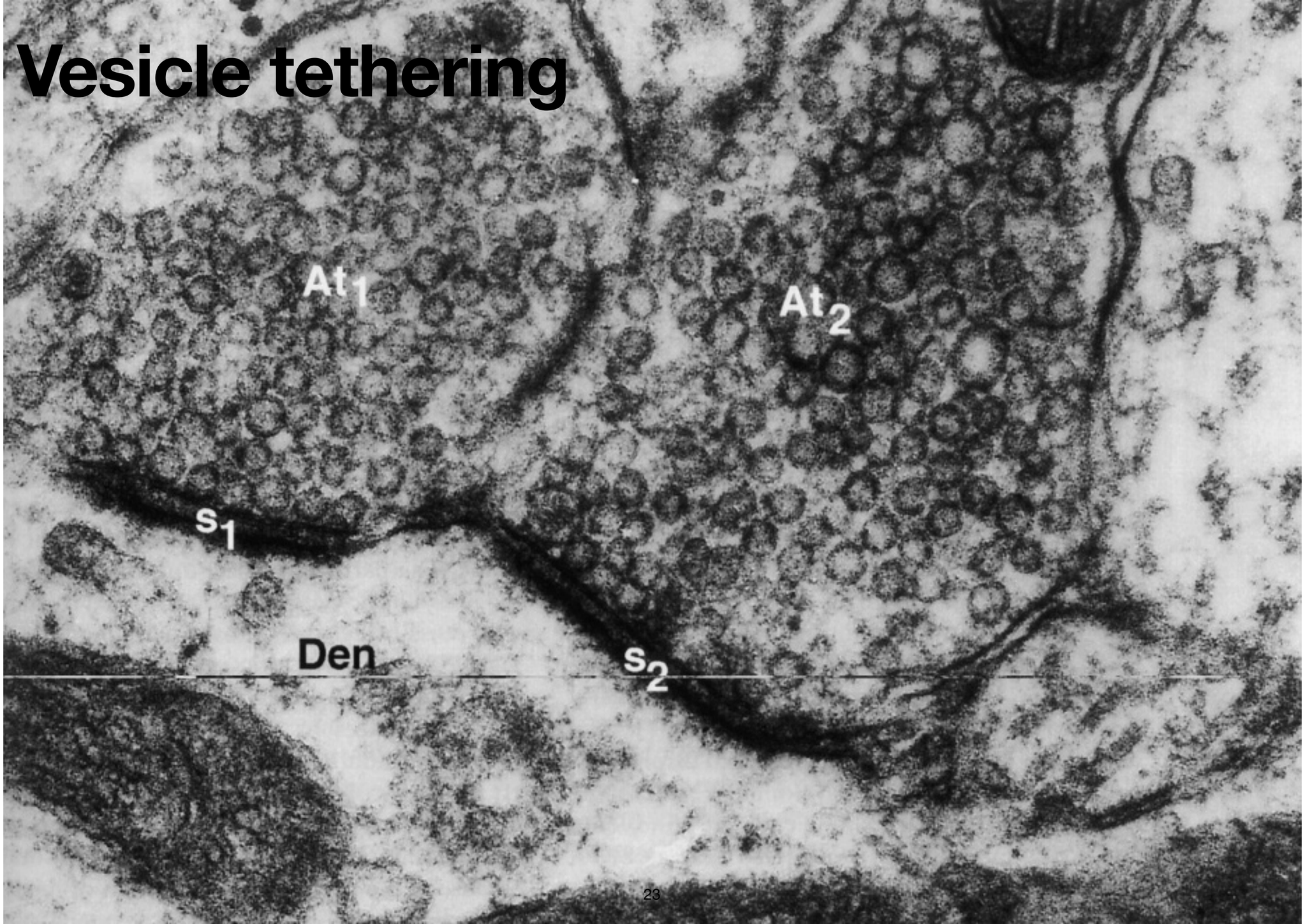
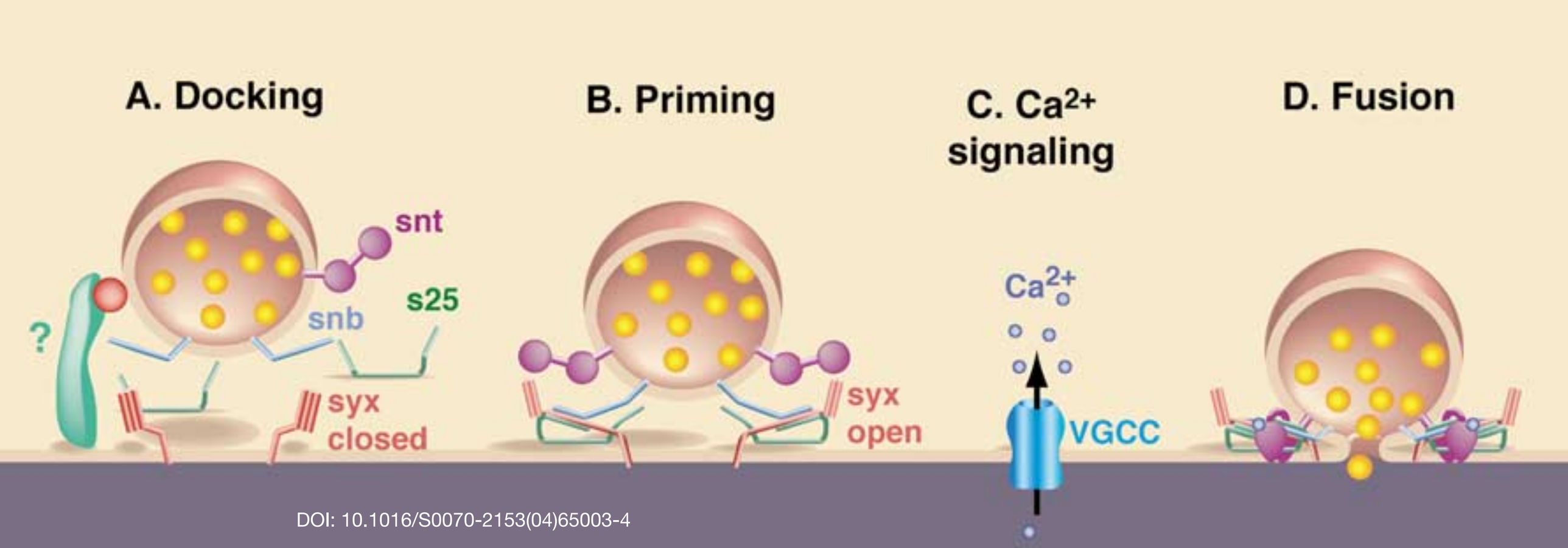


Vesicle tethering



Docking → Priming → Fusion

- **Docking** of an vesicle - a strong connection of protein components of membranes
- Stimulation (**priming**) of vesicles - Ca^{2+}-activated triggering of SNARE protein complex formation
- **Fusion** of the vesicle with the membrane provides the release of the contents of the vesicle into the synaptic space



DOI: 10.1016/S0070-2153(04)65003-4

Synapse electricity

$$I_{synaptic} = N \times P_o \times V_{DF} \times \gamma$$

where N - number of receptors of given type in synapse, P_o - the probability that an agonist bound receptor is open, V_{DF} - electrochemical driving force, γ - conductance of each receptor-channel.

Electrochemical driving force

$$V_{DF} = V_m - V_{eq},$$

where V_m is membrane potential, V_{eq} - equilibrium potential

$$V_{eq}^{Cl^-} = -65mV$$

$$V_{eq}^{Na^+} = +55mV$$

$$V_{eq}^{K^+} = -90mV$$

DOI: 10.1007/s11064-018-2491-1
https://www.physiologyweb.com/lecture_notes/resting_membrane_potential/resting_membrane_potential_electrochemical_driving_force_acting_on_ions.html

Shortest overview of neurotransmitters

- Glutamic acid (glutamate) - ↑ main excitatory neurotransmitter in the CNS
- γ-aminobutyric acid (GABA) - ↓ main inhibitory neurotransmitter in the CNS
- Acetylcholine (ACh) - ↑ muscle tone in the PNS, plasticity, arousal and reward in the CNS
- Monoamines
  - Phenethylamine (PEA) - controller of excretion Ser, DA, NE (TAAR1 signaling)

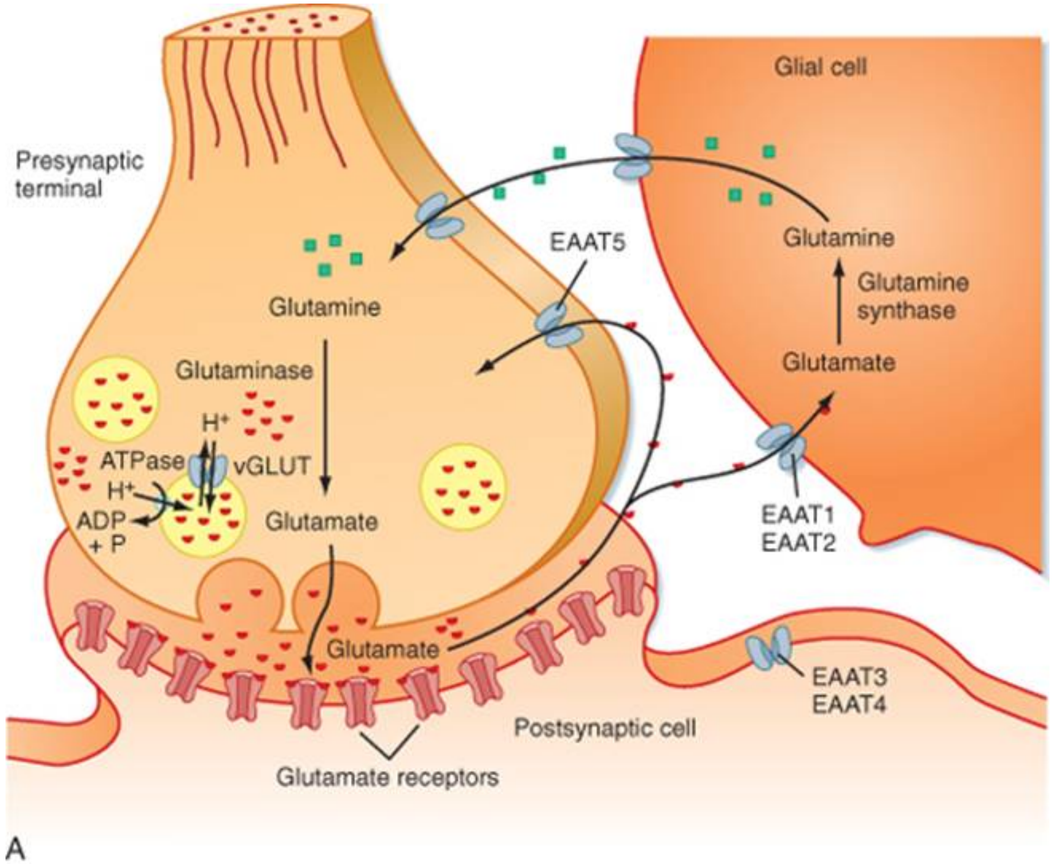
  - Dopamine (DA) - Reinforcement System, Promise of Pleasure
  - Noradrenaline (NE) - "be aware, you may have to hit or run"
  - Adrenaline () - “hit or run”, "fight or flight"

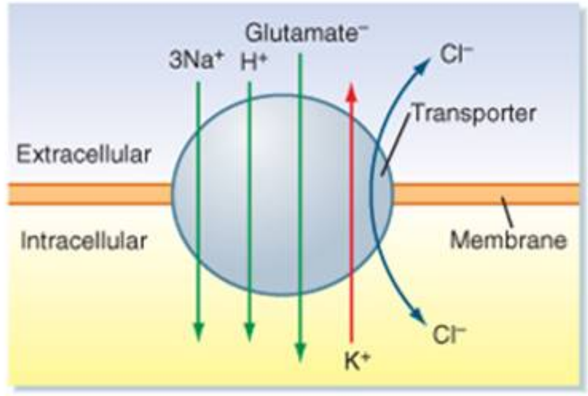
  - Serotonine (Ser) - ~~happiness hormone~~ QoS of the brain
  - Melatonine - circadian rhythm regulation
  - Histamine - participation in the processes of memory and learning (suppression of recall and (re-) consolidation)

- Cannabinoids - Controlling Neurotransmitter Transmission
- Endorphins - pain perception, influence on emotional state

Glutamate

- Glutamic acid is the main *excitatory* mediator of the CNS
- Glutamate is involved not only in *direct*, but also in *volumetric* neurotransmission
- Glutamate *reuptake* is produced by the glia surrounding the synapse
- Excess of glutamate leads to excitotoxicity and neuronal death
- Glutamate receptors: NMDA, AMPA, kainate and a number of metabotropic receptors
- AMPA are fast receptors, NMDA are slow
- AMPA receptor modulators (AMPAkins) are promising NS stimulators without the side effects of traditional stimulants
- NMDA receptors are one of the mechanisms of synaptic plasticity
- Expression of NMDA subunits changes throughout life, which is associated with a deterioration in learning with age





(A): Scheme for the processing of glutamate emitted by the presynaptic terminal. Various glutamate receptors exist on the presynaptic and postsynaptic membranes. Glial cells capture (EAAT1/2) glutamate from being converted to glutamine. After that, glutamine is released and captured (EAAT5) by the presynaptic terminal, where it is converted back to glutamate, packaged into vesicles and reused.

(B): Scheme of the cotransport of ions together with the transport of glutamate through the transporter

Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.
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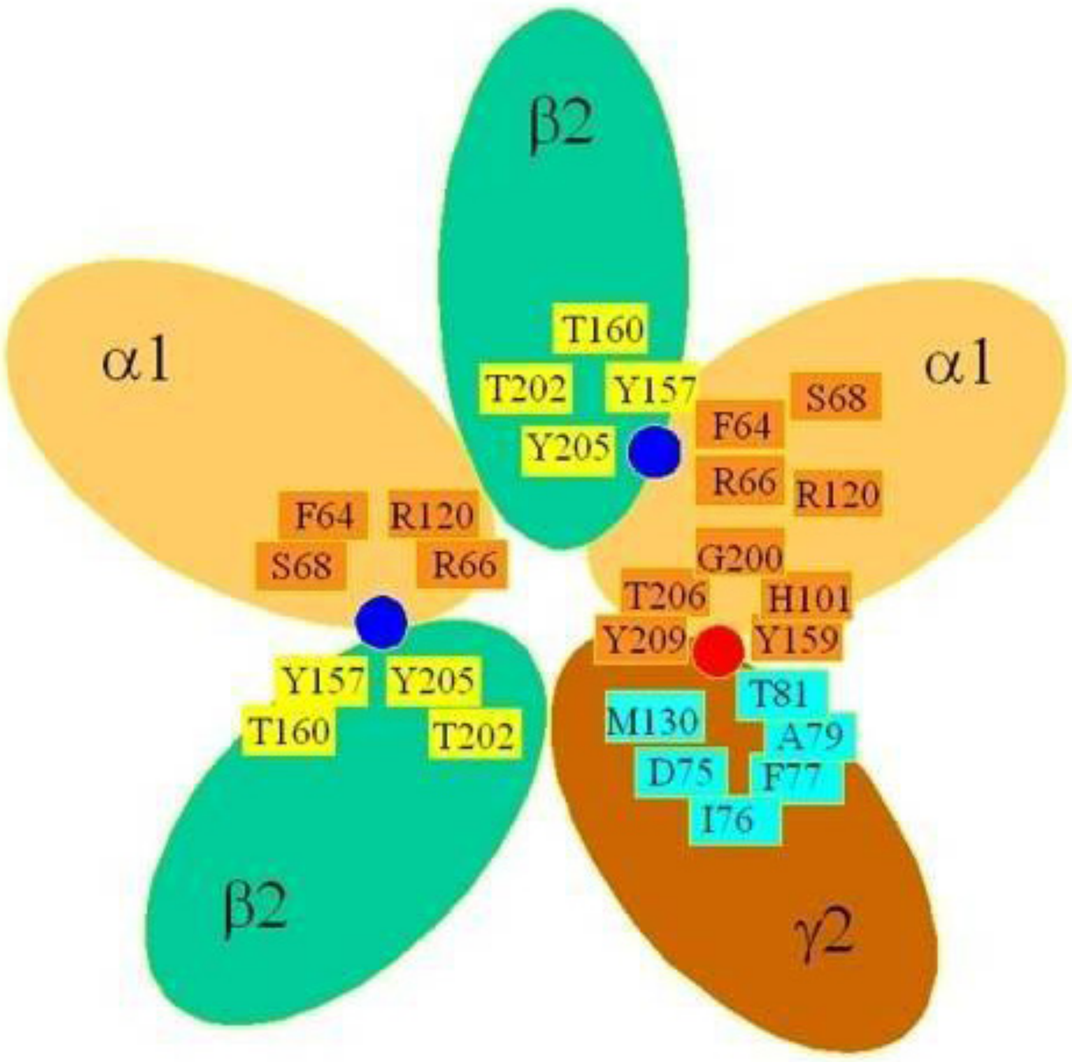
γ-aminobutyric acid (GABA)



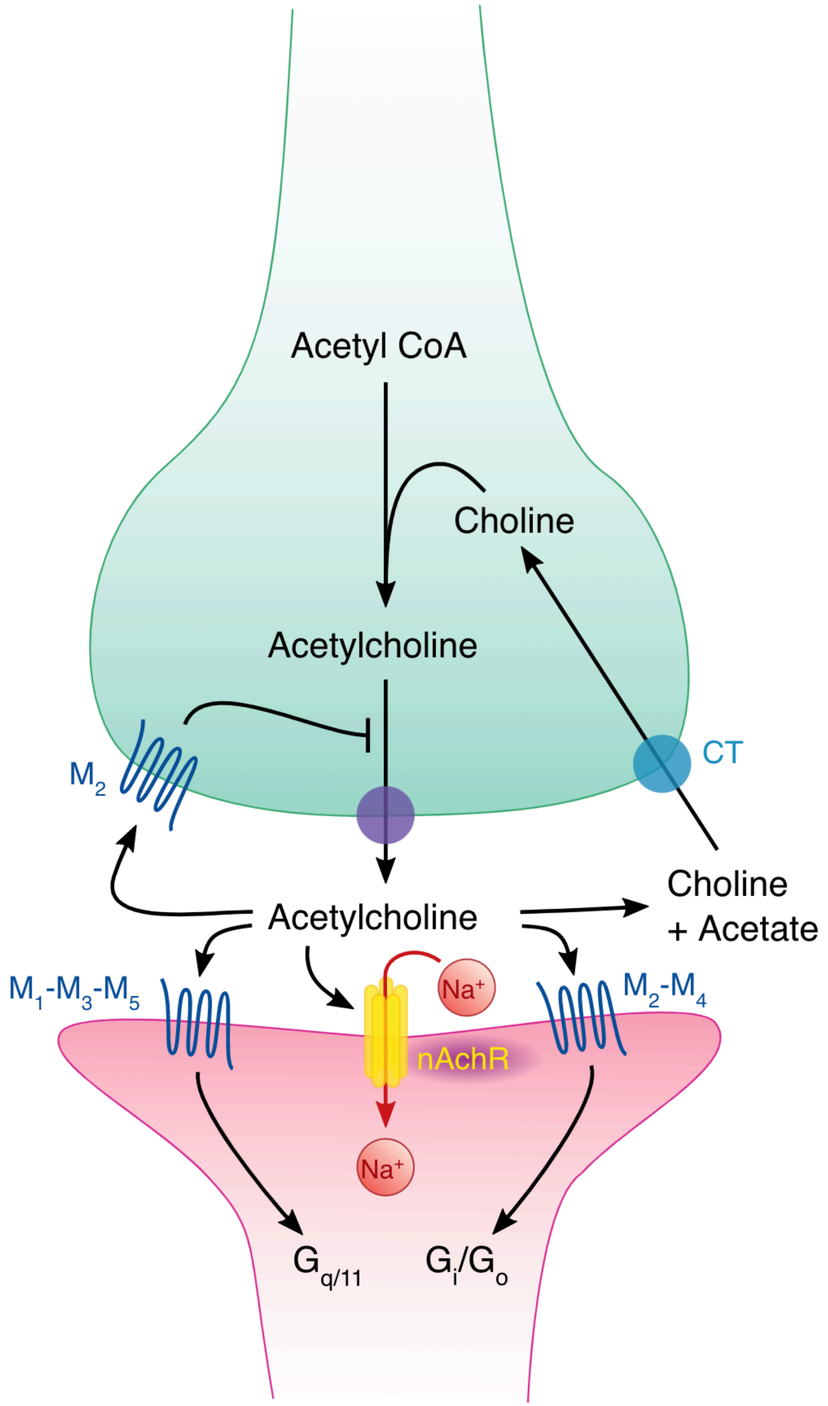
- Gamma-aminobutyric acid - the main inhibitory mediator of the CNS
- GABA was found in the CNS in the mid 50s of the 20th century
- In immature neurons, GABA is an excitatory neurotransmitter (*). As GABA matures, the role of GABA changes
- Receptors for GABA: ionotropic $GABA_A$, $GABA_C$; metabotropic $GABA_B$
- $GABA_A$: fast activation, fast desensitization, low sensitivity
- $GABA_C$: slow activation, slow desensitization, high sensitivity
- Central neurotropic substances (anti/convulsive, hypnotic) act agonist / antagonistically on GABA receptors

Binding sites of GABA and benzodiazepines on the GABAA receptor The pentameric structure of the protein demonstrates the location of the α, β and γ subunits in most GABAA receptors. Agonist binding sites (blue) are formed on the contact surface between subunits of different families, including several amino acid residues of both α and β subunits. Similarly, a single site is formed where benzodiazepines (red) bind between the α and γ subunits. Shown are amino acid residues that are involved in the formation of these binding sites.

* There is a high concentration of Cl^- in immature neurons. Activation of GABA receptors leads to the leakage of chlorine from the neuron → excitatory postsynaptic action potential arises

Acetylcholine

- Acetylcholine is the first discovered neurotransmitter (1915). Nobel Prize 1936
- ACH carries out neuromuscular transmission, the main neurotransmitter in the parasympathetic NS (*)
- ACH is associated with memory functions, with the processes of falling asleep / awakening
- ACh is unstable - AChE rapidly destroys ACh, constant synthesis is required
- Acetylcholine Esterase (AChE) is a specialized enzyme. Vital. AChE inhibitors (**) are powerful toxins whose exposure to the human body usually leads to death from cramps in the respiratory muscles
- Receptors to ACh: ionotropic n-cholinergic receptors; metabotropic: m-cholinergic receptors
- In small doses, ACh is a physiological transmitter of nervous excitement, in large doses it can cause persistent depolarization in the synapse area and block the transmission of excitation



(*) The parasympathetic nervous system innervates the iris, lacrimal gland, submandibular and sublingual glands, parotid gland, lungs and bronchi, heart (decrease in heart rate and strength), esophagus, stomach, large and small intestine (increased secretion of glandular cells). Narrows the pupil, enhances the secretion of the sebaceous and other glands, narrows the coronary vessels, improves peristalsis. The parasympathetic nervous system does not innervate the sweat glands and vessels of the extremities

(**) Organophosphate insecticides, DFP, sarin, soman and V-gases, fasciculin and some other peptides of snake venom

Phenylalanine → Phenylethylamine → Monoamines

- Phenylalanine (Phe) is an essential amino acid
- Phenylethylamine [1-Amino-2-phenylethane] - Phe derivative, monoamine precursor, $TAAR1$ receptor agonist

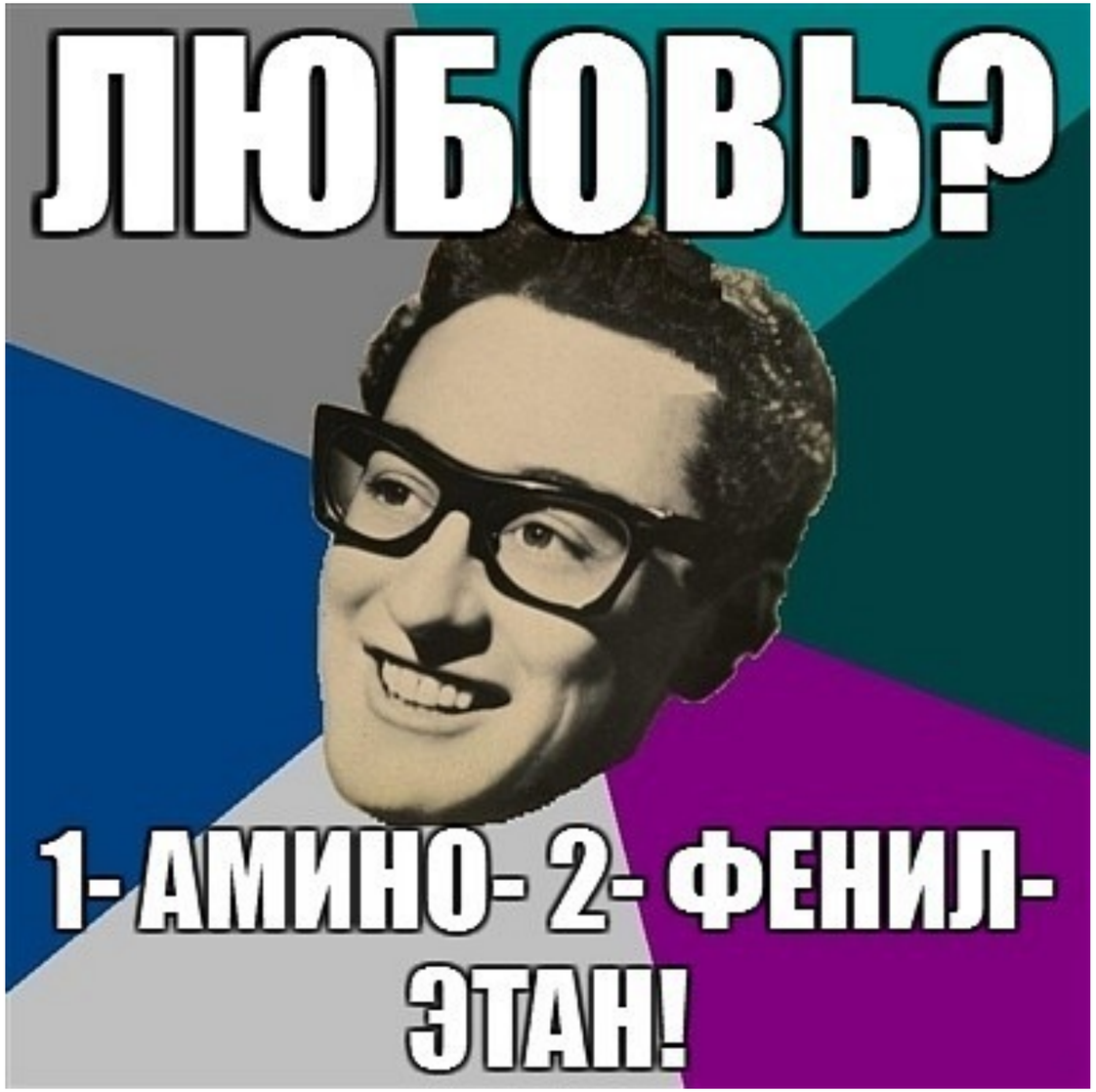
¿We need more Phe?

>>> Thirty minutes of moderate- to high-intensity physical exercise has been shown to induce an increase in urinary phenylacetic acid (PEA), the primary metabolite of phenethylamine [doi:10.1016/j.tips.2005.03.007]

>>> The urinary excretion rate of the endogenous, amphetamine-like substance beta-phenethylamine was markedly elevated in human subjects in association with an initial parachuting experience. The increases were delayed in most subjects and were not correlated with changes in urinary pH or creatinine excretion. The data suggest a stress-related role for beta-phenethylamine. [DOI: 10.1126/science.7063846]

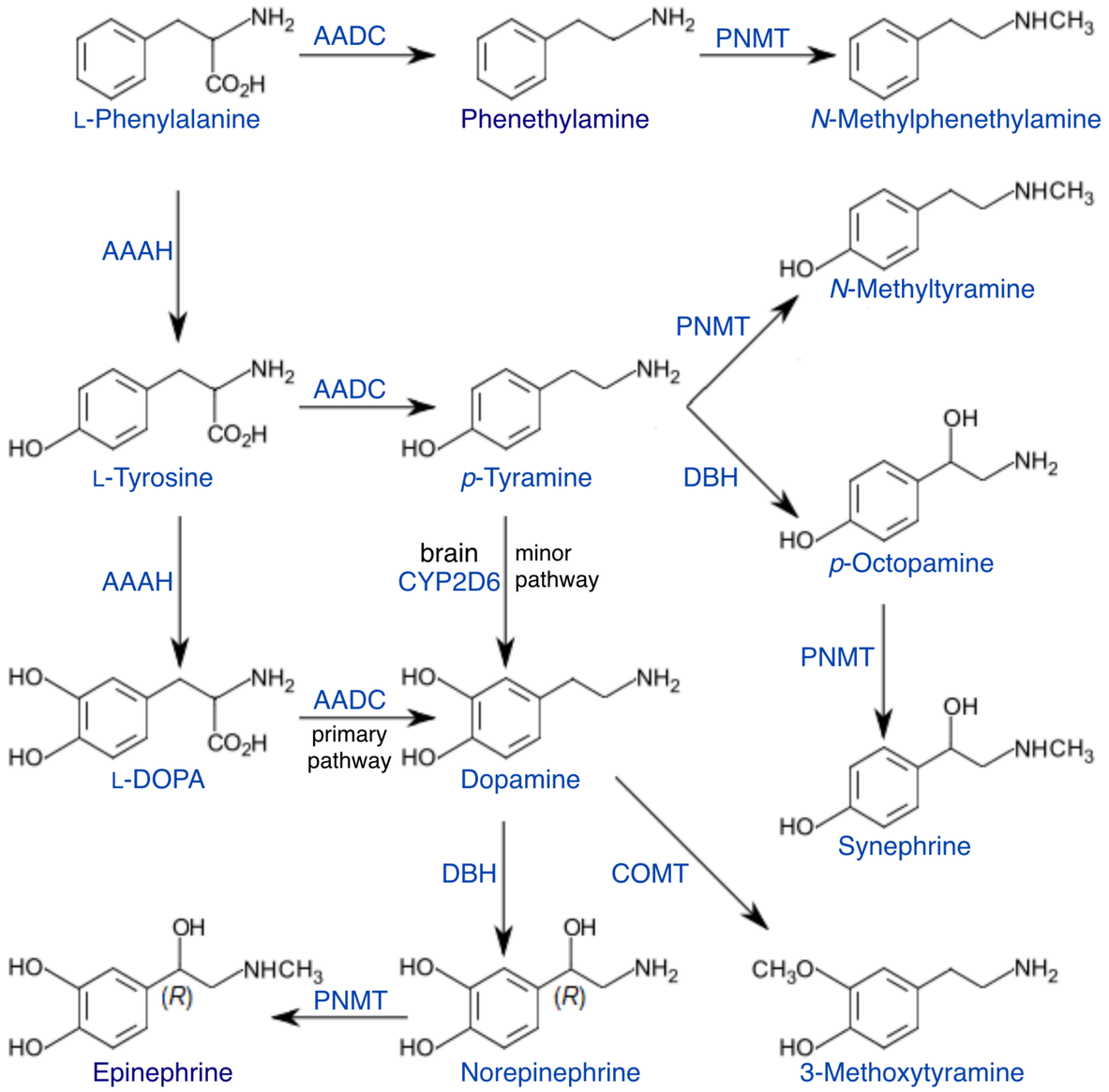
¿ADHD connection?

>>> … three studies confirmed that urinary levels of PEA were significantly lower in patients with ADHD compared with controls. ... Administration of D-amphetamine and methylphenidate resulted in a markedly increased urinary excretion of PEA, suggesting that ADHD treatments normalize PEA levels. ... Similarly, urinary biogenic trace amine PEA levels could be a biomarker for the diagnosis of ADHD [DOI:10.1016/j.jaac.2012.08.015]



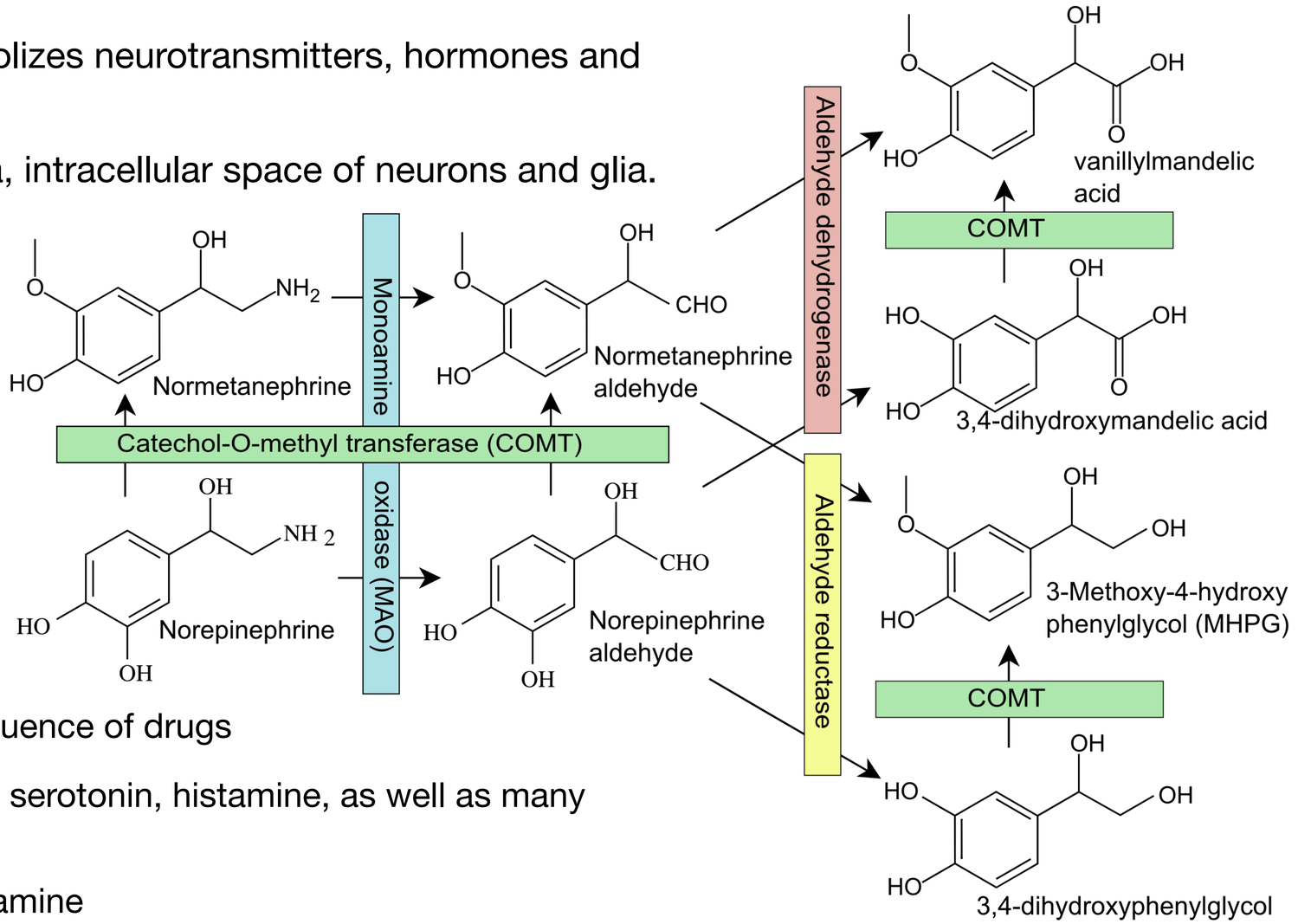
Localisation and function of monoamines

- Monoamine neurons as control systems
  - The central nervous system contains extremely few monoamine neurons (thousands)
  - Monoamine neurons have extensive projections into different areas of the brain
  - Controlling arousal or suppression of specific brain networks (¿traffic routing protocols of the brain?)
- Monoamines as hormones outside the central nervous system
  - Serotonin is an inflammation inducer, synthesised in the intestine
  - Dopamine - ↑ CVS, ↑ blood pressure, ↑ adaptation to stress
  - Norepinephrine is an adrenaline precursor; regulation of blood pressure and peripheral vascular resistance
  - Adrenaline - ↑↑↑ heart rate, ↑↑ blood pressure, ↑ 🔥🔥🔥, stimulation of hematopoiesis and blood coagulation
  - Histamine - 🚨🚨🚨 allergic reaction



Comrade MAO

- MonoAmine Oxidase - an enzyme that metabolizes neurotransmitters, hormones and exogenous substances
- Localization: outer membrane of mitochondria, intracellular space of neurons and glia.

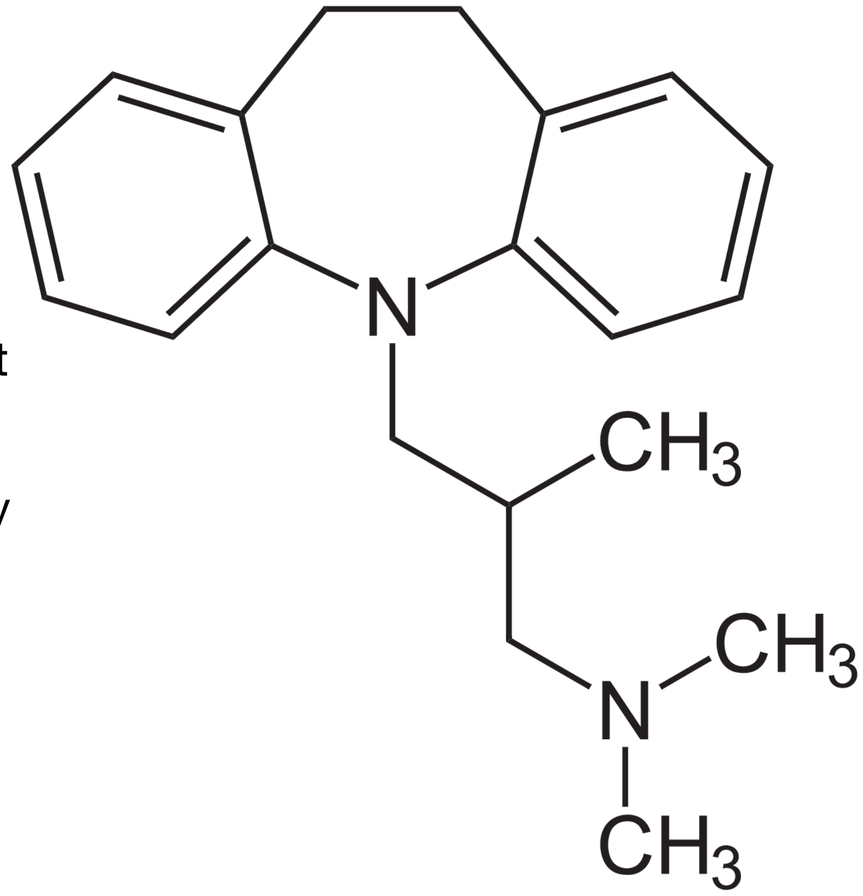


- MAO activity changes with age or under the influence of drugs
- MAO-A deactivates adrenaline, norepinephrine, serotonin, histamine, as well as many phenylethylamine and tryptamine surfactants
- MAO-B deactivates phenylethylamine and dopamine

Norepinephrine degradation. Monoamine oxidase is shown left in the blue box. DOI:10.15347/wjm/2014.008

Reuptake → Transporters

- SERT, DAT, NET have different binding affinity for monoamines
- Transporters combine sodium transport along a concentration gradient with monoamine transport against a gradient
- Other types of monoamines can also be captured, albeit less efficiently
- NET, for example, has high affinity for both dopamine and norepinephrine



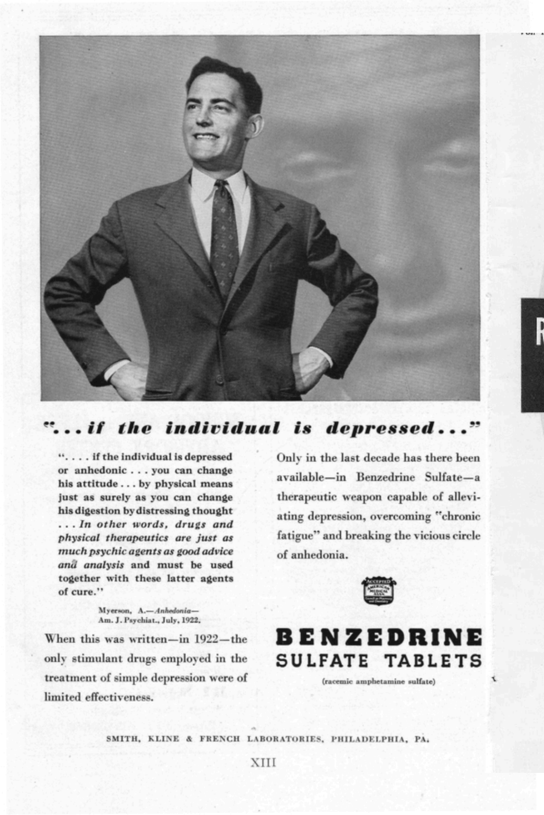
- Monoamine transporters - a frequent target of drugs (antidepressants) and psychoactive substances (amphetamines, MDMA, cocaine, mephedrone, α -PVP)
- SERT: antidepressants (tricyclics, SSRIs) bind to the allosteric binding site and decrease the SERT affinity for serotonin without entering the neuron

Reuptake issues

Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood

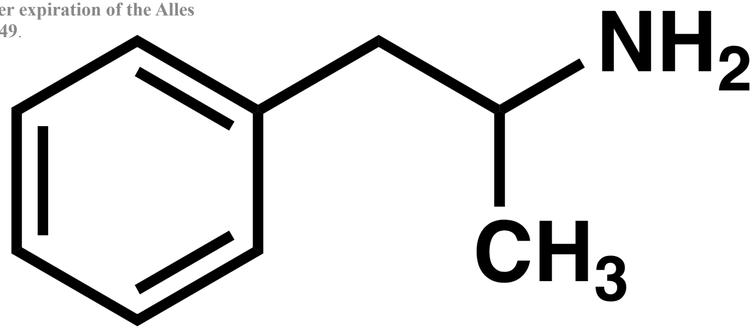
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2377281/

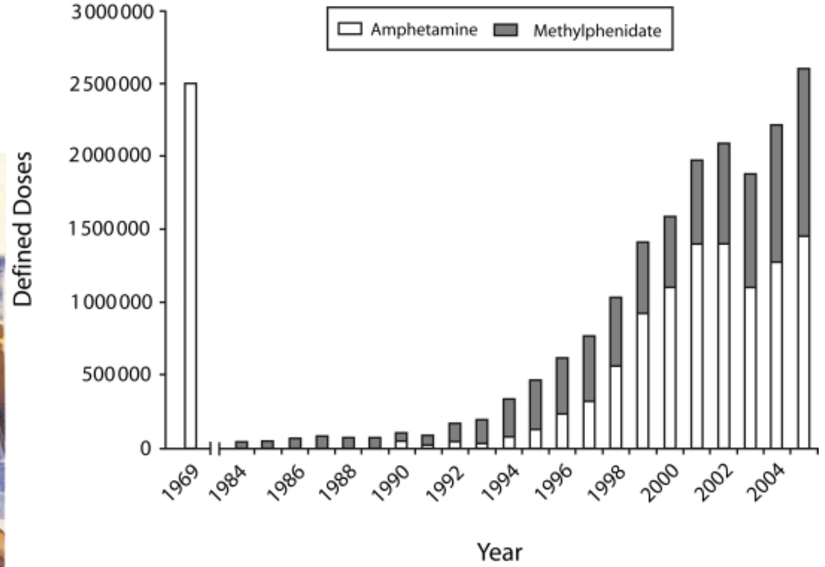
History of amphetamine



Amphetamine was successfully marketed as the first antidepressant in the late 1930s and 1940s, together with a particular understanding of depression as anhedonia.

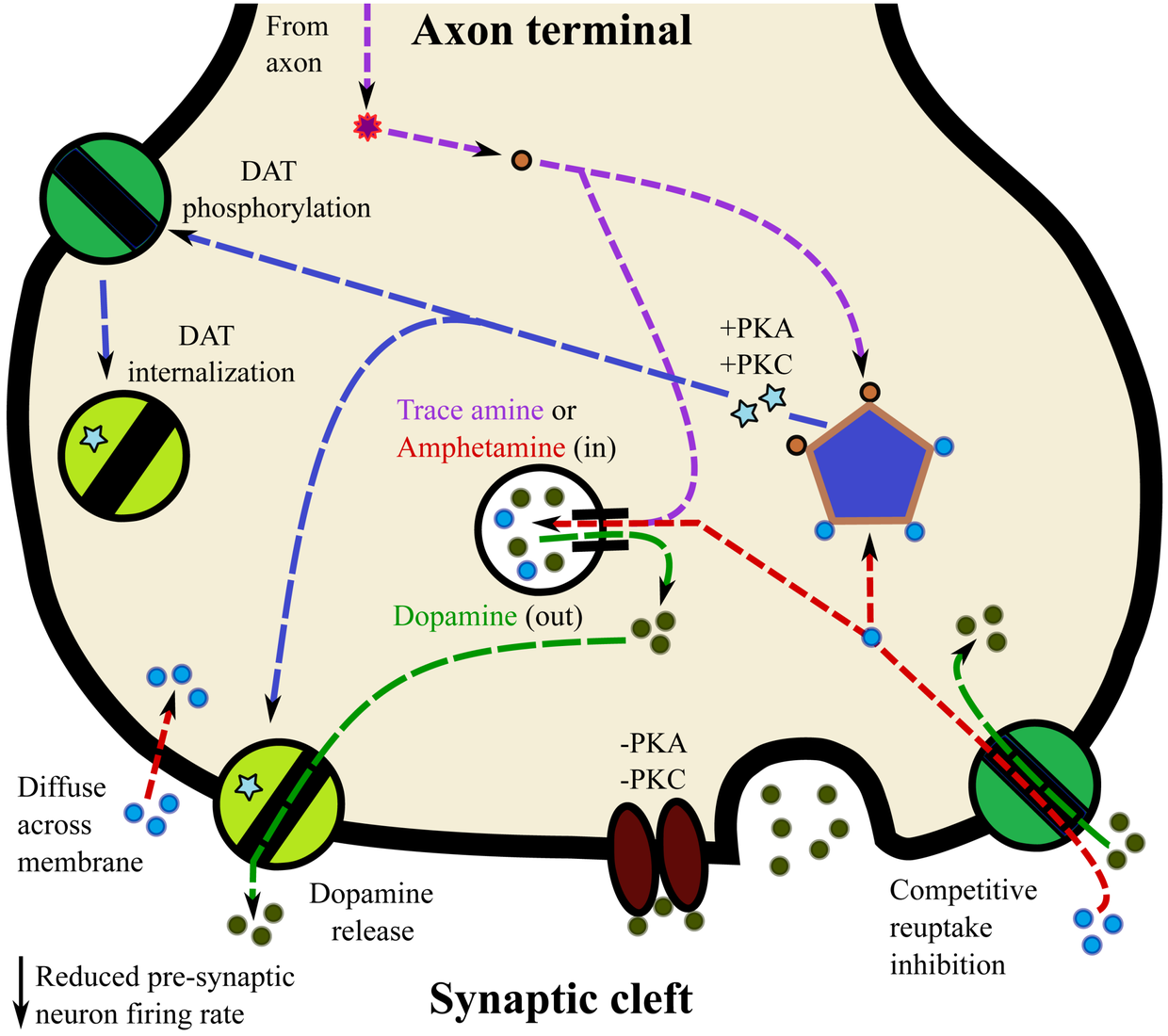
In the 1950s, competition among pharmaceutical firms boosted amphetamine consumption dramatically, **after expiration of the Alles and Smith, Kline and French patent in 1949**.

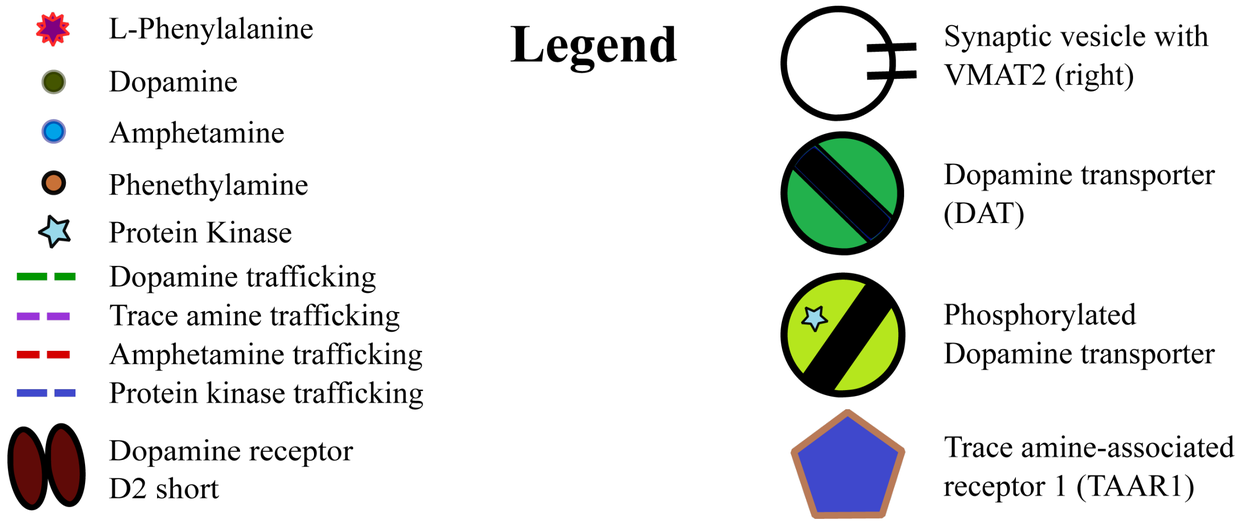




US medical consumption of amphetamine and methylphenidate, expressed as common dosage units (10-mg amphetamine and 30-mg methylphenidate, anhydrous base), based on Drug Enforcement Administration production quota figures

Reuptake altering

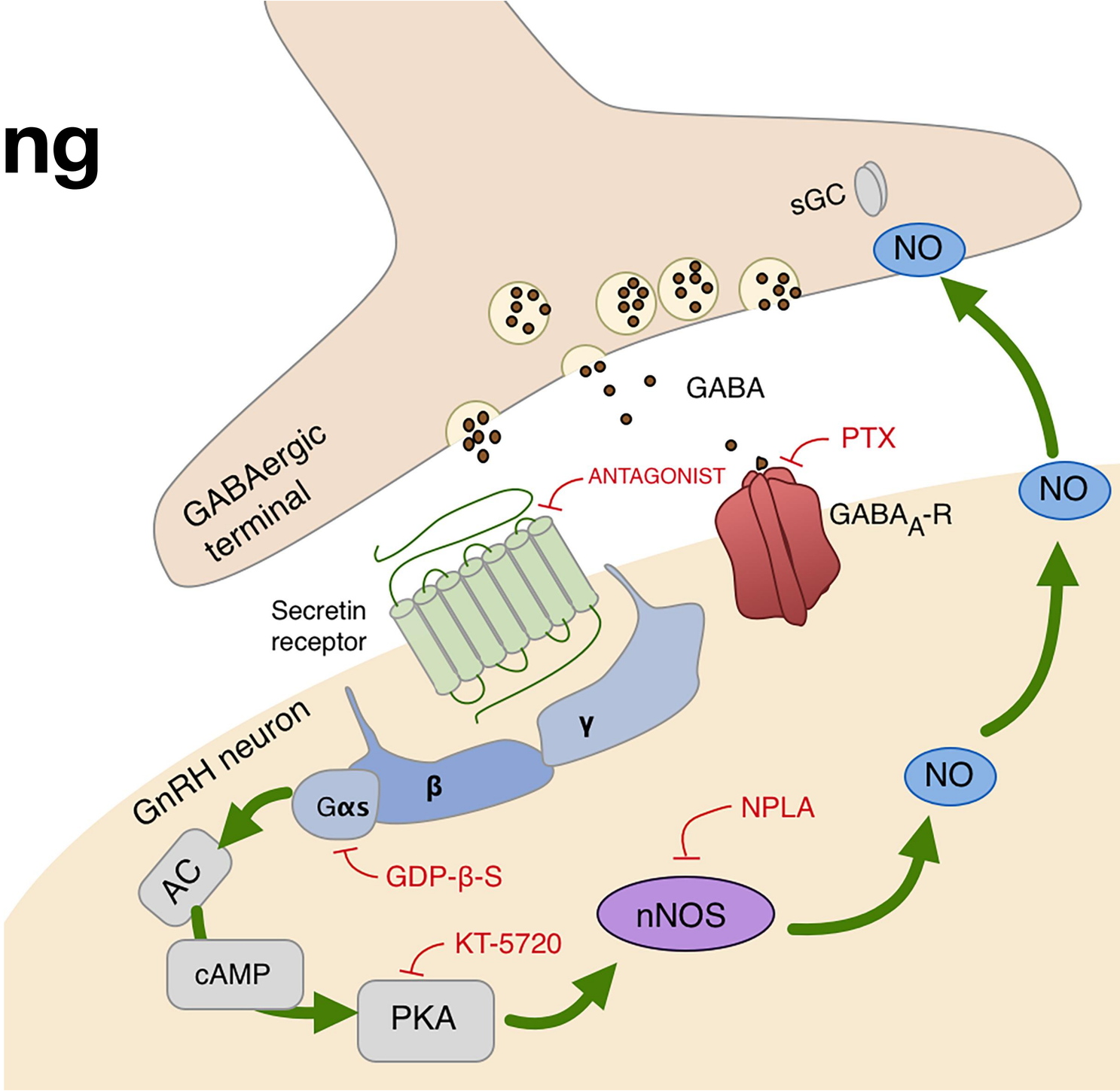




- Amphetamine (AMP) enters the presynaptic neuron via DAT
- AMP enters vesicle via $VMAT2$
- Inside the vesicle AMP alters Ph → causes the release of accumulated dopamine from the vesicle into the cytosol via $VMAT2$
- BTW, In the cytosol, AMP activates:
  - TAAR1 → decrease in dopamine neuron spiking
  - PKA → DAT internalization → decrease dopamine reuptake
  - PKC → DAT reversal → transporter becomes a release
- AMP increases intracellular $Ca2+$ → increase the release of dopamine vesicles into the synapse

Retrograde signaling

- Typically, neurotransmitters spread from the transmitting to the receiving neuron
- Retrograde signaling: the receiving neuron gives a control signal to the transmitting neuron
- Retrograde signaling results from action on metabotropic receptors
- The ultimate goal is **to regulate the release** of common neurotransmitters



🖼️ Gonadotropin-releasing hormone-neuron tells the GABA-neuron to release more GABA after the execution of the signaling pathway triggered by the activation of the secretin receptor