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NEUROCHEMISTRY AND BIOLOGICAL PSYCHIATRY

Biological Psychiatry: Web Pages

My presentation, you can find on Internet on web pages of the First Faculty of Medicine.

Links to information about biological psychiatry are:

1. Educational portal of our faculty:
   - **http://connect.lf1.cuni.cz**
2. Direct link to PowerPoint presentations of all lectures in this course:
   - **https://el.lf1.cuni.cz/psychiatry5**
3. Teaching materials from psychiatry on the website of the Department of Psychiatry, where there is also a link to a recording of my presentation:
   - **https://psychiatrie.lf1.cuni.cz/vyukove-materialy**

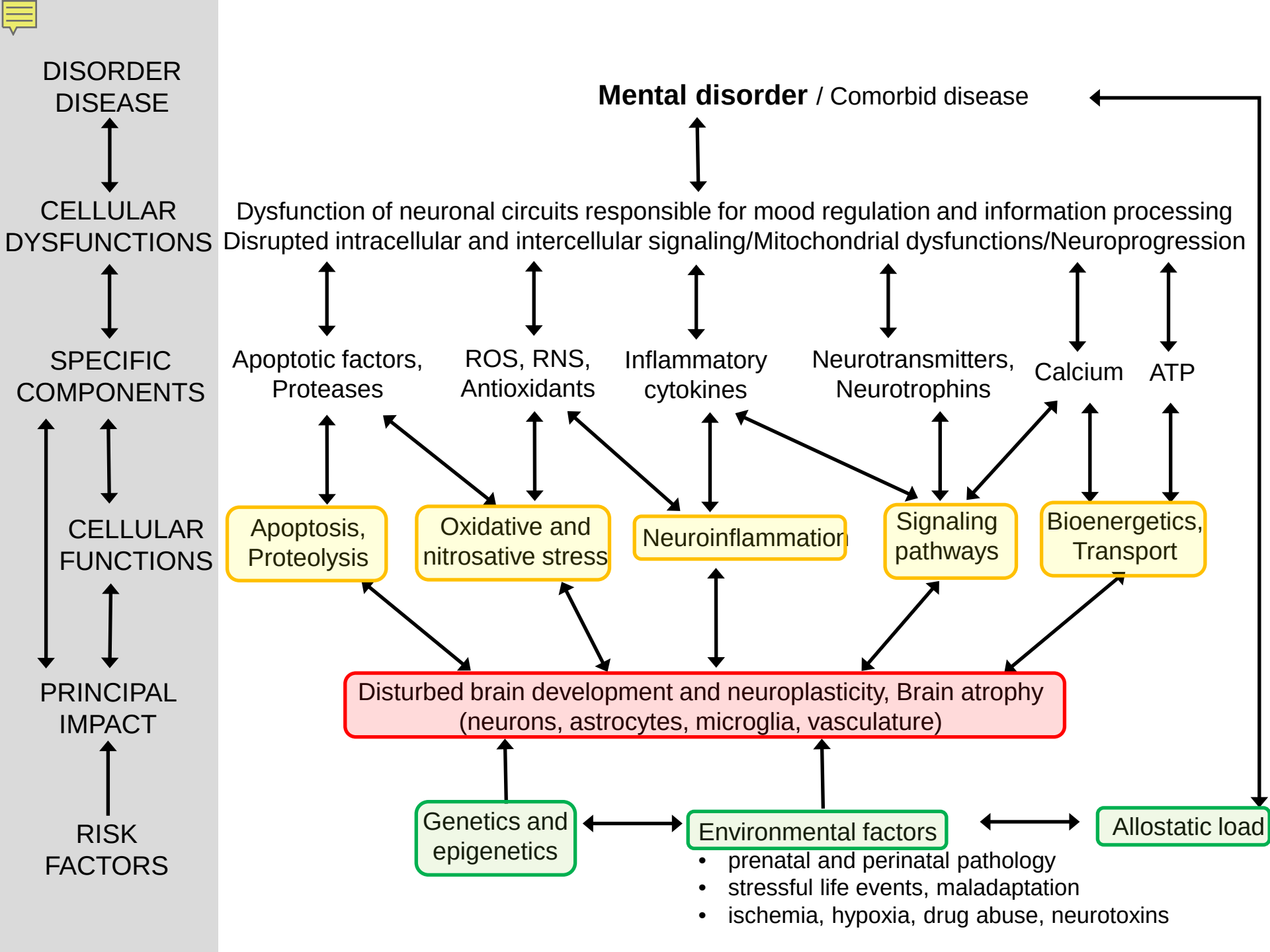
Introduction

- Biological (molecular) psychiatry studies disorders in human mind from the neurochemical, neurophysiological, neuroendocrine and genetic point of view mainly.

- In biological psychiatry, it is assumed that the development of mental disorders and their symptoms are associated with impaired transmission of nerve signals in the brain, especially at the level of chemical synapses. At the molecular level, the transmission and processing of information mediated by neurotransmitters and their receptors and transporters and by intracellular pathways related to the activation of receptors for neurotransmitters and growth factors is disrupted.

Approaches of Biological Psychiatry

BIOLOGY	genetics	vulnerability to mental disorders
	stress	increased sensitivity
	chronobiology	desynchronisation of biological rhythms
NEUROCHEMISTRY	neurotransmitters	availability, metabolism
	receptors	number, affinity, sensitivity
	postreceptor processes	G proteins, 2nd messengers, phosphorylation, transcription
NEURO-IMMUNO-ENDOCRINOLOGY	HPA (hypothalamic-pituitary-adrenocortical) system	increased activity during depression
	immune function	different changes during depression


DISORDER
DISEASE
CELLULAR
DYSFUNCTIONS
SPECIFIC
COMPONENTS
CELLULAR
FUNCTIONS
PRINCIPAL
IMPACT
RISK
FACTORS
Mental disorder / Comorbid disease
Dysfunction of neuronal circuits responsible for mood regulation and information processing
Disrupted intracellular and intercellular signaling/Mitochondrial dysfunctions/Neuroprogression
Apoptotic factors,
Proteases
ROS, RNS,
Antioxidants
Inflammatory
cytokines
Neurotransmitters,
Neurotrophins
Calcium
ATP
Apoptosis,
Proteolysis
Oxidative and
nitrosative stress
Neuroinflammation
Signaling
pathways
Bioenergetics,
Transport
Disturbed brain development and neuroplasticity, Brain atrophy
(neurons, astrocytes, microglia, vasculature)
Genetics and
epigenetics
Environmental factors
Allostatic load
• prenatal and perinatal pathology
• stressful life events, maladaptation
• ischemia, hypoxia, drug abuse, neurotoxins

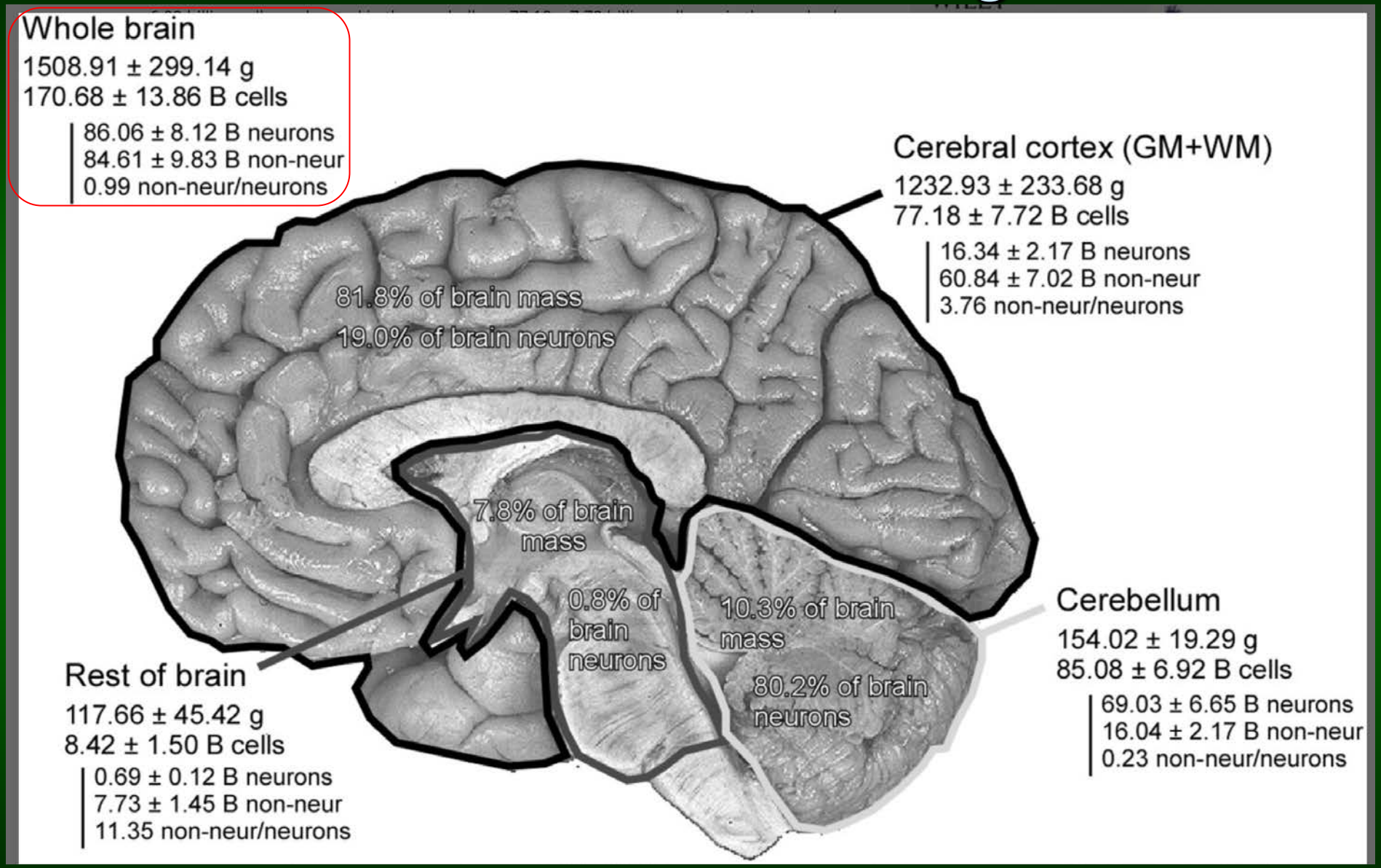
Neurochemistry and Biological Psychiatry

1. Cellular neurochemistry (neurons, action potentials, synapses)
2. Intercellular signalling (neurotransmitters, receptors, growth factors)
3. Intracellular signalling (G proteins, effectors, 2nd messengers, proteinkinases, transcription factors)
4. Psychotropic drugs (antipsychotics, antidepressants)
5. Biological hypotheses of mental disorders (schizophrenia, affective disorders)

Cellular Neurochemistry

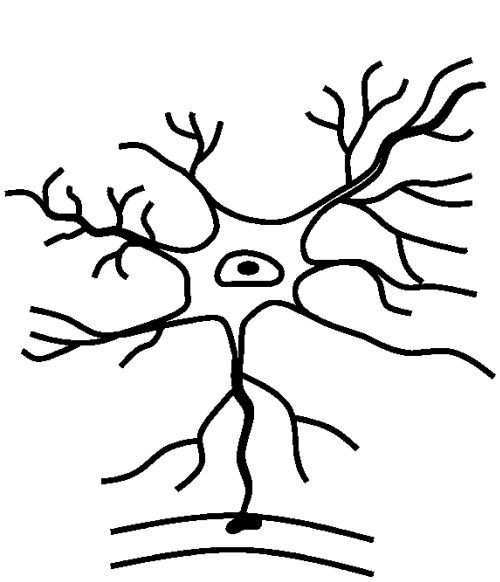
- Neurons and glia
- Action potentials
- Synapses

Brain: neurons and glia

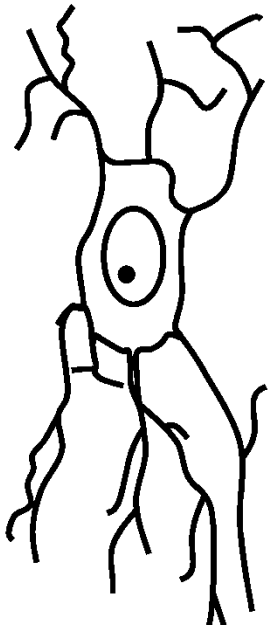


Azevedo et al. J Comp Neurol. 2009;513(5):532-41.

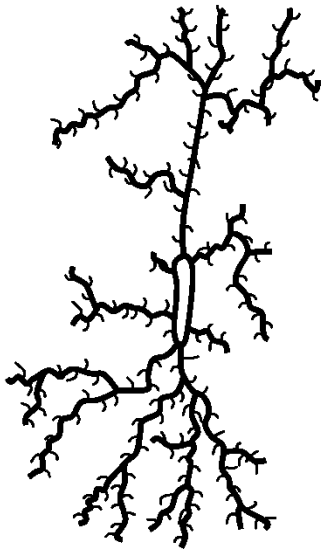
Glia Cells



astrocyte



oligodendrocyte

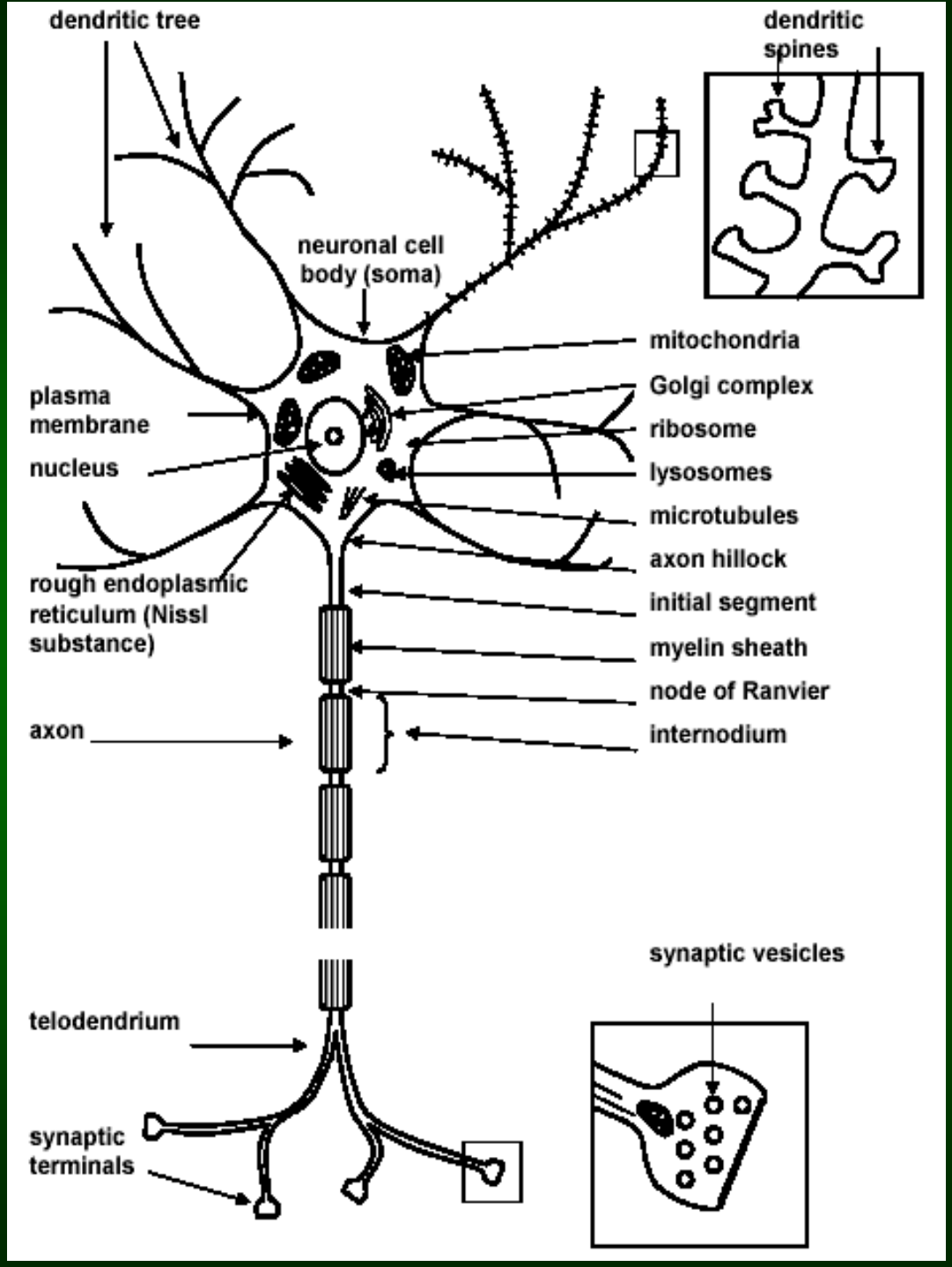


microglia

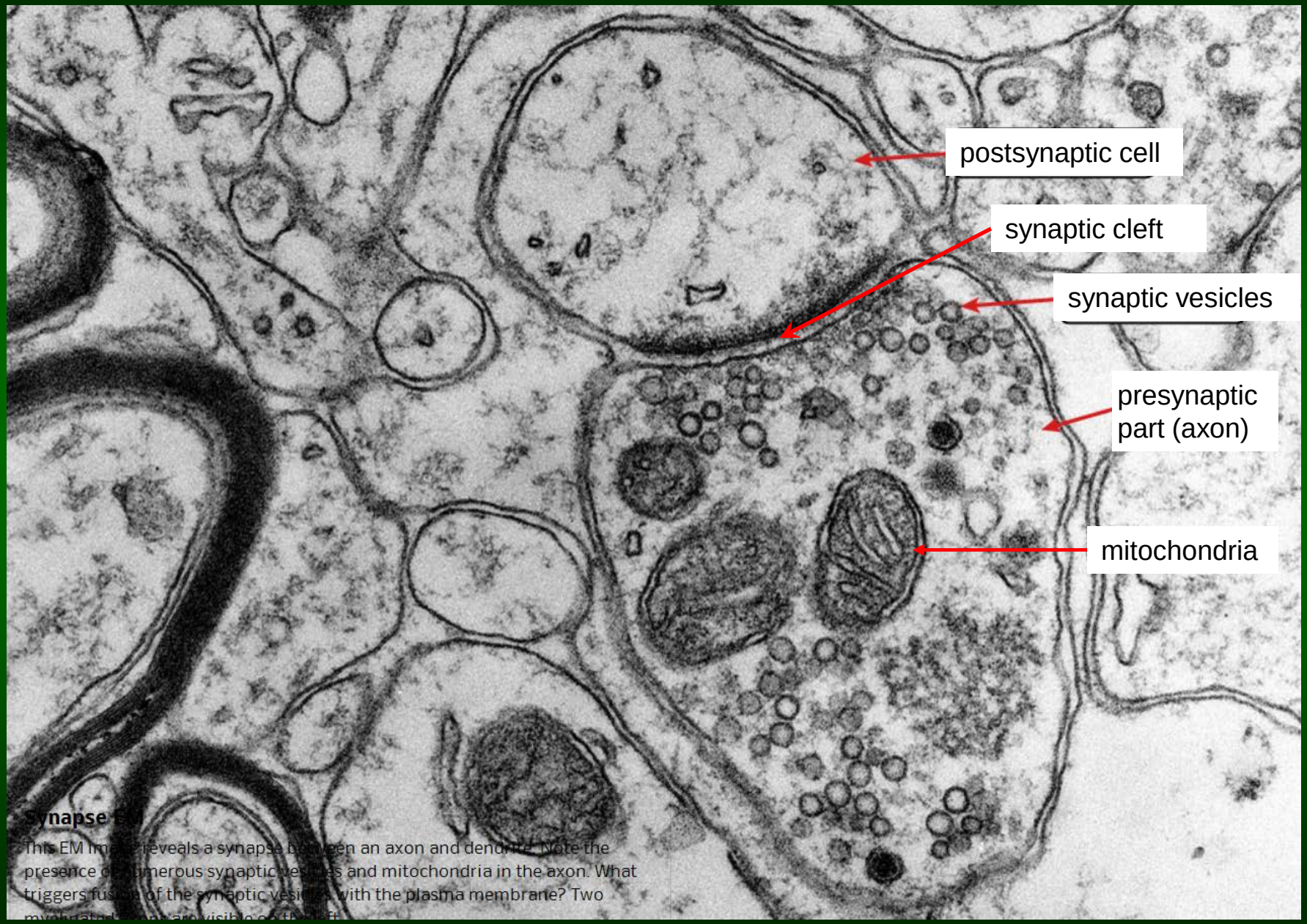
1. Surrounding of neurons and holding them in place.
2. Isolation by myelin sheath.
3. Energy support of neurons.
4. Pathogen destroying and removing of dead neurons.
5. Reuptake of neurotransmitters.

Neuron

- **Neurons** are the brain cells that are responsible for intracellular and intercellular signalling.
- **Dendritic tree** function is reception of signals from the other neurons.
- **Action potential** is large and rapidly reversible fluctuation in the membrane potential, that propagate along the axon.
- At the end of axon there are many **nerve endings** (synaptic terminals, presynaptic parts, synaptic buttons, knobs). Nerve ending form an integral parts of synapse.
- **Synapse** mediates the signal transmission from one neuron to another.

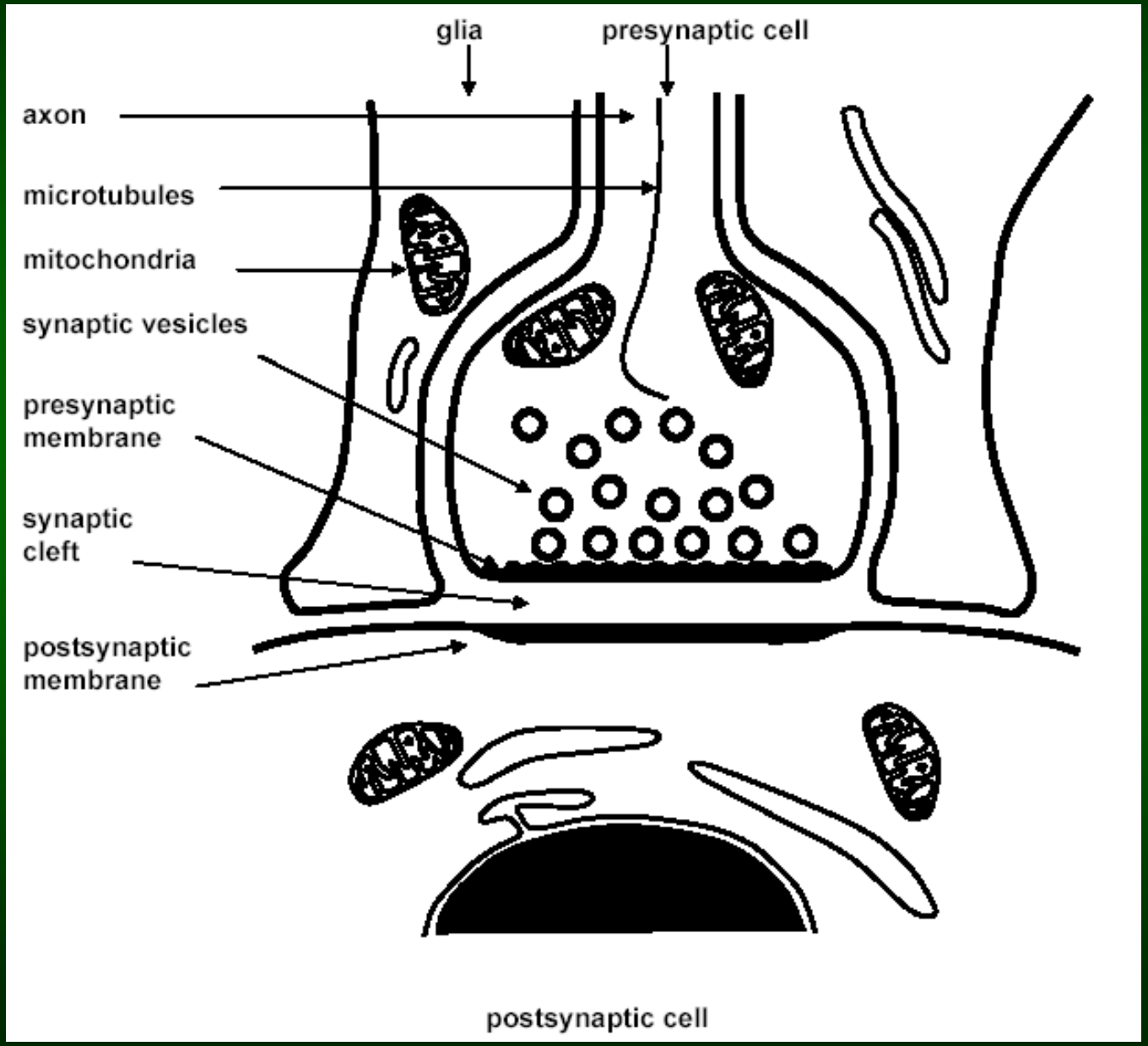


Synapse (EM)

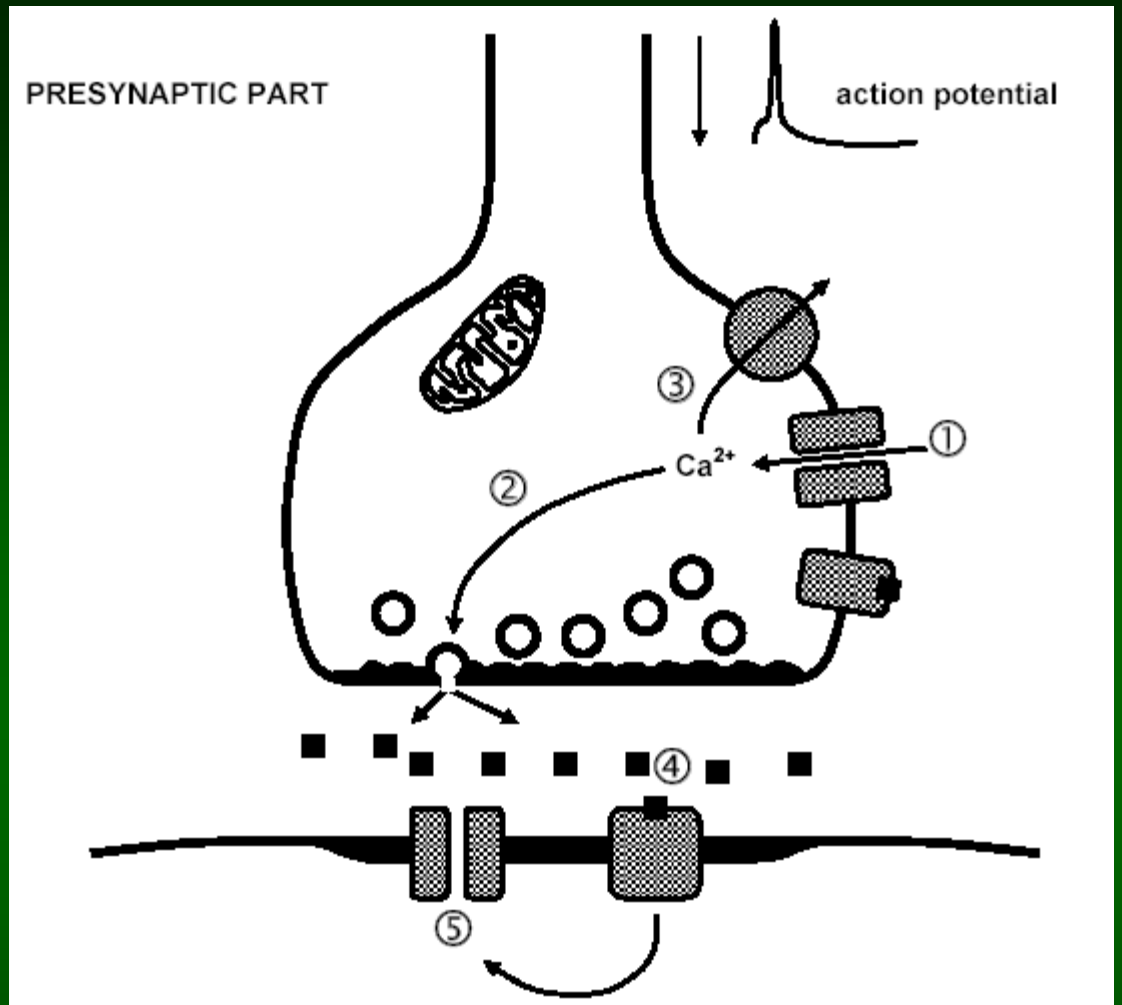


http://medcell.med.yale.edu/histology/nervous_system_lab/synapse_em.php

Morphology of Chemical Synapse



Chemical Synapse: Signal Transduction



① - Ca^{2+} entry through voltage-gated channel

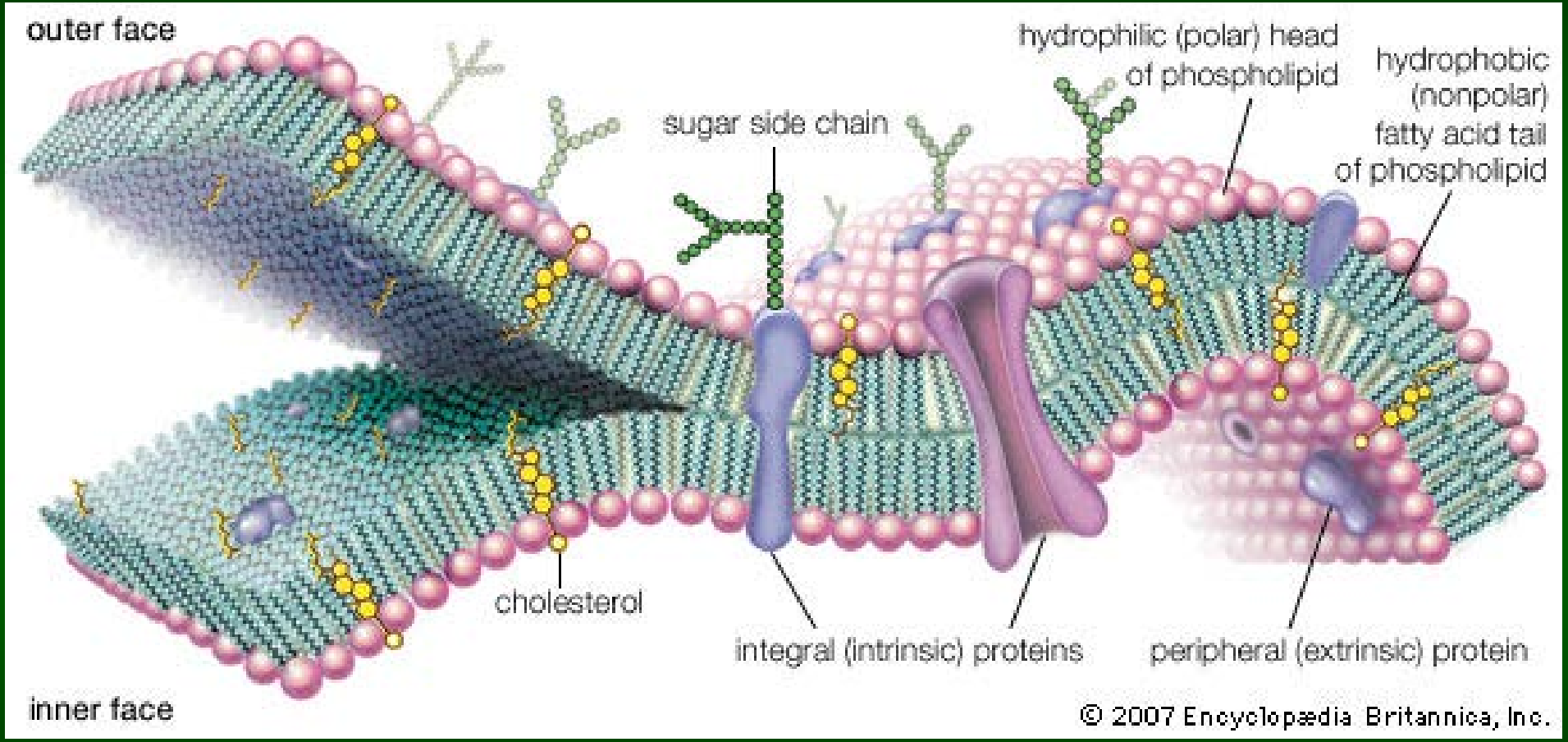
② - Ca^{2+}-catalysed reaction → exocytosis

③ - Inactivation of intracellular Ca^{2+}

④ - Diffusion of neurotransmitter

⑤ - Reaction with receptors of postsynaptic cell and changes in membrane permeability

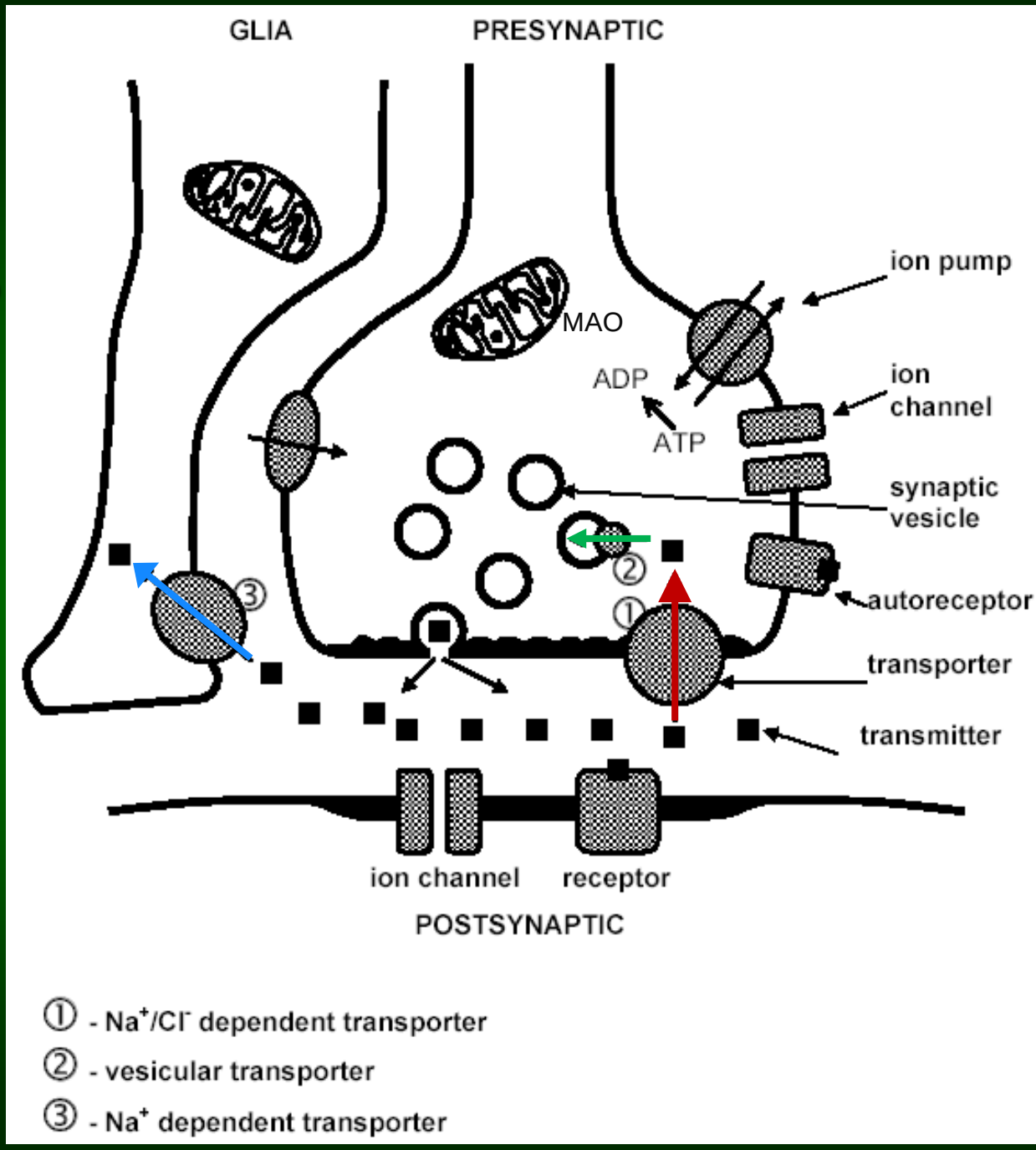
Model of Plasma Membrane



molecular view of the cell membrane. [Art]. Encyclopædia Britannica Online. Retrieved 22 January 2013, from http://www.britannica.com.ezproxy.is.cuni.cz/EBchecked/media/45550/Intrinsic-proteins-penetrate-and-bind-tightly-to-the-lipid-bilayer

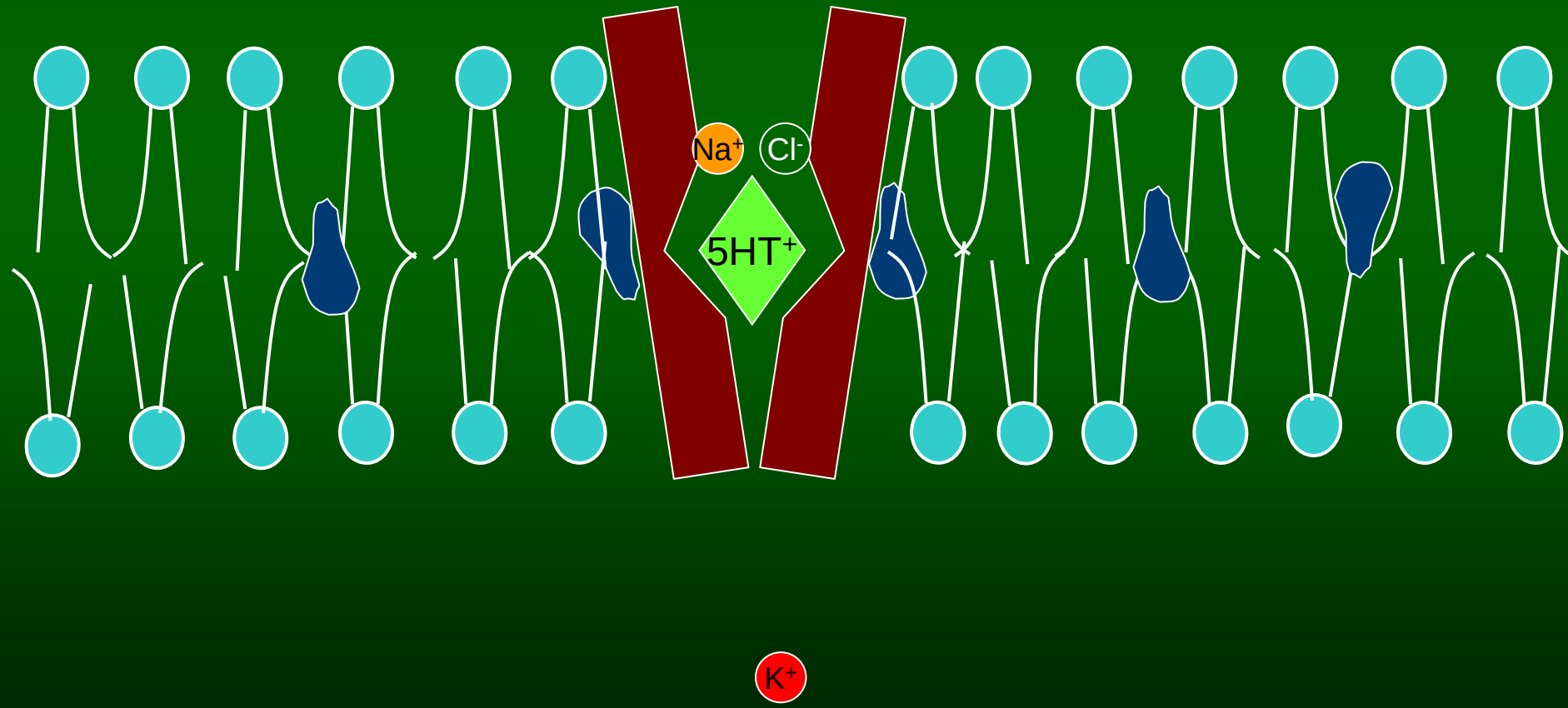
Membrane Transporters

1. Transporters dependent on sodium and chloride
2. Vesicular transporters
3. Sodium dependent transporters



Serotonin transporter

- inhibition: antidepressants, phencyclidine (PCP)
- reversing: cocaine, amphetamines, incl. ecstasy (MDMA)



Intercellular and Intracellular Signalling

- Neurotransmitters
- Growth factors
- Receptors
- G proteins
- Effector systems (2^{nd} messengers, proteinkinases, transcription factors)

Criteria to Identify Neurotransmitter

1.	Presence in presynaptic nerve terminal in high concentration
2.	Synthesis by presynaptic neuron
3.	Releasing on stimulation (membrane depolarization) and existence of mechanism of end of operation
4.	Producing rapid-onset and rapidly reversible responses in the target cell
5.	Existence of specific receptor

There are three main groups of neurotransmitters:

1. **classical neurotransmitters**
2. **neuropeptides**
3. **other:** nitric oxide, carbon oxid or endocannabinoids have a special role in neurotransmission.

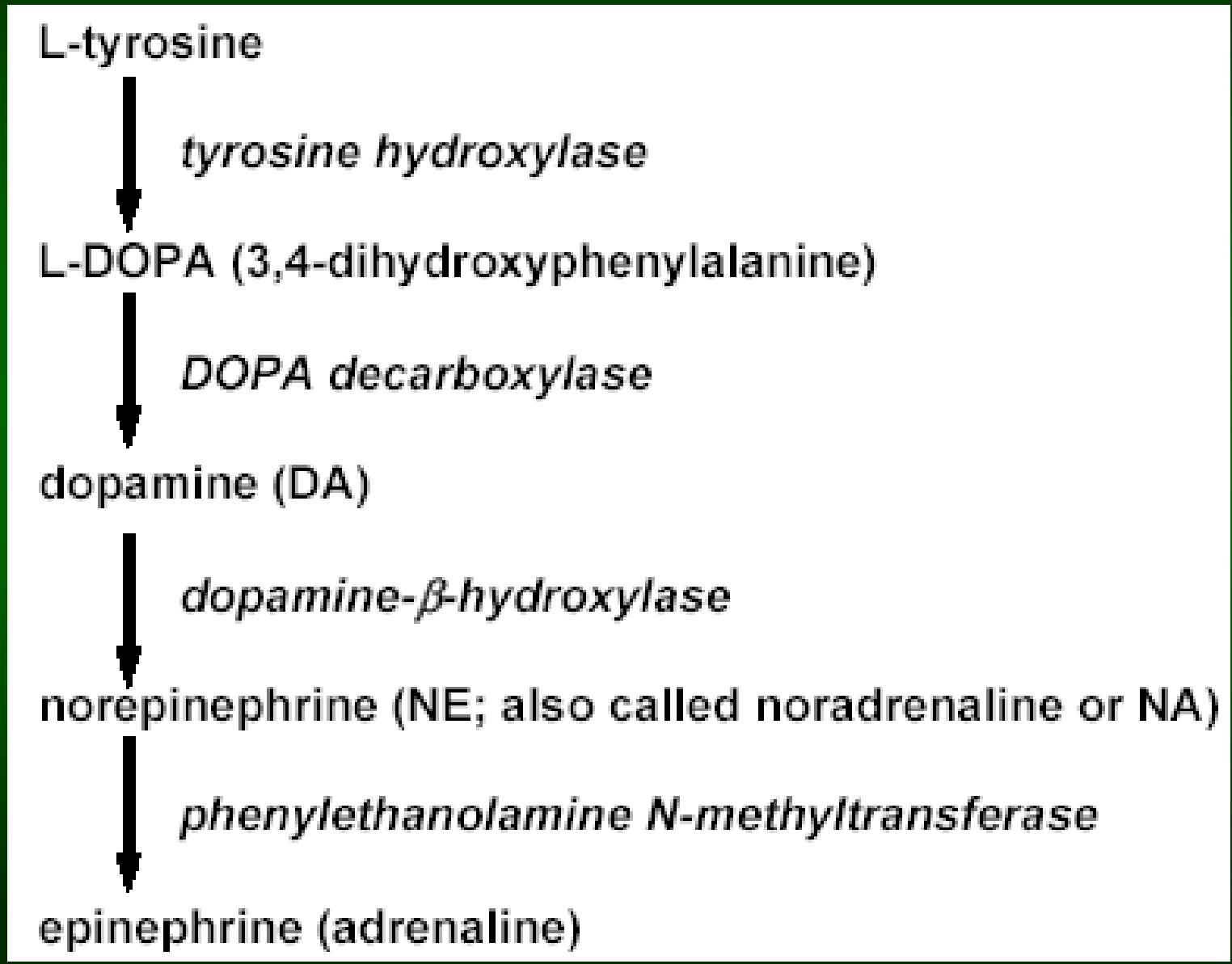
Selected Classical Neurotransmitters

System	*Transmitter*
Cholinergic	acetylcholine
Aminoacidergic	GABA, aspartic acid, glutamic acid, glycine, homocysteine
Monoaminergic	
• *Catecholamines*	dopamine, norepinephrine, epinephrine
• *Indolamines*	tryptamine, serotonin
• *Others, related to aa*	histamine, taurine
Purinergic	adenosine, ADP, AMP, ATP

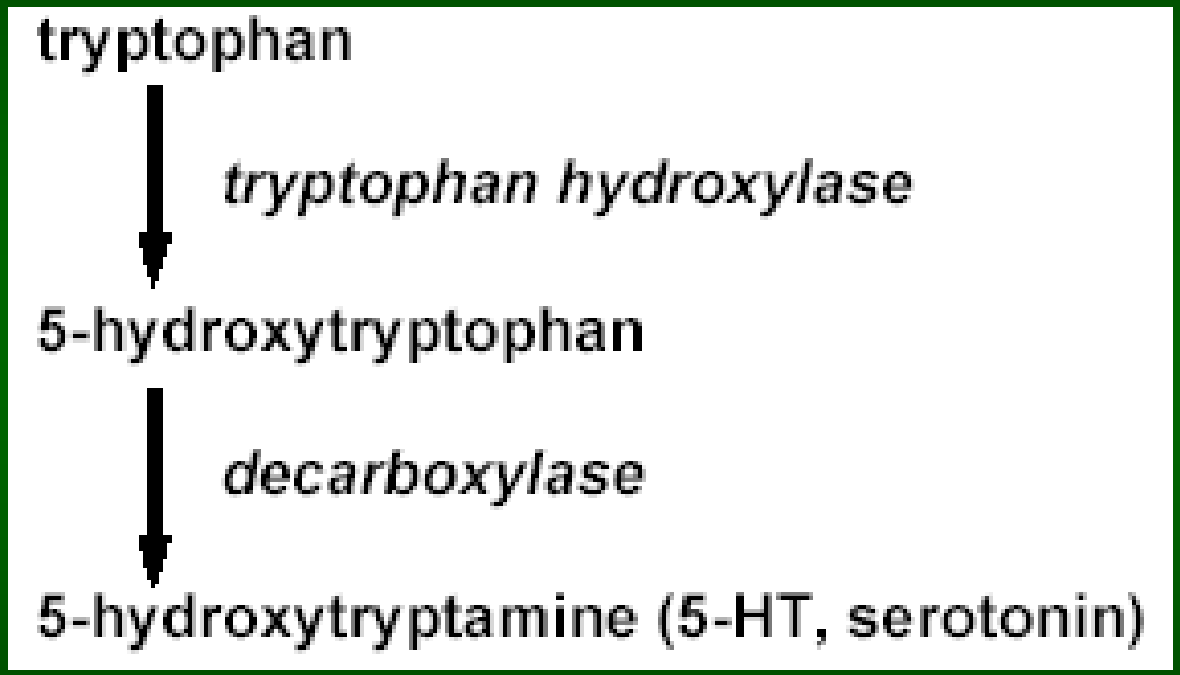
nitric oxide

endocannabinoids

Catecholamine Biosynthesis



Serotonin Biosynthesis



Serotonin depletion

- It is possible to induce artificial depletion of serotonin in the brain by lowering of tryptophan uptake.
- Serotonin depletion in healthy individuals did not induce clinically significant depressive symptomatology. However, serotonin depletion led to recovery of depressive symptoms in depressive patients in remission, which were previously treated by serotonergic antidepressants.
- These results indicate the role of both low serotonin concentration and disturbed serotonin signalling pathways in pathophysiology of depressive disorder.

Elimination of monoamine neurotransmitters from synaptic cleft

1. Reuptake
2. Monoamine oxidase (MAO)
3. Catechol-*O*-methyltransferase (COMT)

- Action both of catecholamines and indolamines on target cells is terminated by removing from synaptic cleft by specific transporters; the active transport of neurotransmitters from extracellular space into synapse is called reuptake.
- The major enzymes involved in the catabolism of dopamine or norepinephrine is monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT).

Selected Bioactive Peptides

Peptide	***Group***
substance P, substance K (tachykinins), neurotensin, cholecystokinin (CCK), gastrin, bombesin	brain and gastrointestinal peptides
galanin, neuromedin K, neuropeptideY (NPY), peptide YY (PYY),	neuronal
corticotropin releasing hormone (CRH)	hypothalamic releasing factors
growth hormone releasing hormone (GHRH), gonadotropin releasing hormone (GnRH), somatostatin, thyrotropin releasing hormone (TRH)	
adrenocorticotropic hormone (ACTH)	pituitary hormones
growth hormone (GH), prolactin (PRL), lutenizing hormone (LH), thyrotropin (TSH)	
oxytocin, vasopressin	neurohypophyseal peptides
atrial natriuretic peptide (ANF), vasoactive intestinal peptide (VIP)	neuronal and endocrine
enkephalines (met-, leu-), dynorphin, nociceptin, **endorphins (α-, β-, γ-)**	opioids peptides

Growth Factors in the Nervous System

Neurotrophins	Nerve growth factor (NGF) **Brain-derived neurotrophic factor (BDNF)** Neurotrophin 3 (NT3) Neurotrophin 4/5 (NT4/5)
Neurokines	Ciliary neurotrophic factor (CNTF) Leukemia inhibitory factor (LIF) Interleukin 6 (IL-6) Cardiotrophin 1 (CT-1)
Fibroblast growth factors	FGF-1 FGF-2
Transforming growth factor β superfamily	Transforming growth factors β (TGFβ) Bone morphogenetic factors (BMPs) Glial-derived neurotrophic factor (GDNF) Neurturin
Epidermal growth factor superfamily	Epidermal growth factor (EGF) Transforming growth factor α (TGFα) Neuregilins
Other growth factors	Platelet-derived growth factor (PDGF) Insulin-like growth factor I (IGF-I)

Neurotransmitter Receptors

- **Receptor** is macromolecule specialized on transmission of information.

- Receptor complex includes:
  1. Specific binding site
  2. Internal ion channel or transduction element
  3. Effector system (ion channels or system of 2^{nd} messengers)

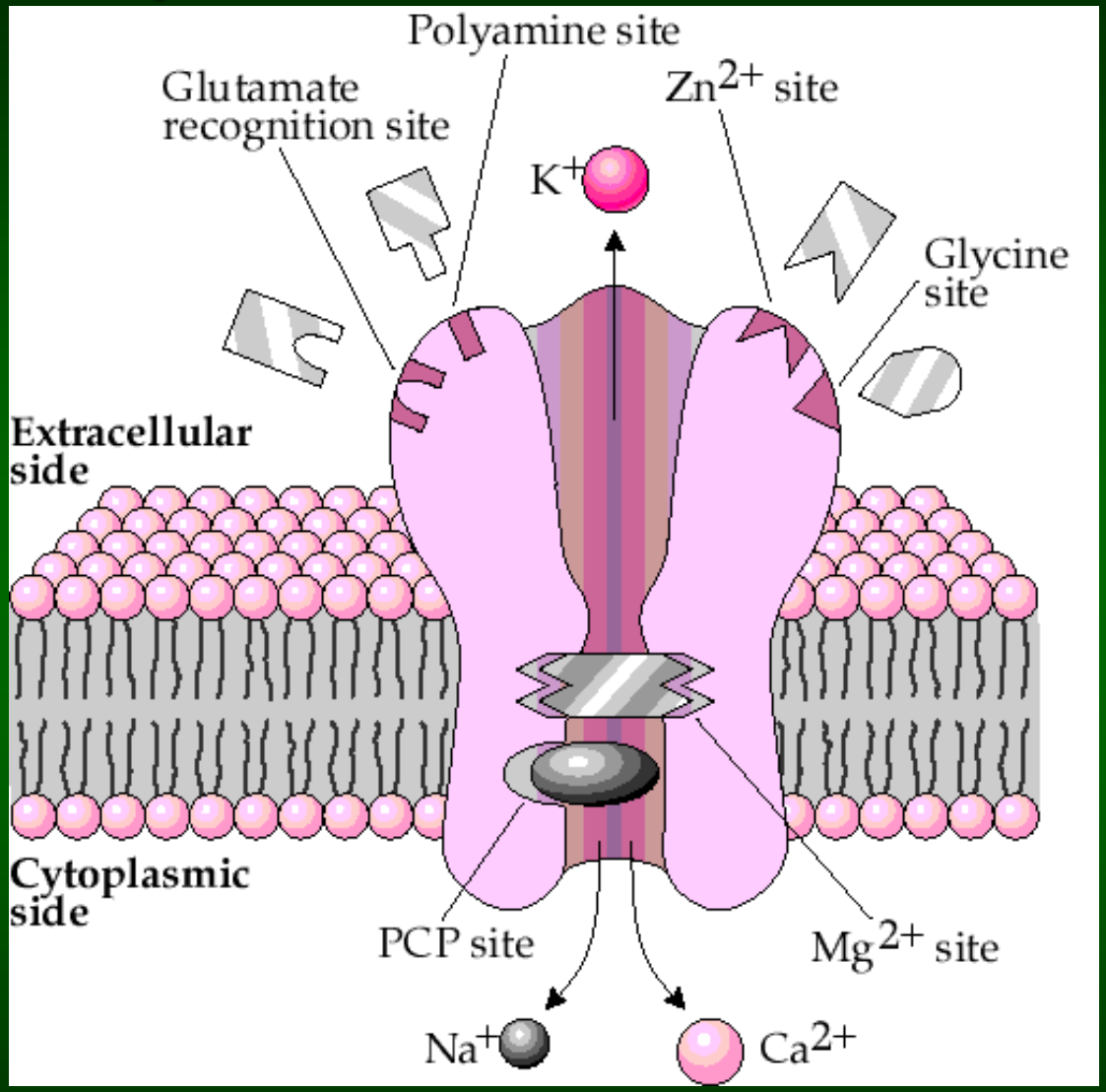
Regulation of Receptors

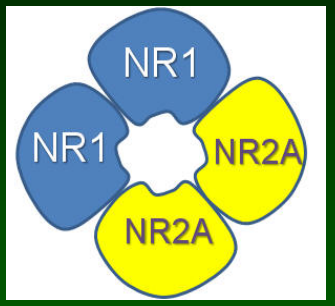
1. Density of receptors (down-regulation, up-regulation)
2. Properties of receptors (desensitisation, hypersensitivity)

Receptor Classification

1. Receptor coupled directly to the ion channel
2. Receptor associated with G protein
3. Receptor associated with enzyme
   - with guanylyl cyclase activity
   - tyrosine kinase activity

1. Receptors with Internal Ion Channel





glutamate NMDA receptor:

both voltage- and ligand-gated receptor

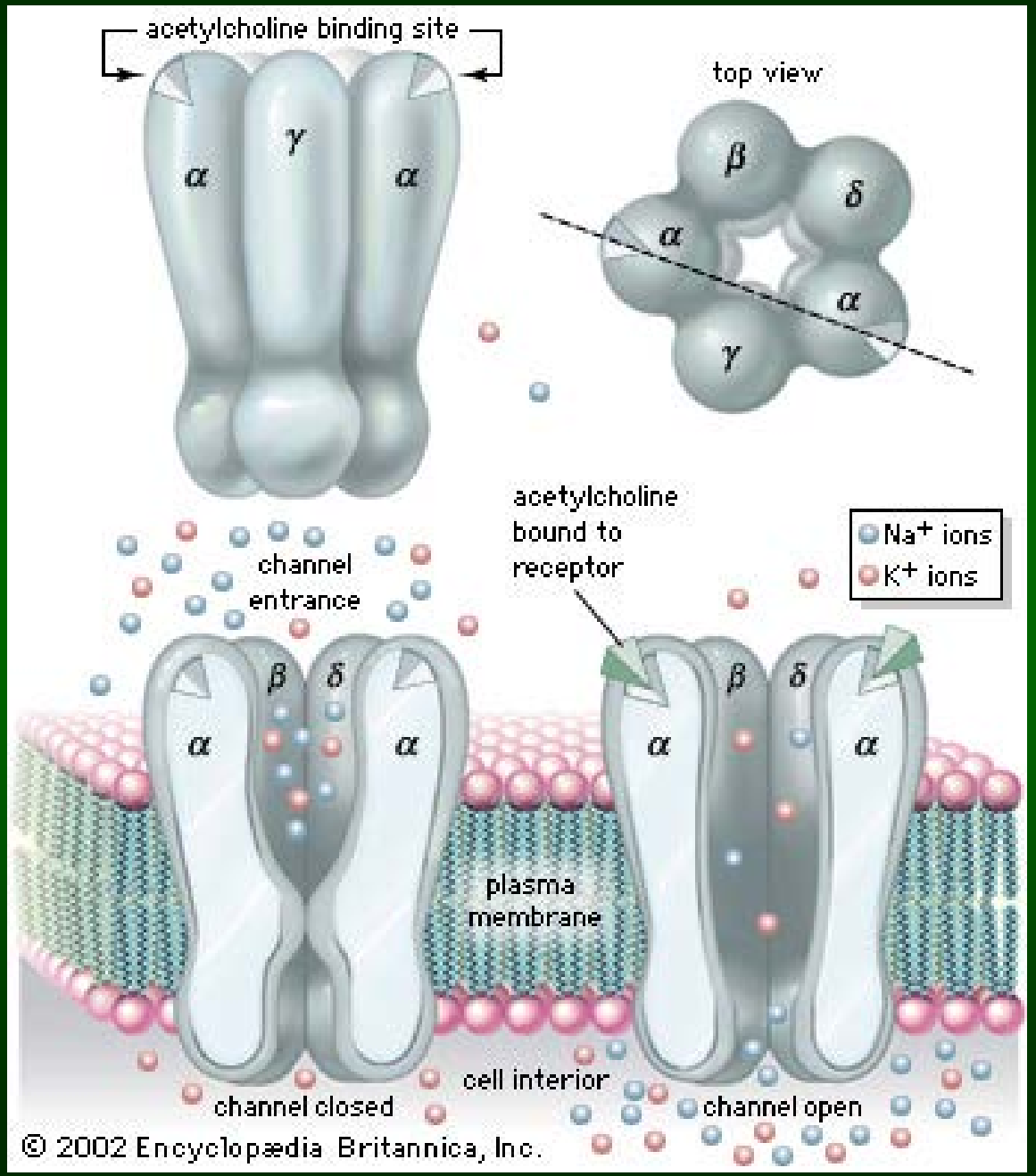
According to the glutamate hypothesis of schizophrenia, impairment of NMDA receptor function is associated with the development of schizophrenia

Zdroj: http://www.securitylab.ru/analytics/241606.php

1. Receptors with Internal Ion Channel

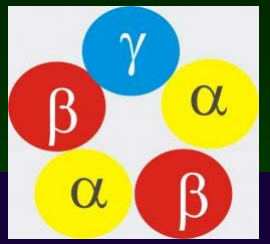
Nicotinic acetylcholine receptor is composed of 5 subunits, 2 of which bind acetylcholine.

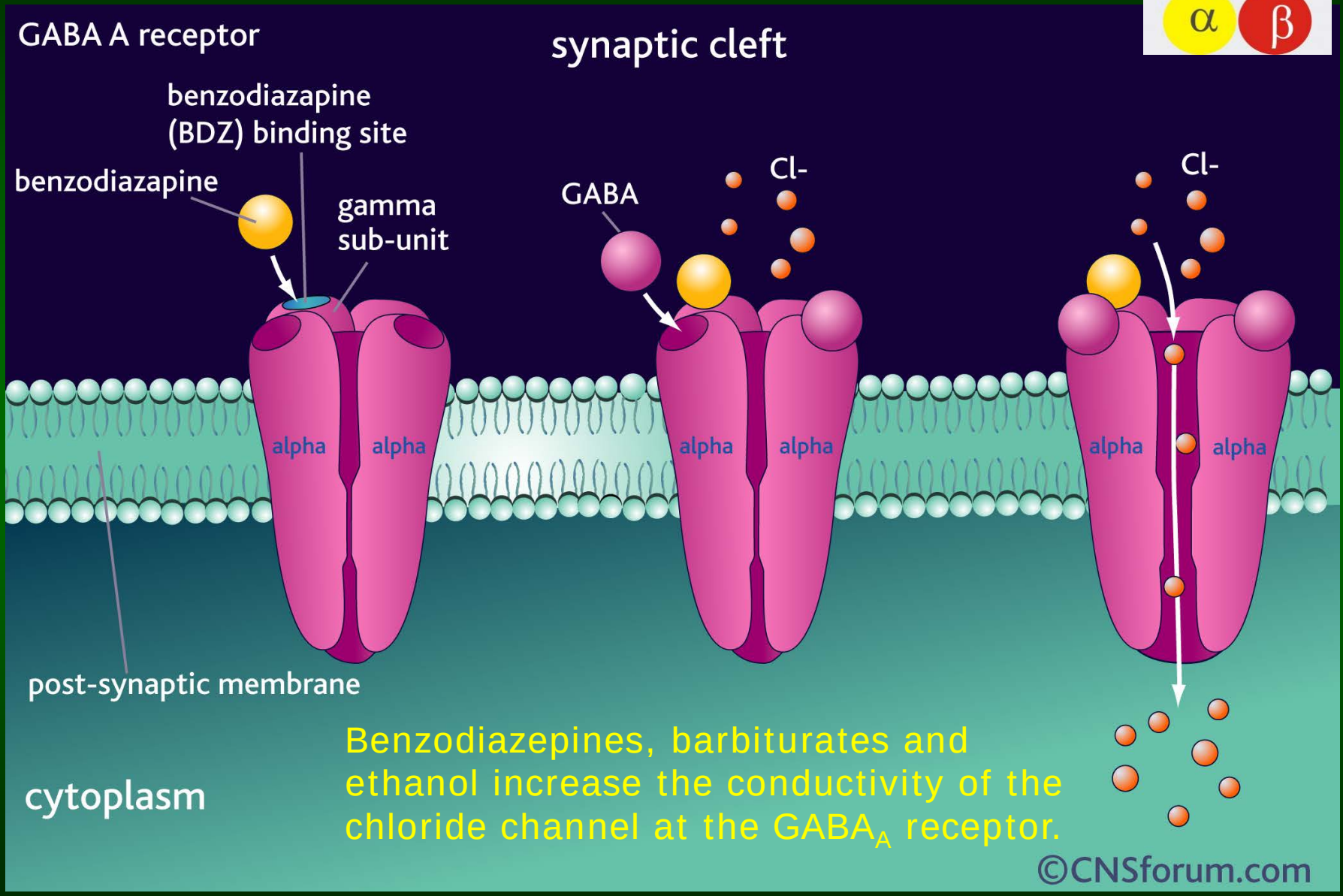
The nicotinic receptor binds acetylcholine, which causes the channel to open and allows diffusion of sodium (Na^+) and potassium (K^+) ions into the cell interior.



http://www.britannica.com.ezproxy.is.cuni.cz/EBchecked/media/66783/The-nicotinic-receptor-Composed-of-two-alpha-subunits-and-beta

1. Receptors with Internal Ion Channel

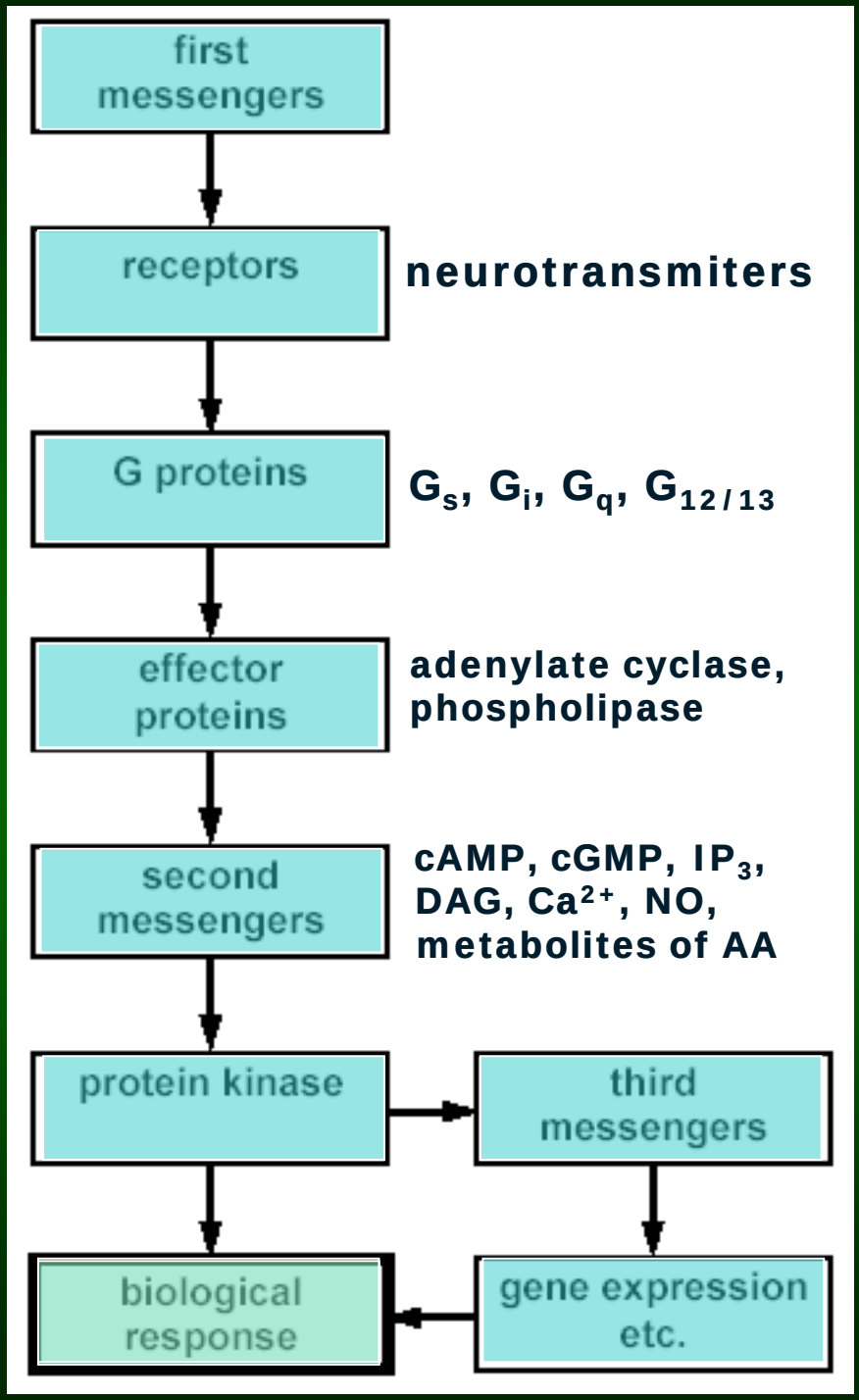




Zdroj: http://www.cnsforum.com/imagebank/item/drug_benzo/default.aspx

2. G Protein Coupled Receptors (GPCR)

1. adenylyl cyclase system
2. phosphoinositide system
3. arachidonic acid system



Types of Receptors

System	*Type*
acetylcholinergic	acetylcholine nicotinic receptors
	acetylcholine muscarinic receptors
monoaminergic	**α_1-adrenoceptors**
	α_2-adrenoceptors
	β-adrenoceptors
	dopamine receptors
	serotonin receptor
aminoacidergic	**GABA receptors**
	glutamate ionotropic receptors
	glutamate metabotropic receptors
	glycine receptors
	histamine receptors
peptidergic	opioid receptors
	other peptide receptors
purinergic	adenosine receptors (P_1 purinoceptors)
	P_2 purinoceptors

Subtypes of Norepinephrine Receptors

RECEPTOR	*Subtype*	*Transducer*		*Structure (aa/TM)*
α_1-adrenoceptor	α_{1A}	$G_{q/11}$	$\uparrow IP_3/DAG$	466/7
	α_{1B}	$G_{q/11}$	$\uparrow IP_3/DAG$	519/7
	α_{1D}	$G_{q/11}$	$\uparrow IP_3/DAG$	572/7
α_2-adrenoceptor	α_{2A}	$G_{i/o}$	$\downarrow$cAMP	450/7
	α_{2B}	$G_{i/o}$	$\downarrow$cAMP	450/7
	α_{2C}	$G_{i/o}$	$\downarrow$cAMP	461/7
	α_{2D}	$G_{i/o}$	$\downarrow$cAMP	450/7
β-adrenoceptor	β_1	G_s	$\uparrow$cAMP	477/7
	β_2	G_s	$\uparrow$cAMP	413/7
	β_3	G_s, $G_{i/o}$	$\uparrow$cAMP	408/7

Subtypes of Dopamine Receptors

RECEPTOR	*Subtype*	*Transducer*		*Structure (aa/TM)*
dopamine	D_1	G_s	$\uparrow$cAMP	446/7
	D_2	G_i $G_{q/11}$	$\downarrow$cAMP $\uparrow IP_3$/DAG, $\uparrow K^+$, $\downarrow Ca^{2+}$	443/7
	D_3	G_i	$\downarrow$cAMP	400/7
	D_4	G_i	$\downarrow$cAMP, $\uparrow K^+$	386/7
	D_5	G_s	$\uparrow$cAMP	477/7

Subtypes of Serotonin Receptors

RECEPTOR	*Subtype*	*Transducer*		*Structure*
5-HT (5-hydroxytryptamine)	5-HT_{1A}	$G_{i/o}$	↓cAMP	421/7
	5-HT_{1B}	$G_{i/o}$	↓cAMP	390/7
	5-HT_{1D}	$G_{i/o}$	↓cAMP	377/7
	5-ht_{1E}	$G_{i/o}$	↓cAMP	365/7
	5-HT_{1F}	$G_{i/o}$	↓cAMP	366/7
	5-HT_{2A}	$G_{q/11}$	↑IP_3/DAG	471/7
	5-HT_{2B}	$G_{q/11}$	↑IP_3/DAG	481/7
	5-HT_{2C}	$G_{q/11}$	↑IP_3/DAG	458/7
	5-HT_{3ABCDE}	internal cationic channel		478
	5-HT_4	G_s	↑cAMP	387/7
	5-ht_{5A}	$G_{i/o}$	↓cAMP	357/7
	5-HT_6	G_s	↑cAMP	440/7
	5-HT_7	G_s	↑cAMP	445/7

Example

- Some antidepressants operates as antagonist of presynaptic alpha$_2$-receptors on serotonergic synapse: NaSSA = noradrenergic and specific serotonergic antidepressant (e.g., mianserin and mirtazapine)
- These drugs induce increased monoaminergic transmission, because alpha$_2$-adrenoceptors are connected with inhibitory G_i proteins. Inhibition of inhibitory presynaptic receptors caused increased serotonin transmission.

RECEPTOR	*Subtype*	*Transducer*		*Structure*
α_2-adrenoceptor	**α_{2A}**	**$G_{i/o}$**	**↓cAMP**	**450/7**
	α_{2B}	**$G_{i/o}$**	**↓cAMP**	**450/7**
	α_{2C}	**$G_{i/o}$**	**↓cAMP**	**461/7**
	α_{2D}	**$G_{i/o}$**	**↓cAMP**	**450/7**

Psychotropic Drugs

Biochemical hypotheses of mental disorders are based on the study of mechanisms of action of psychotropic drugs at the level of:

- chemical synapse
- intracellular processes connected with signal transduction

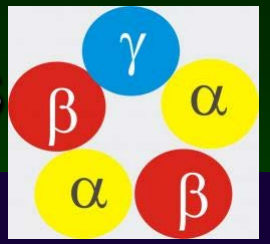
Main Psychotropic Drugs

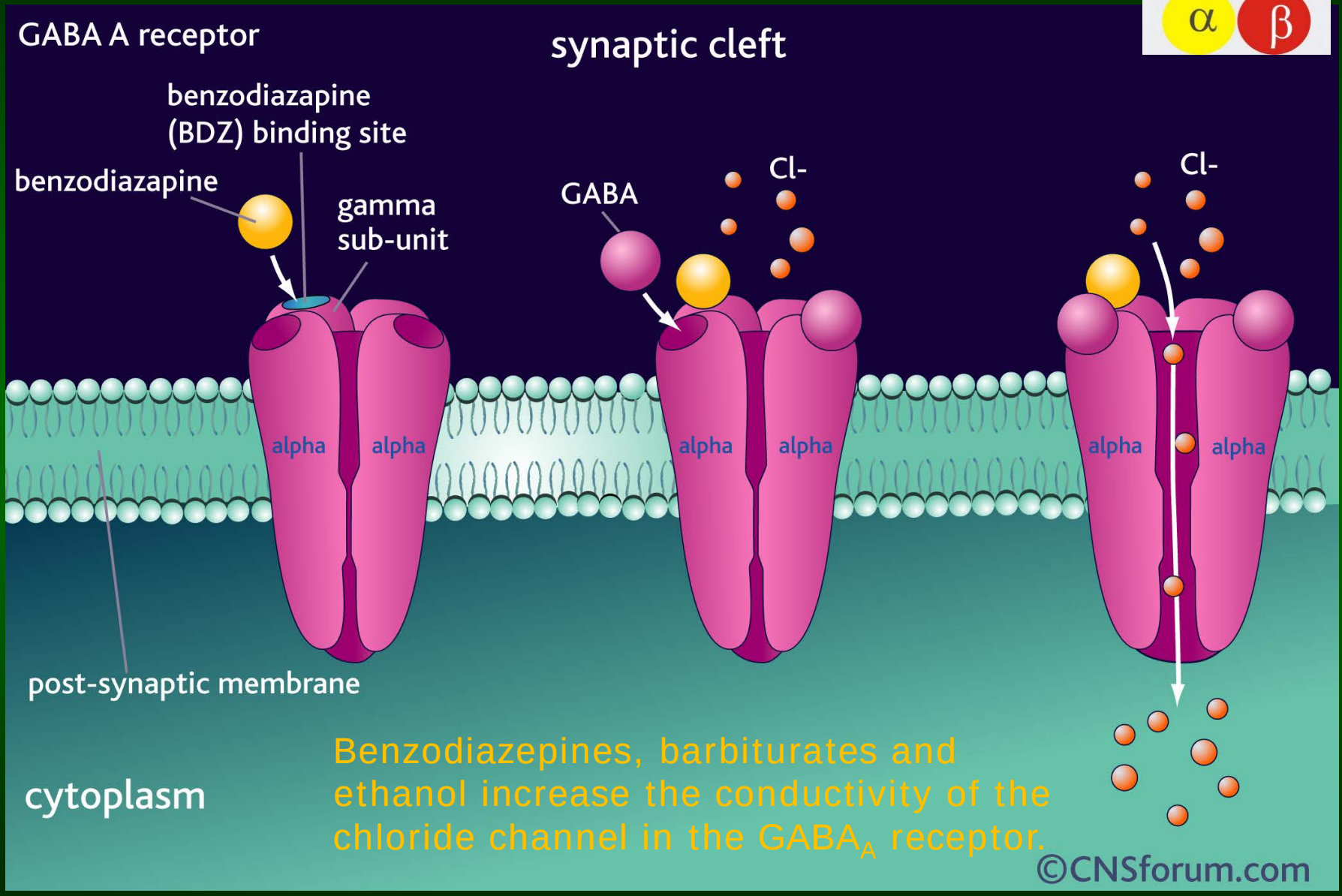
- Antipsychotics
- Antidepressants
- Mood stabilizers
- Anxiolytics
- Hypnotics
- Cognitives
- Psychostimulants
- Hallucinogens

Potential Action of Psychotropics

1. Synthesis and storage of neurotransmitters
2. Releasing of neurotransmitters
3. Receptor-neurotransmitter interactions (agonists, antagonists)
4. Catabolism of neurotransmitters
5. Reuptake of neurotransmitters
6. Transduction element (G protein)
7. Effector's system
8. Transcription factors activity and gene expression

Mechanism of action of benzodiazepines





Zdroj: http://www.cnsforum.com/imagebank/item/drug_benzo/default.aspx

Classification of Antipsychotics

Group	*Examples*
Conventional antipsychotics (classical neuroleptics)	chlorpromazine, chlorprotixene, clopenthixole, levopromazine, periciazine, thioridazine
	droperidole, flupentixol, fluphenazine, fluspirilene, haloperidol, melperone, oxyprothepine, penfluridol, perphenazine, pimozide, prochlorperazine, trifluoperazine
Antipsychotics of 2nd generation (atypical)	amisulpiride, clozapine, olanzapine, quetiapine, risperidone, paliperidon, sertindole, sulpiride, aripiprazole, brexpiprazole, cariprazine

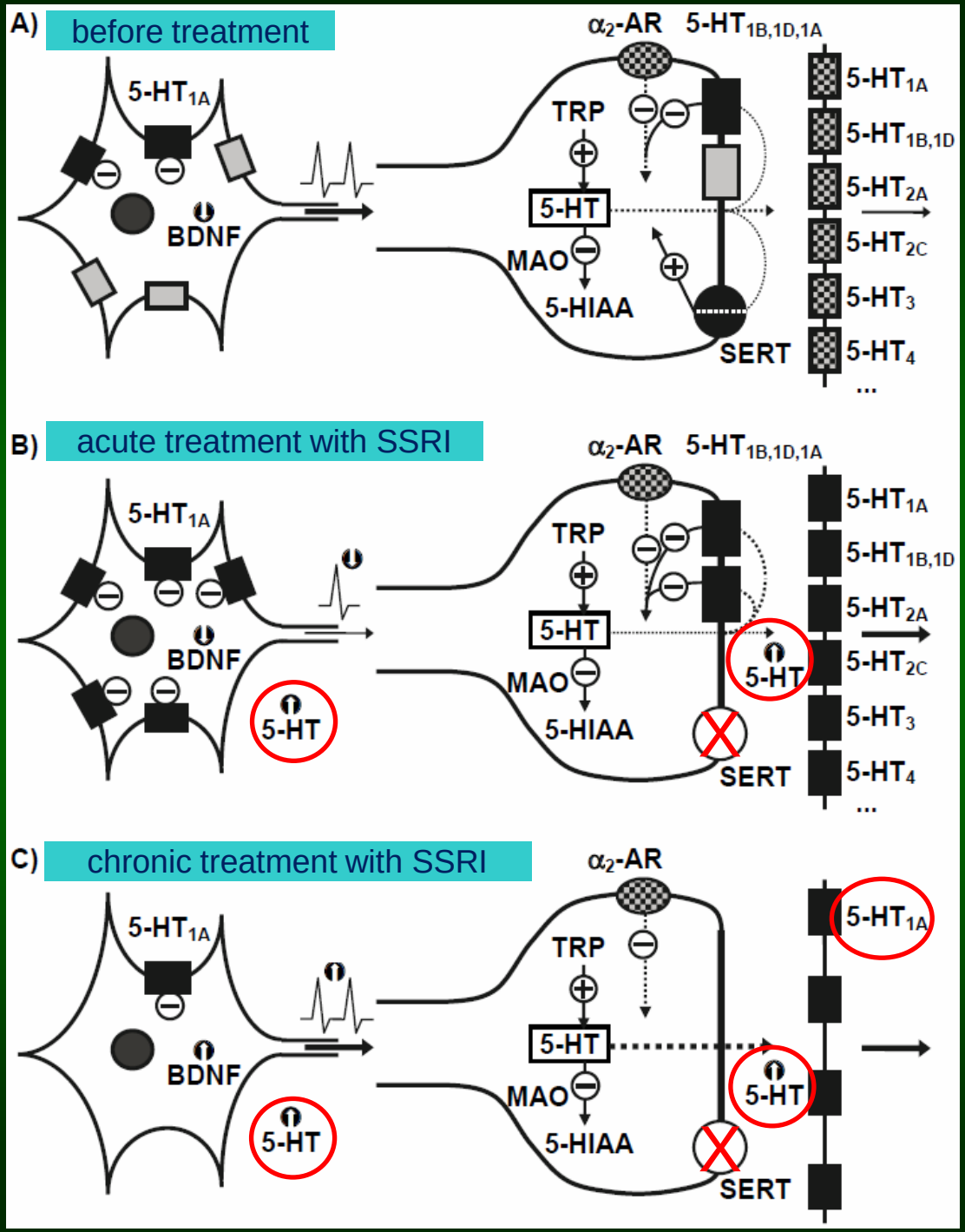
Mechanisms of Action of Antipsychotics

Conventional antipsychotics	• D_2 receptor blockade of postsynaptic in the mesolimbic pathway.
Antipsychotics of 2nd generation	• D_2 receptor modulation of postsynaptic in the mesolimbic pathway to reduce positive symptoms (hallucinations, delusions, bizarre behaviour, and positive formal thinking disorder). • 5-HT_{2A} receptor blockade and enhanced dopamine release and in the mesocortical pathway to reduce negative symptoms (alogia, affective flattening, avolition-apathy, anhedonia-asociality, and attentional deficit). • Other receptor-binding properties may contribute to efficacy in treating cognitive symptoms, aggressive symptoms and depression in schizophrenia

Classification of Antidepressants
(based on direct biochemical actions)

Inhibitors of neurotransmitter catabolism	• monoamine oxidase inhibitors (IMAO)
Reuptake inhibitors	• serotonin reuptake inhibitors (SRI) • norepinephrine reuptake inhibitors (NRI) • selective SRI (SSRI) • selective NRI (SNRI) • serotonin/norepinephrine inhibitors (SNRI) • norepinephrine and dopamine reuptake inhibitors (NDRI) • $5\text{-}HT_{2A}$ antagonist/reuptake inhibitors (SARI)
Agonists of receptors	• $5\text{-}HT_{1A}$
Antagonists of receptors	• α_2-AR • $5\text{-}HT_2$
Inhibitors or stimulators of other components of signal transduction	

Action of SSRI



Sequence of Effects of Antidepressants

Sequence of biochemical events induced by a
for discovery of molecular mechanisms assoc
therapeutic effects.

Direct Effects

- Inhibition of serotonin, norepinephrine or dopamine transporters
- Monoamine oxidase inhibition
- Receptor activation (5-HT_{1A}, sigma)
- Blockade of receptors (α_2-AR, 5-HT_{2A}, 5-HT_{2C}, NMDA)
- Intracellular action

Early Effects

- Increasing of availability and extracellular levels of monoamine neurotransmitters
- Increasing of monoamine receptors activation
- Activation of intracellular signalling pathways (adenylate cyclase, phosphoinositide, calcium)
- Activation of transcription factors (CREB, AP-1, etc.)
- Increasing of gene expression of neurotrophic factors (BDNF, NGF, etc.)
- Activation of neurotrophic signalling pathway
- Feedback effects on neurotransmission

Long-term Effects

1. Neurochemical events:

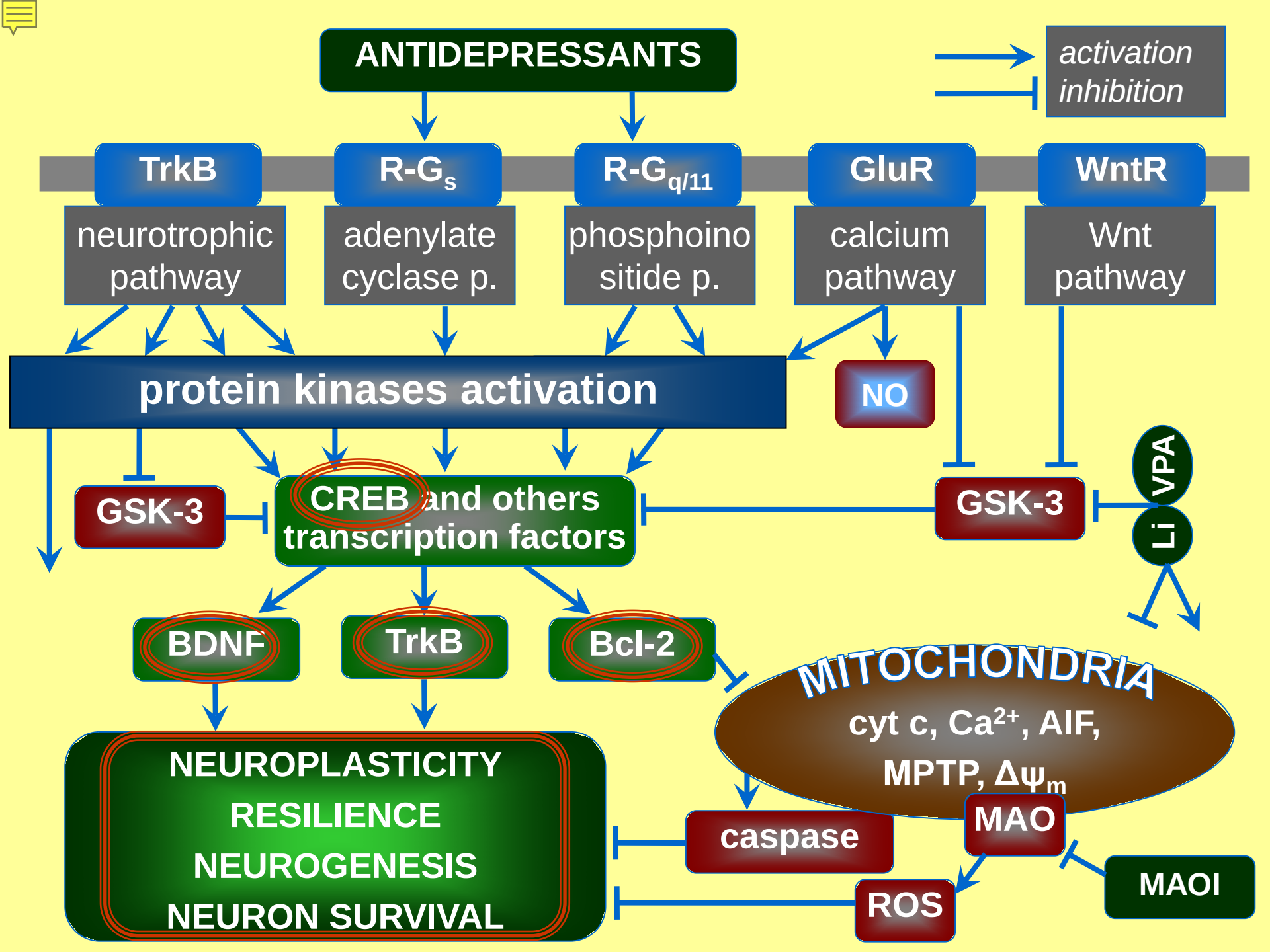
- Receptor adaptation (desensitisation or down-regulation; sensitization or up-regulation)
- Increasing of structural plasticity (synaptogenesis; formation or changes of axons, synapses, dendrites (branching, sprouting) and dendritic spines) and functional plasticity (LTP, LTD, strength of synapse)
- Antiapoptotic effects
- Support of neurogenesis, cellular resilience and neuron survival
- Protection against neurotoxic effects of cellular stress

2. Anti-inflammatory effects

3. HPA axis regulation

4. Synchronization of biol. rhythms

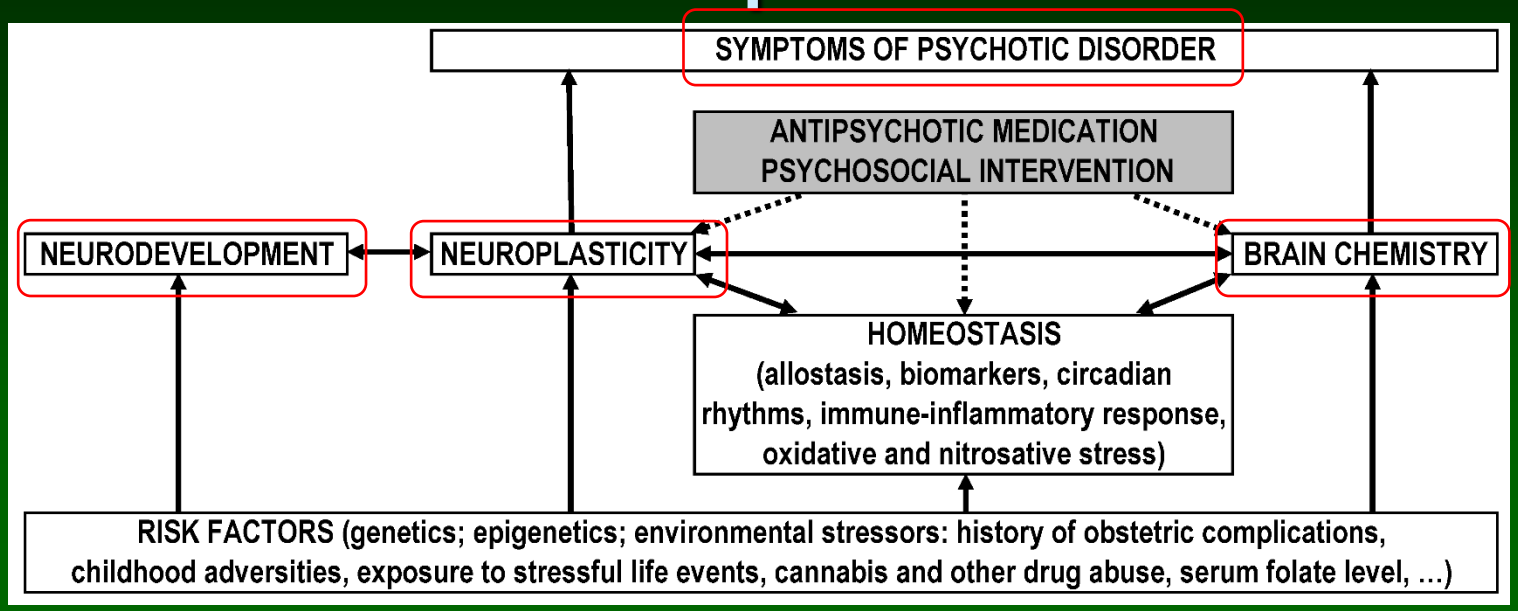
5. Epigenetic changes


ANTIDEPRESSANTS
activation
inhibition
TrkB
R-Gs
R-Gq/11
GluR
WntR
neurotrophic pathway
adenylate cyclase p.
phosphoino sitide p.
calcium pathway
Wnt pathway
protein kinases activation
NO
GSK-3
CREB and others transcription factors
GSK-3
VPA
Li
BDNF
TrkB
Bcl-2
MITOCHONDRIA
cyt c, Ca2+, AIF,
MPTP, Δψm
NEUROPLASTICITY
RESILIENCE
NEUROGENESIS
NEURON SURVIVAL
caspase
MAO
MAOI
ROS

Biological Hypotheses of Mental Disorders

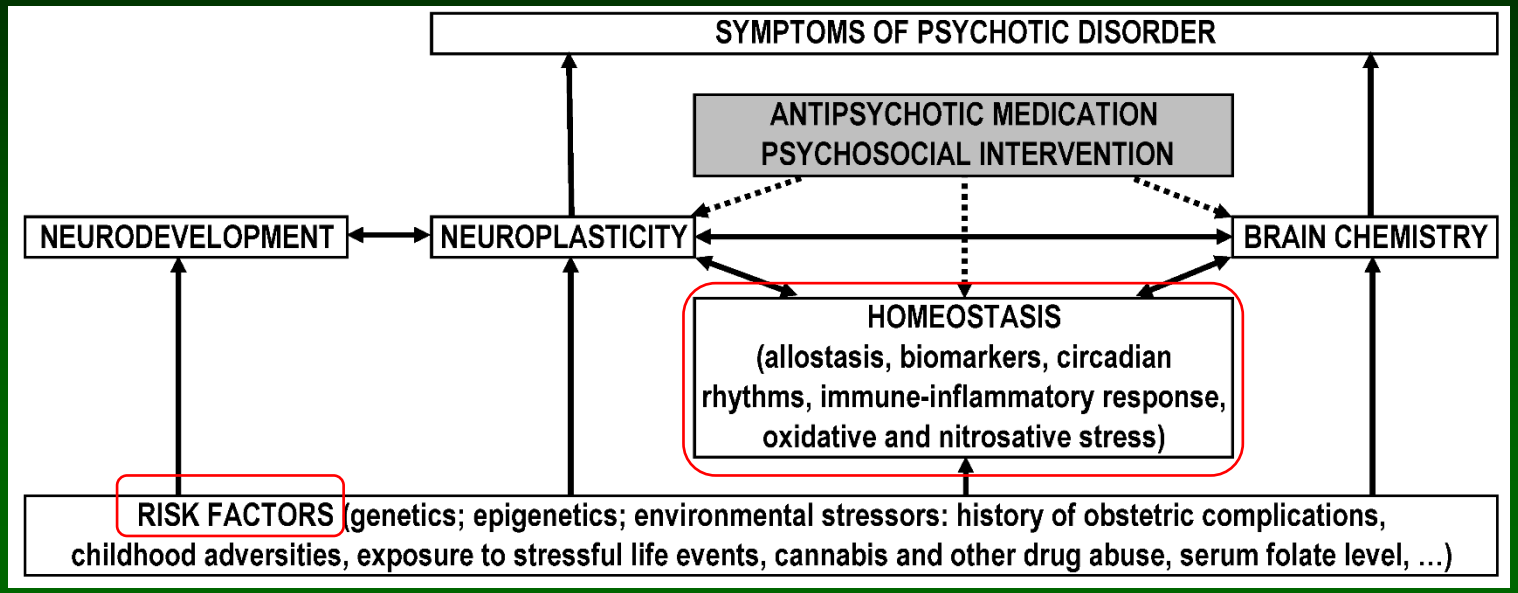
- Schizophrenia
  - schizophrenia is specifically a human psychotic disease of unknown etiology manifested by disorders of thinking, acting, perception, emotion and will.
- Affective (mood) disorders
  - mood disorders are characterized by depression, mania, or both
  - there are two groups of mood disorders with different pathophysiology: depressive disorders and bipolar disorder

Schizophrenia



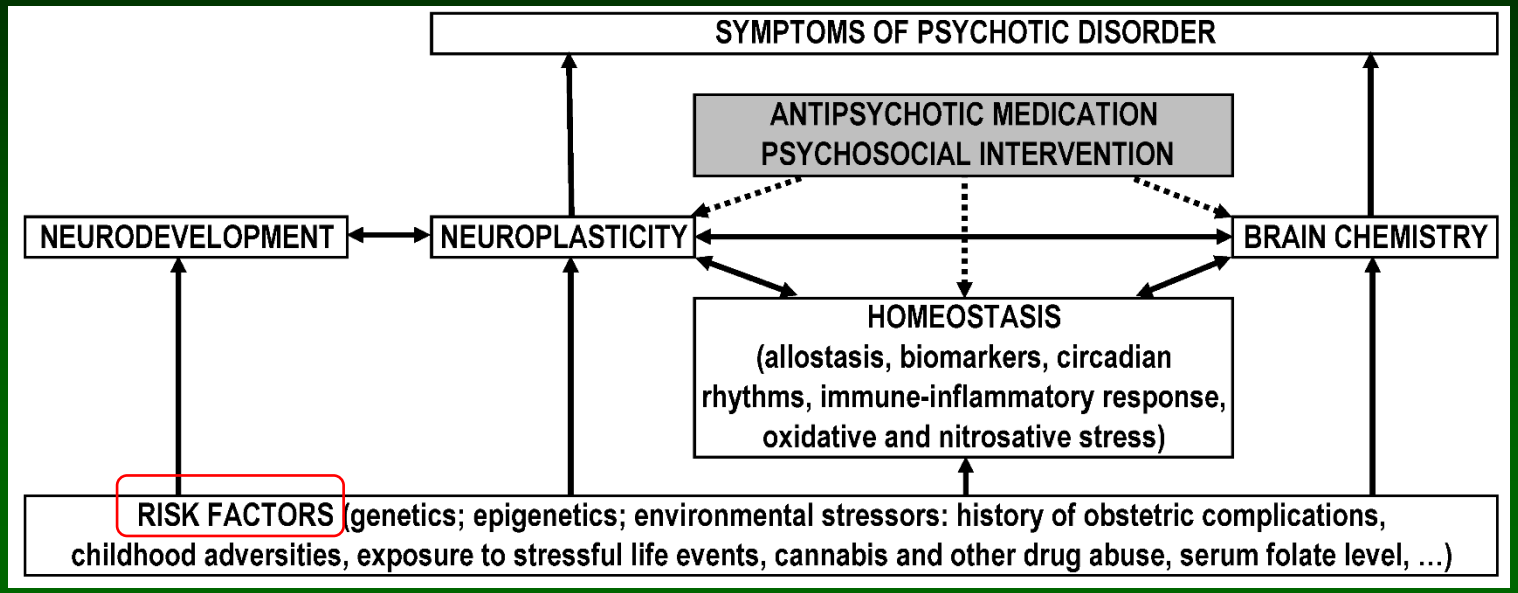
- Schizophrenia has long been thought of as a neurodevelopmental disease whose symptoms are caused by impaired brain neuroplasticity and synaptic signal transduction.

Schizophrenia



- The etiology of schizophrenia is multifactorial and reflects an interaction between genetic vulnerability and environmental contributors.
- Both the onset and chronic course of schizophrenia seem to be associated with risk factors-induced disruption of homeostatic mechanisms, with elevated allostatic load, activation of central and peripheral immune-inflammatory pathways, and increased oxidative and nitrosative stress contributing to the establishment of a new homeostatic setpoint.

Schizophrenia



- Risk factors for schizophrenia may be divided into:
  1. biological factors, which include genetic factors, prenatal and perinatal events, drug abuse, and disturbed neurodevelopment and neurotransmission; and
  2. environmental-social factors, which include urban residence, migration, childhood and adult adversity (*Stilo and Murray 2010, 2019*).

Biological models of schizophrenia

- Several biological hypotheses have been proposed to explain the neuropathology of schizophrenia, focusing on factors:
  - environmental,
  - genetic,
  - neurodevelopmental, and
  - neurochemical.
- Unifying hypotheses are currently being presented.

Schizophrenia - environmental approach

- Environmental risk factors for schizophrenia include:
  1. history of obstetric complications,
  2. exposure to stressful events in adulthood or childhood adversity, and
  3. cannabis use.
- The vulnerability-stress model of schizophrenia *(Zubin and Spring, 1977)* proposes that when stress exceeds the vulnerability threshold, the person is likely to develop a psychotic episode.

- A study of the role of both genetic and environmental influences on the development of schizophrenia is necessary to explain the fact that monozygotic twins do not share a diagnosis of schizophrenia in 100% of cases *(Brown, 2011)*.

Schizophrenia – genetic models

- Genetic models conceive of schizophrenia as a genetic disorder of the synapse and cortical microcircuits, i.e., they assume that changes in neurotransmission, neuroplasticity and synaptogenesis in schizophrenia are largely genetically determined.
- It was concluded that schizophrenia is a multifactorial disorder with a strong genetic component in the susceptibility to the disease - combination of risk genes with small effects is necessary. Genetic factors together with environmental influences can cause schizophrenia.

Schizophrenia – genetic models

- The genetic component of schizophrenia is high (heritability > 80%) with shared influence of the environment of 11% *(Sullivan et al., 2003)*. The Psychiatric Genomics Consortium (http://pgc.unc.edu) reported a systematic analysis of schizophrenia data in a multi-stage genome-wide association study (GWAS) *(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014)*. The study resulted in identification of 128 independent associations spanning 108 conservatively defined loci with genome-wide significance. Thus, genes for schizophrenia have been found. However, the identified loci do not directly imply the involvement of specific genes and explain only a small part of the hereditary risk *(Lee et al., 2012)*.
- Recently, attention is paid to the roles of
  1. non-coding RNAs,
  2. mutations, polymorphisms and deletions of mitochondrial DNA, and
  3. to the role of epigenetic changes in mental disorders *(Snyder and Gao, 2020).*

Schizophrenia - neurodevelopmental approach

- The neurodevelopmental model posits that increased risk of developing schizophrenia is the result of abnormal neurodevelopment of the brain caused by genetic and environmental factors years before the onset of the disease *(Rapoport et al., 2005, 2012)*.

- The dysplastic model of schizophrenia suggests that impaired neuroplasticity during brain development may underlie cognitive and deficit symptoms and may lead to reorganization in other neuronal circuits, which may lead to affective and psychotic symptoms *(Keshavan et al., 2015)*.

Schizophrenia - neurodevelopmental approach

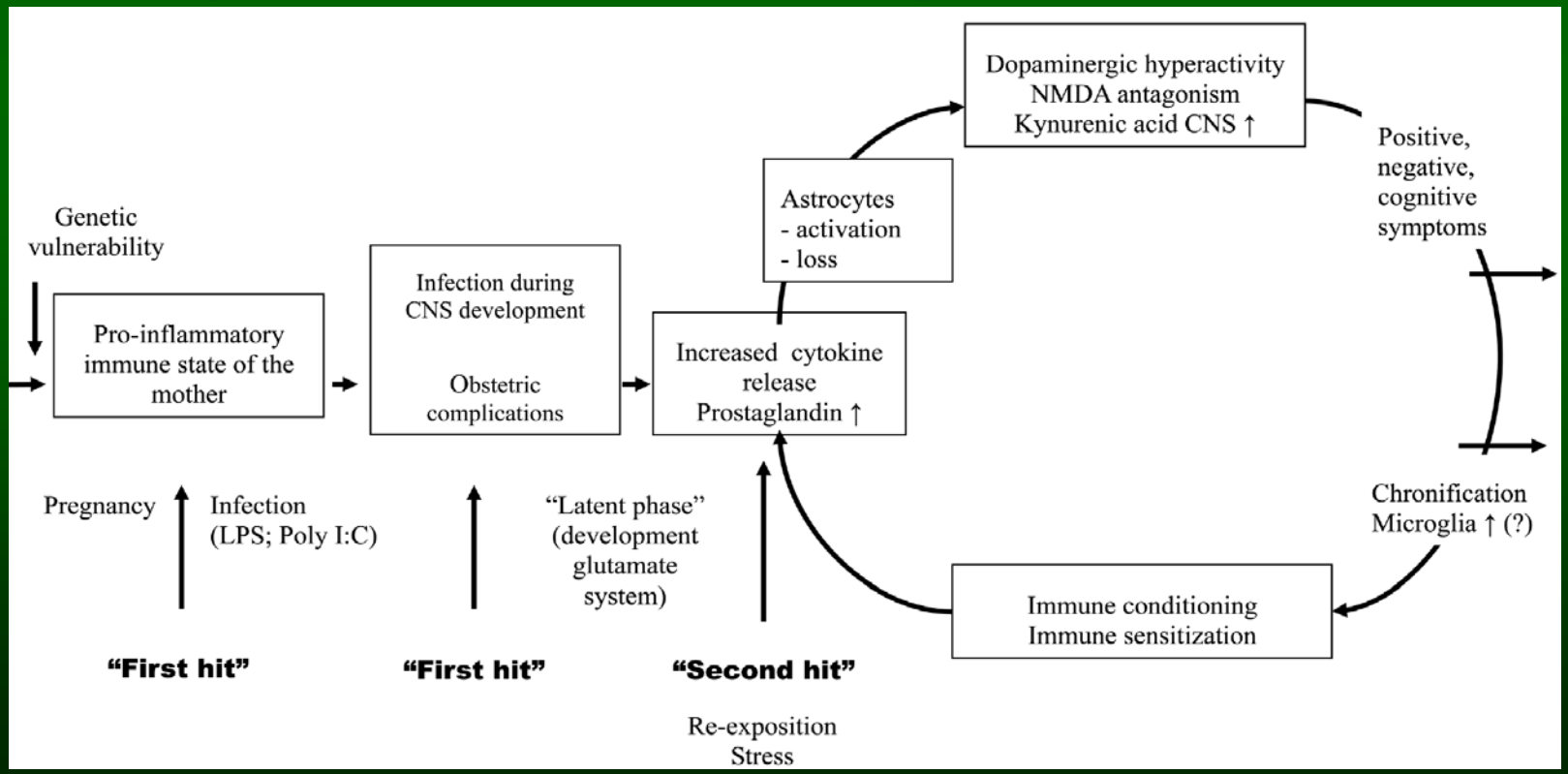
- Based on a summary of schizophrenia risk factors, a multiple hit theory of schizophrenia has been proposed *(Davis et al., 2016)*, according to which schizophrenia can be conceptualized as a process involving multiple vulnerability factors across numerous neurodevelopmental windows, where some hits are applied prenatally, in childhood, in adolescence, and in adulthood. Thus, the development of schizophrenia is driven by genetic vulnerability in interactions with environmental influences (including prenatal vitamin D, nutrition, childhood trauma, viral infections, IQ, smoking, cannabis use, and social defeat), which are cumulative and interact with each other. The neurodevelopmental phase involves changes in synaptogenesis, synaptic enhancement, and myelination, leading to excessive elimination of synapses and loss of neuroplasticity.

Schizophrenia – integrative and neurochemical hypotheses

- Neuroinflammation, mitochondrial dysfunction, and oxidative and nitrosative stress in conjunction with impaired brain development may be processes that trigger pathological changes in neurotransmitter systems leading to symptoms of schizophrenia.
- According to the mitochondrial hypothesis of schizophrenia *(Ben-Shachar, 2020)*, mitochondrial dysfunction leads to distorted neuronal activity and plasticity, causing imbalanced brain circuitry and finally abnormal behavior.

Schizophrenia - neurochemical hypotheses

- Based on observations that schizophrenia is often associated with chronic neuroinflammation in CNS *(Anderson et al., 2013)*, the vulnerability-stress model has been expanded to the vulnerability-stress-inflammation model *(Müller, 2018)*, which supposes that the symptoms of schizophrenia are associated with specific changes in dopaminergic, serotonergic, noradrenergic and glutamatergic neurotransmission following neuroinflammation and microglial activation.



Schizophrenia - neurochemical hypotheses

- According to redox-induced prefrontal oligodendrocyte precursor cell-dysfunctioning hypothesis of cognitive symptomatology in schizophrenia *(Maas et al., 2017)*, the combination of environmental factors and genetic predisposition causes oxidative stress, which includes the accumulation of ROS in oligodendrocyte precursor cells. Dysfunction of oligodendrocyte precursor cells cause hypomyelination and disruption of connectivity in the prefrontal cortex, which results in cognitive symptoms of schizophrenia.

Schizophrenia - dopamine hypothesis

- According to the classical (receptor) dopamine hypothesis of schizophrenia, psychotic symptoms are related to dopaminergic hyperactivity in the brain. Hyperactivity of dopaminergic systems during schizophrenia is result of increased sensitivity and density of dopamine 2 receptors. This increased activity can be localized in specific brain regions *(Meltzer and Stahl, 1976; Snyder, 1976; Carlsson, 1988)*.
- The dopamine hypothesis does not assume that dopamine hyperactivity fully explains schizophrenia. Overactivation of D_2 receptors appears to be only one effect of the overall dysregulation of chemical synapses in this disease.
- The modified dopamine hypothesis assumes that schizophrenia is characterized by abnormally low prefrontal dopamine activity (negative symptoms are caused by frontal hypodopaminergia) leading to excessive dopamine activity in mesolimbic dopamine neurons (positive symptoms are caused by striatal hyperdopaminergia) *(Davis et al., 1991)*.

Evidence for the dopamine hypothesis of schizophrenia

Evidence for dopamine hypothesis include:

(1) Drug abuse effects: amphetamine, cocaine and similar stimulatory drugs increase levels of dopamine in the brain and can cause symptoms which resemble those present in psychosis; hallucinogens may enhance dopaminergic transmission via 5-HT_{2A} receptor blockade *(Lieberman et al., 1987; López-Giménez and González-Maeso, 2018)*.

(2) Effects of antipsychotics: almost all antipsychotics, which are effective in the treatment of schizophrenia symptoms, has been found to antagonize dopamine binding, particularly at dopamine 2 receptors *(Seeman, 1987; Grinchii and Dremencov, 2020)*.

(3) Increased dopamine synthesis and dopamine release capacity in striatum in schizophrenia *(Howes and Murray, 2014)*.

Schizophrenia - neurochemical hypotheses

- The unifying version of the dopamine hypothesis of schizophrenia suppose that multiple environmental and genetic risk factors (genes, stress, drugs, and frontotemporal dysfunction) interact, resulting in striatal dopamine dysregulation, which alters the signal transmission and leads to psychosis *(Howes and Kapur, 2009)*.

- The hypothesis no longer focuses closely on the dopamine system, but combines risk factors, including pregnancy and obstetric complications, stress and trauma, drug abuse, and genetic predisposition and environment–gene interactions, with both increased presynaptic striatal dopaminergic function and affecting other brain functions that underlie negative and cognitive symptoms.
- A model has been presented, of how genes and environmental factors may sensitize the dopamine system so that it is vulnerable to acute stress, leading to progressive dysregulation and the onset of psychosis *(Howes et al., 2017)*.

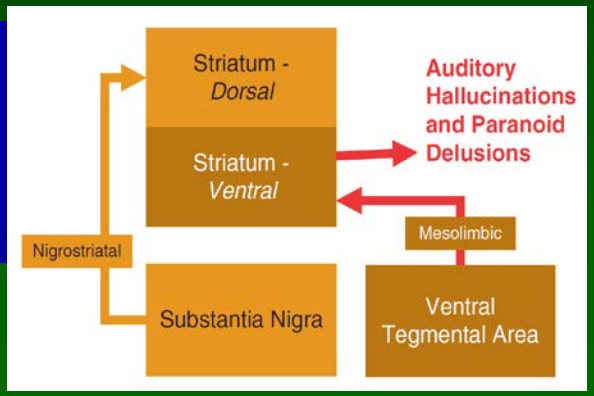
Schizophrenia - glutamate hypothesis

- NMDA receptor hypofunction hypothesis of schizophrenia *(Snyder and Gao, 2020)* assumes that genetic and other risk factors induce epigenetic alterations leading to glutamate NMDA receptor hypofunction.
- NMDA receptor hypofunction induces a cascade of downstream disturbances in neuronal activity, calcium entry, and epigenetic machinery. Changes in neurotransmission results in cognitive decline and social deficit found in schizophrenia.
- According to this hypothesis, changes in the dopamine system are secondary to NMDA receptor hypofunction.

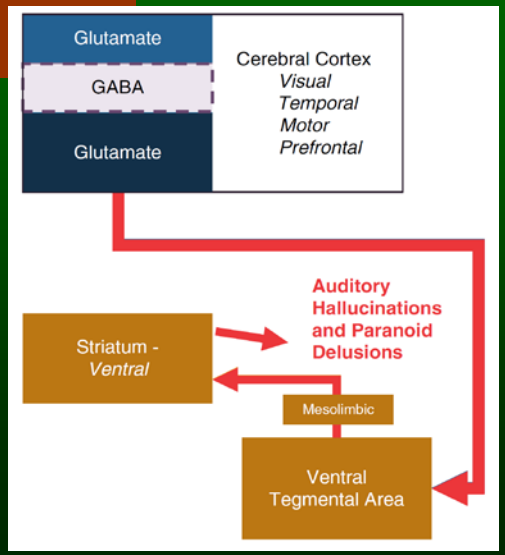
Schizophrenia - neurochemical hypotheses

There are 3 interconnected pathways hypothetically associated with hallucinations and delusions - all 3 pathways can lead to hyperactivity of the mesolimbic dopamine pathway *(Stahl SM. CNS Spectrums (2018), 23, 187–191)*:

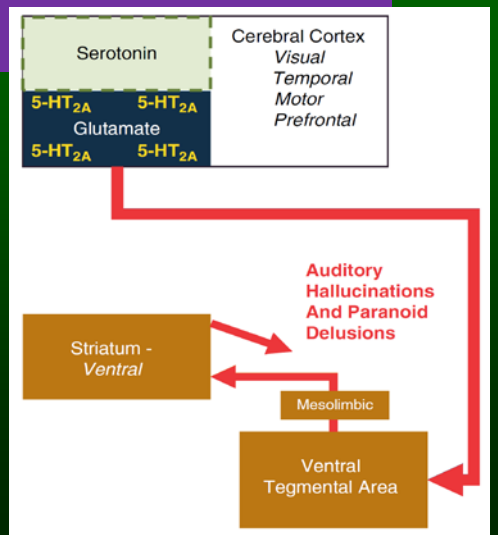
1. Dopamine hyperactivity at D_2 dopamine receptors in the mesolimbic pathway, which extends from the ventral tegmental area (VTA) to the ventral striatum.



2. Glutamate NMDA receptor hypoactivity on GABAergic interneurons in the prefronal cortex.



3. Serotonin hyperactivity of 5-HT_{2A} receptors on glutamate neurons in the cerebral cortex.



Schizophrenia - cannabinoid hypothesis

According to the cannabinoid hypothesis *(Emrich et al., 1997; Müller-Vahl and Emrich, 2008; El Khoury et al., 2012)*, changes in the endocannabinoid system may contribute to the pathogenesis of schizophrenia. The hypothesis proposes that increased activation of the endocannabinoid system through CB_1 receptors on GABAergic interneurons in the ventral tegmental area, basolateral amygdala, and medial prefrontal cortex may lead to hyperdopaminergic and hypoglutamatergic status, which may cause schizophrenia.

Schizophrenia - integrative hypothesis

The biological hypotheses of schizophrenia can be summarized in a neurodevelopmental-vulnerabilty-neurochemical model:

Schizophrenia is a neurodevelopmental disease whose symptoms are caused by impaired synaptic plasticity and impaired neurotransmission in certain neuronal circuits in the brain. Neurodevelopmental disorder can be caused by both genetic and epigenetic influences, as well as environmental influences (birth complications, stress, toxins, and drugs) and gene-gene or gene-environment interactions over time. Impaired neurodevelopment leads to an increased susceptibility to schizophrenia through an increased sensitivity or pathological response to stress and/or neuroinflammation. The onset of symptoms of schizophrenia is associated with impaired function of neuronal circuits due to impaired neurotransmission, especially at the level of signal transduction through the chemical synapse. Impaired synaptic plasticity includes impaired cellular energy and transport and changes in the number and strength of synapses, i.e., processes associated with response to stress events, neuroinflammation, calcium imbalance, and mitochondrial dysfunction.

Mood Disorders

- Mood disorders are characterized by depression, mania, or both.
- There are two groups of mood disorders (with different pathophysiology):
  - depressive disorders
  - bipolar disorder

Mood disorders – monoamine hypothesis

- According to the neurotransmitter monoamine hypothesis of depression, decreased concentrations of monoamine neurotransmitters in the brain are the pathophysiological basis of depression.
- Due to the delayed therapeutic effects of antidepressants, various receptor monoamine hypotheses have been proposed that have linked depressive symptoms to long-term adaptive mechanisms including sensitization or desensitization and upregulation or downregulation of certain receptors and neurotransmitter transporters.
  - The most commonly observed receptor changes induced by long-term administration of antidepressants were regulation by a decrease in the number of ß1-adrenergic receptors or a decrease in the response to somatodendritic 5-HT_{1A} receptor agonists. However, changes have also been observed in other receptor systems.

Mood disorders – monoamine hypothesis

- The advanced monoamine hypothesis suggests that elevated MAO-A levels may be considered a general process for lowering monoamines in the brain (unrelated to certain symptoms), while regional density of monoamine transporters (especially serotonins) has a selective effect on individual monoamines strongly related to certain symptoms of depressive disorder. So, both MAO-A activity and density of transporters are supposed to be included in the pathophysiology of affective disorders.

- To explain why life stress is a predictor of a depressive episode in some individuals, gene x environment interactions have been studied. It is thought that a serotonin-transporter-linked promoter region (5-HTTLPR) polymorphism may alleviate the effect of an adverse environment on the development of depression.

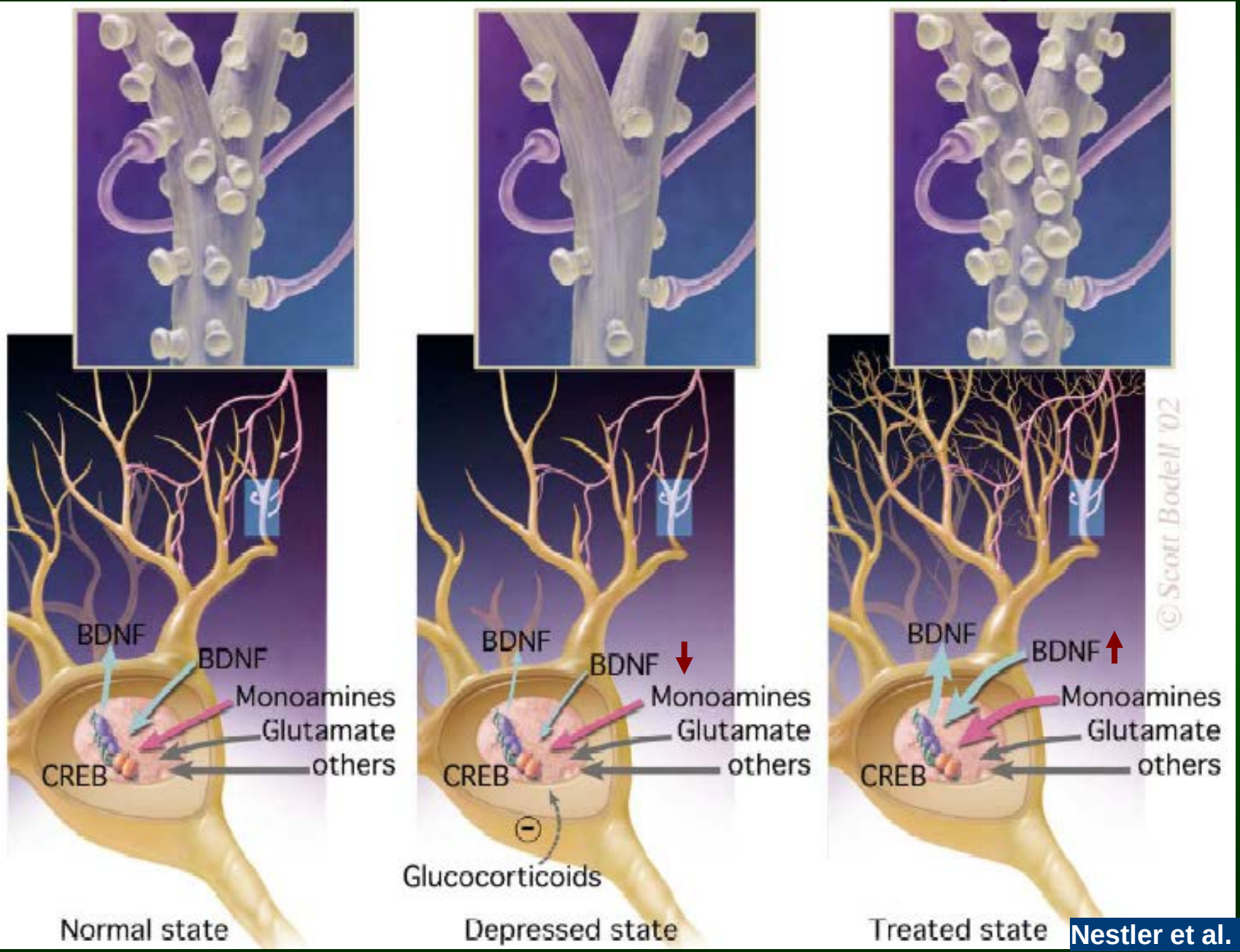
Mood disorders – neurotrophic hypothesis

Neurotrophic hypothesis of depression:

Transcription factor, **cAMP response element-binding protein** (CREB), is one intracellular target of long-term antidepressant treatment and **brain-derived neurotrophic factor** (BDNF) is one target gene of CREB. Chronic stress leads to decrease in expression of BDNF in hippocampus. Long-term increase in levels of glucocorticoids, ischemia, neurotoxins, hypoglycaemia etc. decreases neuron survival. Long-term antidepressant treatment leads to increase in expression of BDNF and his receptor trkB through elevated function of serotonin and norepinephrine systems.

Duman et al. 1997

Neurotrophic Effects of Antidepressants



Nestler et al. 2002

Mood disorders – inflammatory and neurodegenerative hypothesis

- The inflammatory and neurodegenerative hypothesis of depression supposes that depression is associated with both inflammatory processes, as well as with neurodegeneration and reduced neurogenesis. According to this hypothesis, enhanced neurodegeneration and defects in neurogenesis in depression are caused by inflammatory processes, related to the production of oxidative and nitrosative stress, tryptophan catabolites along the indoleamine-2,3-dioxygenase pathway, proinflammatory cytokines and lowered ω-3 polyunsaturated fatty acid status. Anti-inflammatory compounds should be able to counteract at least partly the enhanced neurodegeneration and decreased neurogenesis.

Maes et al. 2009

Mood disorders – mitochondrial hypothesis

- The hypothesis of mitochondrial dysfunction in bipolar disorder (*Stork and Renshaw 2005*) was proposed that disorder involves impaired oxidative phosphorylation, a shift toward glycolytic energy production, a decrease in total energy production and/or substrate availability and altered phospholipid metabolism.
- According to calcium and mitochondrial dysfunction hypothesis of bipolar disorder *(Kato 2008)*, mitochondrial DNA (mtDNA) polymorphisms/mutations or mtRNA deletions caused by nuclear gene mutations can cause mitochondrial dysregulation of calcium leading to symptoms of bipolar disorder.
- Mitochondrial hypotheses correspond to, above mentioned, neurotrophic hypothesis because of an important role of calcium signalling pathway in synaptic plasticity regulation.

Mood disorders - conclusion

- It is suggested that the changes in cognitive functions, learning, memory and the emotions during depression are caused by damaged neuroplasticity in hippocampus, amygdala and cerebral cortex.
- The exact neurobiological processes included in both mood disorders and schizophrenia have not yet been sufficiently explored. The main attention has been focused on changes in monoaminergic and glutamatergic neurotransmission and in neuroplasticity.

Thank you for your attention