Neurochemistry

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**Transmitters of Autonomic Nervous System** – see p. A34

**Neurotransmitter** – endogenous chemical agent that relays information from one neuron to another through synapse; released by presynaptic cell (upon excitation), crosses synapse to *stimulate* or *inhibit*\* postsynaptic cell by binding to receptor.

\*final result (hyperpolarization or depolarization) is dependent on both **transmitter** and its **receptor**.

* to qualify as neurotransmitter, five classic criteria must be demonstrated:
	1. presence within neurons
	2. synthetic pathways with identified enzymes
	3. release mechanisms from neuron into synapse
	4. metabolic pathways to effect removal from synapse
	5. mimicry of neuronal activity by iatrogenic application of neurochemical.

N.B. few neurotransmitters actually fulfill all criteria within CNS.

* original **Dale-Feldberg law**: single neuron makes use of ***the same transmitter*** at all of its synapses (i.e. each neuron releases one and only one neurotransmitter).
* reformulated **Dale-Feldberg law**: single neuron makes use of ***the same combination of chemical messengers*** at all of its synapses.

***More than one neurotransmitter may be released at any given synapse!***

* one transmitter may predominate (others – **cotransmitters, comodulators**) – classification of neuronal systems.
* tobulėjant tyrimo metodikoms, atrandami vis nauji transmiteriai ir specifiniai traktai.

pvz. dauguma katecholaminerginių traktų (labai ploni, nemielinizuoti) atrasta tik naudojant fluorescence microscopy).

Classification of neurotransmitters

1. Monoaminergic – modulating action in CNS (cell bodies in relatively few locations with multiple branched axons projecting to almost all parts of CNS):
	1. **Catecholaminergic**:
		* 1. **dopamine**
			2. **noradrenaline**
			3. **adrenaline**
	2. **Serotonergic** – **serotonin**
	3. **Histaminergic** – **histamine**
2. Cholinergic – **acetylcholine** – major transmitter in PNS (except postganglionic sympathetic neurons)
3. Amino acids – major transmitters in CNS:
	* 1. **Excitatory** – **glutamate**, **aspartate**, **cysteic acid**, **homocysteic acid**.
		2. **Inhibitory** – **γ-aminobutyric acid (GABA)**, **glycine**, **taurine**, **β-alanine**.
4. Peptidergic – žinomi 28 peptidai (substance P & other tachykinins, ADH, oxytocin, CRH, TRH, GnRH, GRH, somatostatin, opioids, CKK, VIP, neurotensin, gastrin, glucagon, motilin, secretin, calcitonin gene-related peptide, neuropeptide Y, activins, inhibins, angiotensin II, galanin, ANP, brain natriuretic peptide, etc.)
* peptidinių transmiterių gausa pasižymi hypothalamus.
1. Purines:
2. **adenosine** (general CNS depressant, coronarodilator; *stimulatory effects of caffeine and theophylline* are due to adenosine receptors blockade).
3. **ATP**
4. Lipids: **anandamide**.
5. Gases – small gaseous molecules: **NO**, **CO**.

Neurochemical pathways that *bypass thalamus* on their way to cerebral cortex:

* neurotransmitter – nucleus of origin:
	1. **acetylcholine** – nucleus basalis of Meynert, hypothalamus
	2. **GABA, neuropeptides, histamine** – hypothalamus
	3. **dopamine** – substantia nigra, ventral midbrain tegmental nuclei
	4. **serotonin** – raphe nuclei (midbrain)
	5. **noradrenaline** – locus ceruleus
* features:
	+ - tai discrete nuclei (basal forebrain, hypothalamus, midbrain tegmentum).
		- direct, diffuse, profuse projections to entire cortex – **modulatory action**.
		- most ending form *true synapses*; some endings are *not true synapses* (noradrenerginės ir serotonerginės skaidulos).
* ***neurotransmiterių balansas limbinėje sistemoje*** nulemia mūsų nuotaikas, drives, instinctual behaviors; todėl reikia klausti ne “How are you?”, bet “Which neurochemical system predominates today – serotonergic, dopaminergic, cholinergic, or peptidergic?”.
* gausiausiai įvairių transmiterių randama in **circuits of basal motor nuclei**:



Catecholamines

biosynthesis & catabolism

see 812 p. (*biochemistry*), 2723 p. (*endocrine system*)

* sintezuojami iš **Tyrosine**.
* NA ir A katabolizuojami į **VMA (vanillylmandelic acid)**; dopamine katabolizuojamas į **homovanillic acid**.

N.B. ***neuronuose*** katabolizmą vykdo monoamine oxidase (MAO)! ***ekstraceliulinius*** katecholaminus ardo catechol-O-methyltransferase (COMT)

Monoamine oxidase is predominantly *intraneuronal* enzyme (located in outer membrane of mitochondria).

* in human brain, at least two forms of MAO have been identified:

type A (specifically inhibited by clorgyline)

type B (specifically inhibited by deprenyl)

location

CNS

* katecholaminerginių neuronų taisyklė:

dopaminerginiai – in midbrain

noradrenerginiai – in pons

adrenerginiai – in medulla

* ***catecholaminergic projections*** (except dopaminergic) are diffuse, having less distinct body topography – modulate or gate many general functions (e.g. mood, attention).

Noradrenaline (s. Norepinephrine, Levarterenol)

|  |
| --- |
| * stored in characteristic **small vesicles with dense core** (granulated vesicles); transport into vesicles is blocked by reserpine, tetrabenazine.
* **release into synapse** is blocked by guanethidine, bretylium.
* **reuptake** is major mechanism of NA removal from synaptic cleft;
* noradrenergic neuron damage → no reuptake → more NA from other sources is available to stimulate receptors (*denervation hypersensitivity*).
* reuptake is blocked by tricyclic antidepressants**,** cocaine.
* reuptaken NA is *oxidized* by **monoamine oxidase (MAO)**; deaminated derivatives (3,4-dihydroxy-mandellic acid, 3,4-dihydroxy-phenylglycol) enter circulation and are *O-methylated* in liver by **catechol-O-methyltransferase (COMT)**.
 |

* secreted extracellular NA is *O-methylated* by **COMT**, then normetanephrine is oxidized by **MAO** in liver.
* end product of catabolism (by either way) is **vanillylmandelic acid (VMA)** – secreted into urine.

 

X, receptor

Release of NE is modulated by NE itself (acting on presynaptic α2-autoreceptors), and by ACh, angiotensin II:



Noradrenerginiai neuronai in CNS tęsiasi nuo medulla iki basal forebrain, but most concentrate in pons:

1. **nucleus locus ceruleus:**
* pagrindinės **aferentės** – *dorsal raphe nucleus of midbrain* (serotonerginis); šiaip aferentės labai plačios.
* **eferentės** į visas CNS struktūras (branduolys su plačiausiomis projekcijomis!) – aksonai šakojasi tūkstančius kartų.
* normal function of locus ceruleus system remains mystery (may be related to behavioral vigilance – orientation to unexpected external sensory stimuli).
* degeneruoja sergant parkinsonizmu (šalia substantia nigra degeneracijos).
1. **other tegmental pontine nuclei (of RF)** – projekcijos ne tokios plačios.
* noradrenerginės skaidulos keliauja:
	1. periventricular pathway (dorsal longitudinal fasciculus of Schütz, etc.)
	2. central tegmental tract
	3. ventral tegmental-medial forebrain bundle tract
* žievėje noradrenerginės skaidulos nesudaro aiškių sinapsių.
* noradrenergic axons have tendency to regenerate! (at least in lower animals)
* noradrenergic system↓ may cause ***depression***, and ↑ may cause ***mania*** (now this **catecholaminergic theory of mood disorders** is questioned).

In PNS - most **postganglionic sympathetic** endings.

N.B. epinephrine is not mediator at postganglionic sympathetic endings!

Receptors

* serpentine receptors **coupled via Gs/i/q proteins** to adenylyl cyclase, K+ channels, phospholipase C.

|  |  |  |
| --- | --- | --- |
| **Receptor Type** | **Second Messenger** | **Net Channel Effects** |
| α1A, α1B, α1D | ↑ IP3 & DAG | ↓ K+ |
| α2A, α2B, α2C | ↓ cAMP | ↑ K+, ↓ Ca2+ |
| β1 | ↑ cAMP |  |
| β2 | ↑ cAMP |  |
| β3 | ↑ cAMP |  |

|  |  |  |
| --- | --- | --- |
| **Receptor** | Agonist activity | * NA has greater affinity to **α receptors**; A – to **β receptors**.
* **α receptors** are sensitive to both NA and A; **β receptors** are sensitive to A but relatively insensitive to NA.
* isoproterenol is strongest **β receptor** agonist.

N.B. epinephrine is single most active endogenous amine on both **α** and **β receptors**! |
| α1 | NA > A > isoproterenol |
| α2 | A > NA > isoproterenol |
| β1 | isoproterenol > A = NA |
| β2 | isoproterenol > A >> NA |

also see A34, A35 p.

Epinephrine

* cell bodies in **medulla**; project to hypothalamus (function is uncertain), thalamus, periaqueductal gray, and spinal cord.

Dopamine

pharmacology – see A35 p.

**catabolism**

≈ as in NA (i.e. reuptake, MAO, COMT); end product – **homovanillic acid (HVA)**.

**location**

1. small intensely fluorescent (SIF) cells in autonomic ganglia
2. CNS
3. adrenomedullary cells

Regions of CNS lacking dopaminergic perikarya:

* 1. Spinal cord
	2. Nuclei of cranial nerves
	3. Thalamus
	4. Cerebral cortex & cerebellar cortex

Location of dopaminergic perikarya and axonal distribution

I. **Telencephalon**:

1. **Olfactory bulb** (periglomerular cells) – have **no axons** at all (amacrine interneurons)\*
2. **Septal area**

II. **Diencephalon**:

1. **Retina** – have **no axons** at all (amacrine interneurons)\*
2. **Zona incerta** – have **short axons**
3. **Hypothalamus** (arcuate and periventricular nuclei) – have **short axons** - *tuberoinfundibular tract* (secretes dopamine into portal hypophysial vessels to inhibit prolactin secretion).

\*inhibit lateral transfer of excitatory activity (signal-to-noise ratio↑)

III. **Midbrain tegmentum**:

1. **Substantia nigra** (***pars compacta*** – pigmented dorsal part) – **axons of medium length** run rostrally to:
	* **corpus striatum** (*nigrostriatal* tract) – main projection!; highly organized according to body topography!
	* **thalamic motor nuclei, nucleus subthalamicus, hypothalamus** (*nigrodiencephalic* fibers).
	* **motor cortex** (*nigrocortical* fibers).

N.B. in normal humans there is steady loss of dopamine receptors in basal ganglia with age (men > women)

1. **Ventral tegmental nuclei** – send **long axons** – ryšiai platesni negu substantia nigra:
	* 1. ***kaudaliai*** (!) pasiekia spinal cord.
		2. ***rostraliai*** projektuojasi į:

entire cortex (*mesocortical tract*);

limbic structures (*mesolimbic tract*) - role in addiction to drugs, schizophrenia.

Receptors

|  |  |  |
| --- | --- | --- |
| **Receptor Type** | **Second Messenger** | **Net Channel Effects** |
| D1, D5 | ↑ cAMP |  |
| D2 | ↓ cAMP | ↑ K+, ↓ Ca2+ |
| D3, D4 | ↓ cAMP |  |

* serpentine receptors **coupled to G proteins**.
* D1, D2 receptors are present in ***striatum*** - control extrapyramidal system; D1 also relaxes ***renal*** ***vascular*** smooth muscle.
* D3, D4, D5 receptors are present in ***limbic system***.
* D3 and D4 play role in thought control (limit negative symptoms of schizophrenic processes); D4 receptors have greater affinity for "atypical" antipsychotic drug clozapine - effective in schizophrenia (number of D4 receptors is increased sixfold in schizophrenia).

Modulation of Dopamine activity

Dopamine activity can be **increased** by four mechanisms: see Mov10 p. for *pharmacology*

1. **increased synthesis** - by giving levodopa, s.l-dopa - it is product beyond rate-limiting enzyme (*tyrosine hydroxylase*) + there is abundant amount of next enzyme (*aromatic amino acid decarboxylase*) in CNS;
* if dopa is combined with peripherally active *DOPA decarboxylase* inhibitor **carbidopa**, more dopa is delivered across BBB.
* levodopa + carbidopa action is enhanced by *COMT* inhibitor **tolcapone**. see Mov10 p.
1. **increased release** – by drugs forcing release of presynaptic catecholamines (amphetamine, cocaine, methylphenidate).
2. **prolongation of activity**:
	1. by blocking re-uptake (amantadine – also stimulates dopamine release).
	2. by blocking catabolism - with *MAO B* inhibitors(deprenyl, s. selegiline)
3. **receptor stimulation** - by direct agonists at receptor level (bromocriptine, pergolide, pramipexole, ropinirole).

N.B. orally administered dopamine cannot cross blood-brain barrier!

Dopamine function can be **antagonized** by three mechanisms:

1. **decreased synthesis** - α-methyl para-tyrosine inhibits tyrosine hydroxylase.
2. **decreased release (dopamine depleters)** - reserpine and tetrabenazine (block vesicular packaging of dopamine).
3. **D receptor** **blockade** - **neuroleptics**.

Clinical Effects:

dopamine↓ → extrapyramidal movement disorders (dopamine D2 receptor blockade).

dopamine↑ → psychomotor activation, aggravation of psychoses.

**Dysfunction of dopaminergic systems** priklauso nuo:

1. *dopamine* kiekio
2. *receptorių* jautrumo

jei ↑ - ***involuntary movements***

jei ↓ - ***bradykinesia, akinesia*** (parkinsonism)

**Schizophrenia** – overactive ***limbic*** dopaminergic system;

* dopamine antagonists pagerina būklę, tačiau sukelia parkinsonizmą;
* ilgai gydant dopamine antagonists, padidėja dopamino receptorių jautrumas → hyperkinesias (tardive dyskinesia).

Serotonin (s. 5-hydroxytryptamine, 5-HT)

|  |  |
| --- | --- |
| * sintezuojamas iš **Tryptophan** :
1. rate-limiting step (regulated by availability of substrate and cofactors; not influenced by 5-HT concentration!) - hydroxylation by *tryptophan hydroxylase* to form 5-hydroxytryptophan (5-HTP).
2. decarboxylation by *amino acid decarboxylase* to serotonin.
* transportą į sinaptines pūsleles blokuoja reserpine, tetrabenazine.
* katabolizuojamas (after reuptake) su **MAO** (primarily MAO-A) į **5-hydroxyindoleacetic acid (5-HIAA)**

see 813 p. (*biochemistry*) * urinary 5-HIAA is index of serotonin metabolism rate.
* **melatonin** is ***N-acetylated*** derivative of serotonin;

***N-methylated*** and ***N-formylated*** derivatives are also formed in brain (may be related to psychosis). | D:\Viktoro\Neuroscience\A. Neuroscience Basics\A3-5. Neuron, Synapsis, Neurochemistry\00. Pictures\Serotonergic ending.jpg |

Highest 5-HT concentrations are in platelets and GI tract (90% of body’s serotonin; enterochromaffin cells, myenteric plexus).

* *carcinoid tumors* synthesize large quantities of serotonin.

In CNS esti tik 2% viso organizmo serotonino - serotonerginiai neuronai susitelkę in *(para)median plane of brain stem tegmentum* – **raphe nuclei** (nucl. raphes dorsalis, nucl. raphes medianus, nucl. raphes magnus, nucl. raphes pallidus, etc.).

* *raphe nuclei degeneruoja* (→ brain dysfunction) in Alzheimer disease (nucleus raphe dorsalis), chronic alcoholism.
* serotonerginiai neuronai turi primitive, large, relatively unbranched dendrites (isodendritic).
* dendritai sudaro persipinančius pluoštelius, kurie artimai kontaktuoja su ***blood vessels*** ir ***ventricular surfaces*** – chemical sampling of blood and CSF.
* serotonerginės projekcijos (kaip ir noradrenerginės) į visas CNS struktūras – **augmenting and modulating role**.
	+ ***largest and most dense innervation to cerebral cortex*** (of known neurochemical systems) – diffusely and profusely!
	+ neaišku, kiek serotonerginių skaidulų sudaro tikras sinapses žievėje – serotonergic terminals form baskets around cortical neurons.

Serotonin – **inhibitory neurotransmitter**

* + inhibicinės sinapsės ant preganglinių simpatinių neuronų nugaros smegenyse (cardiovascular control).
	+ inhibicinės sinapsės in substantia gelatinosa (increase pain threshold); stimulation of periaqueductal gray matter → skausmas↓.
	+ **trūkstant serotonino** (iš serotonino sintezuojamas melatoninas!) – insomnia, depresija.
	+ **serotonino perteklius** – mania (serotonin may be involved in pathogenesis of obsessive-compulsive disorder), insomnia, GI & orgasmic disturbances.
	+ *tricyclic antidepressants*, cocaine block reuptake → nuotaika↑; naujausi antidepresantai – *selective serotonin reuptake inhibitors (SSRI)*; ecstasy causes serotonin release (euphoria) → serotonin depletion (depression).
	+ **hyperserotonemia** gali sąlygoti autizmą.
	+ discharge in serotonergic neurons in ***dorsal raphe nucleus*** causes migraine.
	+ certain **methylated serotonin derivatives** (formed in brain as errors in metabolism) may cause psychosis.

Serotonino funkcijos nepilnai ištirtos; įtakoja:

1. **homeostasis** (water balance, appetite, blood circulation\*, temperature control, respiration, etc.)

\*directly serotonin constricts splanchnic and renal vessels, and dilates skeletal muscle vessels; positive chronotropic & inotropic effects

1. **behavior**:
	* activity level, aggression.
	* sexual
	* self-stimulation.
2. **pain** responses.
3. regulation of **circadian rhythms** (prominent serotonergic innervation of suprachiasmatic nuclei of hypothalamus)
4. **sleep** (serotonergic neurons discharge rapidly in awake state, slowly during drowsiness, more slowly with bursts during sleep, and not at all during REM sleep).

**Receptors**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Receptor Type** | **Second Messenger** | **Net Channel Effects** | **Agonists** | **Antagonists** |
| **5HT1A**(raphe nuclei, hippocampus) | ↓ cAMP | ↑ K+ | buspirone, ergots (ergotamine, dihydroergotamine,methysergide) |  |
| **5HT1B**(striatum) | ↓ cAMP |  | -triptans |  |
| **5HT1C**(choroid plexus) |  |  |  |  |
| **5HT1D** – similar to 5HT1B | ↓ cAMP | ↓ K+ | -triptans |  |
| **5HT2A** (neocortex, hippocampus, platelets) | ↑ IP3 & DAG | ↓ K+ | hallucinogens (LSD, psilocin, mescaline, DOM, DMT) | methysergide,cyproheptadine, ketanserin, hypnotics (eplivanserin, pimavanserin, pruvanserin, volinanserin) |
| **5HT2C** | ↑ IP3 & DAG |  |  |  |
| **5HT3** | - | ↑ Na+ |  | -setrons |
| **5HT4** | ↑ cAMP |  |  |  |
| **5HT5A, 5HT5B** |  |  |  |  |
| **5HT6** |  |  |  |  |
| **5HT7** |  |  |  |  |

* serpentine receptors **coupled via G proteins** to adenylyl cyclase, phospholipase C.
* 5HT2A mediate behavioral effects of serotonin.
* 5HT3 are **ligand-gated ion channels**; 5HT3 receptors are present in **GI tract** and **area postrema** - related to vomiting.
* 5HT6 receptors have high affinity for antidepressant drugs.

Histamine

synthesis & catabolism

* formed by decarboxylation of **Histidine**.
* catabolized:
1. to methylhistamine → **methylimidazoleacetic acid** by **MAO**.
2. to **imidazoleacetic acid** (less important in humans) by **diamine oxidase (histaminase)**.

Location & function

* **posterior hypothalamus** (tuberomammillary nucleus).
* axons project to all CNS parts.
* function is uncertain, but histamine has been related to arousal, sexual behavior, regulation of some anterior pituitary hormones secretion, blood pressure, drinking, pain thresholds.

Receptors

|  |  |  |
| --- | --- | --- |
| **Receptor Type** | **Second Messenger** | **Effects** |
| H1 | ↑ IP3 & DAG | allergy mediator (nasal and bronchial mucus production, contraction of bronchioles, pruritus, pain) |
| H2 | ↑ cAMP | gastric acid secretion↑ |
| H3 (presynaptic) |  |  |

* all three receptor types are found in peripheral tissues and brain.

Acetylcholine

Biosynthesis & catabolism

|  |  |
| --- | --- |
| D:\Viktoro\Neuroscience\A. Neuroscience Basics\A3-5. Neuron, Synapsis, Neurochemistry\00. Pictures\Acetylcholine.gif | **choline** + **acetyl-CoA** ↓ choline acetyltransferase (CAT)**acetylcholine** (acetyl ester of choline; quaternary ammonium) ↓ acetylcholinesterase**choline** + **acetate** |

 ↓

 active **choline** uptake into presynaptic neuron

* **choline** is not synthesized in CNS; it is transported into brain.
* **choline** transport (cotransport with Na+) into neuron can be blocked by hemicholinium.

|  |  |
| --- | --- |
| D:\Viktoro\Neuroscience\A. Neuroscience Basics\A3-5. Neuron, Synapsis, Neurochemistry\00. Pictures\Cholinergic ending.jpgASE, acetylcholinesterase;X, receptor | Acch transport into vesicles (refill of recycled membrane vesicles):* vesicle membrane has H+-ATPase;
* energy contained in H+ gradient is used to pump Acch into vesicle (**secondary active transport**).
* each vesicle contains 5000-10000 Acch molecules (Acch quantum).

**Cholinesterases*** Acch rapidly dissociates from receptor and must be rapidly removed if repolarization is to occur.
* removal occurs by hydrolysis by **acetylcholinesterase** (s. **true** or **specific cholinesterase**);
	+ clustered in postsynaptic membrane and in synaptic cleft; some is found in glia.
	+ greatest affinity for Acch, but also hydrolyzes other choline esters.
* **pseudocholinesterase** (s. **nonspecific cholinesterase**) - found in plasma (synthesized in liver); also capable of hydrolyzing Acch.
 |

N.B. cholinergic synapse is unique – transmitter is inactivated by **enzymatic destruction** (vs. in other synapses – by transmitter **diffusion / active reuptake** from synaptic cleft).

function & location

Acetylcholine – **excitatory neurotransmitter**.

Most significant functions of Acch – **movement** and **memory-cognition**.

Major transmitter of PNS:

1. myoneural junction
2. preganglionic autonomic endings
3. postganglionic autonomic endings:
	* + parasympathetic
		+ sympathetic to sweat gland, and muscle vasodilator

In CNS cholinerginius neuronus galima lokalizuoti tik netiesiogiai – aptinkant **choline acetyltransferase** arba **acetylcholinesterase**:

1. **Striatum** – intrinsic neurons.
2. **Basal forebrain** – *nucleus basalis of Meynert* in gigantocellular complex of basal forebrain (projects diffusely to hippocampus and entire cortex - involved in motivation, perception, and cognition); degenerates in *Alzheimer disease*.
3. **RF** (*nucleus pedunculopontinus, nucleus laterodorsalis*) – project strongly to intralaminar nuclei (dalis ARAS sistemos); ponto-geniculo-occipital spike system responsible for REM sleep is cholinergic.
4. Some amacrine cells in **retina**.
	* distribution of cholinergic neurons *resembles that of monoaminergic systems* (cholinergic neurons project diffusely to much of brain) but differs in that there are also cholinergic interneurons and short cholinergic systems throughout CNS.

**Receptors**

**Nicotinic (N) cholinergic receptors**

* located in:
	1. **neuromuscular junctions** (muscle type N receptors)
	2. **autonomic ganglia** (neuronal type N receptors) also see A34, A35 p.
	3. **CNS** (some N receptors are located *presynaptically* on glutamine-secreting axon terminals - facilitate glutamate release)

palengvinimas – **N** receptoriai esti pirmosiose sinapsėse už C**N**S ribų

* **ligand-gated ion channels** - activated receptor permits passage of Na+ (and other cations\*) through central channel in receptor molecule.

\* *neuronal type N receptors* have high permeability to Ca2+

(role in synaptic facilitation and learning);

*muscular type N receptors* also permit K+ efflux, but Na+ influx is much greater

(due to greater electrochemical gradient) → depolarization.

* receptor is made of 5 subunits (α, α, β, δ, γ); both α subunits must bind 1 Acch molecule each to activate whole receptor (i.e. open ion channel).

**Muscarinic (M) cholinergic receptors**

* located in:
1. parasympathetic postaganglionic synapses (smooth muscle, heart, glands). see A34, A35 p.
2. CNS (e.g. in striatum).
* serpentine receptors **coupled via G proteins** to adenylyl cyclase, K+ channels, phospholipase C.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Receptor Type** | **Second Messenger** | **Net Channel Effects** | **Agonists** | **Antagonists** |
| N1 (neuronal type + adrenal medulla) | – | ↑ Na+, Ca2+ | nicotine (initialy stimulates but then blocks) | hexamethonium |
| N2 (muscle type) | ↑ Na+, K+ | α-bungarotoxin (snake venom), curare |
| M1 (brain, gastric parietal cells) | ↑ IP3 & DAG | ↑ Ca2+ | muscarine (alkaloid in toadstools, Amanita muscaria) | atropine, scopolamine,selective M3 antagonists (tolterodine, darifenacin, solifenacin) |
| M2 (cardiac cells, smooth muscle) | ↓ cAMP | ↑ K+ (hyperpolarization) |
| M3 (salivary glands, smooth muscle\*, iris) | ↓ cAMP |  |
| M4 (glands, smooth muscle) | ↑ IP3 & DAG |  |
| M5 | ↑ IP3 & DAG |  |

\*GI, urinary bladder

**M receptors** affinities: muscarine > Acch > nicotine

**N receptors** affinities: nicotine > Acch > muscarine

**Disorders**

**Acetylcholine**↓:

* botulinum toxins – *Acch sekrecijos inhibicija* mioneuralinėje sinapsėje;
* Lambert-Eaton myasthenic syndrome– *Acch sekrecijos inhibicija* mioneuralinėje sinapsėje (antibodies to presynaptic Ca2+ channels);
* aminoglycosides – *Acch sekrecijos inhibicija* mioneuralinėje sinapsėje (inhibited presynaptic Ca2+ channels);
* myasthenia gravis – Acch receptorių autoimuninė inaktyvacija;
* α-bungarotoxin, curare – Acch receptorių blokada mioneuralinėje sinapsėje.

**Acetylcholine**↑:

* black widow spider venom – masyvi Acch sekrecija.
* organophosphates, carbamates, *Amanita muscaria* – acetilcholinesterazės inhibitoriai.
* *Inocybe, Clitocybe* mushrooms (toadstools) – contain muscarine (stimulation of M receptors).

Amino acids

Glutamate, Aspartate

**synthesis & catabolism**

* glutamate is formed by *reductive amination* of Krebs cycle intermediate **α-ketoglutarate**.
* aspartate is formed by *transamination* of Krebs cycle intermediate **oxaloacetate**.
* both reactions are reversible, and catabolism occurs via **Krebs cycle**.

**location & functions**

Principal **excitatory transmitters** of CNS! (as acetylcholine in PNS).

* depolarize many different mammalian neurons when delivered directly on their cell membranes.
* glutamate is responsible for 75% excitatory transmission in brain.
* aspartate is transmitter in pyramidal cells, spiny stellate cells in visual cortex.
* glutamate is **excitotoxin** - can kill cells by overstimulating them (huge Ca2+ influx);
	+ glutamate reuptake (into neurons and glia) is important to prevent this.
	+ during **ischemia, anoxia, trauma**, glutamate reuptake is inhibited → cascade of events that leads to cell death

**Receptors**

|  |  |  |
| --- | --- | --- |
| Glutamate **Receptor Type** | **Second Messenger** | **Net Channel Effects** |
| **Metabotropic** (11 subtypes) | ↓ cAMP or ↑ IP3 & DAG | Ca2+↑ |
| **Ionotropic**: |
| AMPA, kainate |  | ↑ Na+ |
| NMDA |  | ↑ Na+, Ca2+ |

**Metabotropic** receptors are serpentine **G protein-coupled** receptors → activate phospholipase C;

* widely distributed in brain.
* involved in ***synaptic plasticity*** (particularly in hippocampus and cerebellum) – slow prolonged changes of cellular excitability.

**Ionotropic** receptors are **ligand-gated ion channels**.

* serve for ***fast neurotransmission***.
* three general types, each named for glutamate congeners to which they respond in maximum fashion:
1. **kainate receptors** (kainate is acid isolated from seaweed)
2. **AMPA receptors** (for α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate)
3. **NMDA receptors** (for *N*-methyl-D-aspartate).

NMDA receptors:

* + permits passage of relatively large amounts of **Ca2+**.
	+ glycine binds to it and is essential for its normal response to glutamate.
	+ at normal membrane potentials, channel is blocked by **Mg2+**; block is removed only when neuron is partially depolarized by activation of AMPA or other channels.
	+ glutamate increases NO synthesis.
	+ high concentration in *hippocampus* (receptor blockade prevents **long-term potentiation**) - NMDA receptors are generally assumed to be associated with learning and memory.
	+ NMDA receptoriai gausiausi srityse, jautriausiose hipoksijai (cortex, striatum, hippocampus, cerebellum); insulto, hipoksijos, epilepsijos gydymui bandoma taikyti *NMDA receptor antagonists, Ca2+ channel blockers, glycine*.
	+ manoma, kad **inhaliaciniai anestetikai** veikia per NMDA receptorius.
	+ NMDA antagonists phencyclidine and ketamine (which produce amnesia and feeling of dissociation from environment) bind to site inside channel.
	+ NMDA antagonist memantine – FDA approved for advanced Alzheimer disease.
	+ NMDA antagonist are investigated as neuroprotective agents in ischemic stroke. see Vas5 p.



Synaptic actions of glutamate are terminated mainly by **uptake** through Na+-dependent glutamate transporters (GT) on glia.

* + 60% ALS (amyotrophic lateral sclerosis) patients have large decrease in glutamate transport activity.
	+ riluzole (glutamate antagonist) – FDA approved for ALS.
	+ acamprosate (glutamate antagonist) – alcoholism treatment.
* in astrocyte, glutamate is converted into glutamine (by glutamine synthetase).
* glutamine can be shuttled back to neurons for reconversion into glutamate.

γ-aminobutyric acid (GABA)

**synthesis & catabolism**

* formed by decarboxylation of **glutamate** by glutamate decarboxylase(GAD)\*.
* catabolized (by transamination) to **succinic semialdehyde** by GABA transaminase (GABA-t)\* → **succinate** → citric acid cycle.

\*reikalingas kofaktorius vit.B6

* there is in addition active **GABA reuptake**.

**localization & functions**

* localization of GABAergic systems is based on concentrations of:
	1. **GABA**
	2. **GAD** – preferred, nes:
		+ glial cells also take up GABA;
		+ glutamate (GABA precursor) itself acts as transmitter;
		+ GABA often coexists with other transmitters.

# GABAerginiai neuronai esti tik CNS

* GABA – principal **inhibitory transmitter** of CNS!

**GABA** vyrauja ***galvos smegenyse***, vykdo ***presynaptic inhibition***. see A4 p.

**glycine** vyrauja ***nugaros smegenyse***, vykdo ***postsynaptic inhibition***.

* GABA agonistai naudojami **epilepsijai** gydyti;
* GABA activity↓ → **anxiety**.
* GABA is present in 20-60% CNS synapses.
* GABA is 200-1000 times more abundant than dopamine or NE.
* ***žievėje*** GABAerginiai neuronai pasiskirstę tolygiai, bet negausiai (only 30% cortical interneurons use GABA as primary transmitter).
* GABAerginiai neuronai (Golgi II type) pagrinde sudaro short interneuronal circuits of entire CNS!
* some intermediate length GABAergic tracts:
	1. most **intrinsic neurons of cerebellum** (esp. Purkinje cells)
	2. **substantia nigra** (pars reticulata) **striatum** *interneurons*

 **substantia nigra** **pallidum**

**Huntington disease** – loss of small striatum interneurons (→ GABA↓ in striatum) → hyperkinesias (dėl dopamine overactivity), tačiau GABAmimetic drugs are ineffective!

Autoantibodies to GAD (→ GABA deficiency) causes **stiff-man syndrome (SMS)**.

**Receptors & pharmacology**

|  |  |  |
| --- | --- | --- |
| **Receptor Type** | **Second Messenger** | **Net Channel Effects** |
| GABAA |  | ↑ Cl- |
| GABAB | ↑ IP3 & DAG | ↑ K+, ↓ Ca2+ |
| GABAC (only in retina) |  | ↑ Cl- |

* GABAA & GABACare **ligand-gated ion channels**; GABABis **G protein-coupled**.
* GABAAis coupled to Cl- channels (***increases Cl- conductance***).
* GABABis coupled (via G protein) to K+ channels (***increases K+ conductance***).
* GABAAis located *postsynaptically* (induction of IPSP), whereas GABABis located *presynaptically* (inhibits release of excitatory neurotransmitter).

GABAAagonists:

* 1. **benzodiazepines** - increase frequency of openings of Cl- channels
	2. **barbiturates** - increase duration of openings of Cl- channels
	3. newer **anticonvulsants** (e.g. lamotrigine, topiramate).
	4. alcohol, progesterone & deoxycorticosterone metabolites, muscimol (poison of *Amanita muscaria*).

GABAB agonist -baclofen (spasticity treatment).

GABA receptor blockers:

* + - 1. tetanus toxin
			2. picrotoxin, bicuculline (convulsant).

Glycine

**Functions & receptors**

1. **excitatory effect** (by action on **NMDA receptors**).
2. **postsynaptic inhibition** (primarily in ***brain stem*** ***& spinal cord***)
	* glycine receptor is **ligand-gated Cl- channel**.
	* action is antagonized by **strychnine** (→ convulsions and muscular hyperactivity).
	* glycine receptor mutation (glycine-gated channel defect) → hyperactive startle reflexes (**startle disease, s. hyperexplexia**); H: valproate, clonazepam.
	* **tetanus toxin (tetanospasmin)** blocks glycine receptors.

Three kinds of neurons responsible for **direct inhibition in spinal cord**:

* + 1. neurons that secrete glycine
		2. neurons that secrete GABA
		3. neurons that secrete both (glycine and GABA in the same vesicles).

Neuropeptides

* peptidai, gausiai randami nervų sistemoje (išsk. cerebellum!!!); taip pat randama ir kitur (e.g. VIP).
* gaminami ribosomose ant mRNA matricos (in ***perikarya***, ***dendrites***, but not in ***axons***!); proteolytic enzymes cleave neuropeptides from precursor proteins.
* supakuoti į vesicles, keliauja į axon terminal.
* **CNS ir PNS kotransmiteriai** (excitatory, inhibitory) – modify action of primary transmitters!
* traktai, kurie naudoja tą patį primary transmitter, gali naudoti skirtingus neuropeptides, i.e. pathways are neuropeptide-coded (“**neuropeptide signature**”).
* manoma, kad ontogenezėje neuronai gali keisti savo neuropeptidinę transmisiją – neuronų plastiškumo mechanizmas? (sąlyginiai refleksai, learning, memory)

Neuropeptidų klasifikacija

**A. Hormones** (neurohypophyseal neuropeptides) – oxytocin, ADH.

**B. Releasing and inhibitory factors for hormones** (adenohypophyseal releasing neuropeptides) – produced in hypothalamus.

**C. Neurotransmitters** (neuromodulators)\*:

1. Opioid (e.g. endorphins, enkephalins).

2. Nonopioid (e.g. substance P, VIP, kai kurie adenohipofizės hormonai ir releasing-faktoriai).

\*N.B. it seems that *all of neuropeptides* may function as neurotransmitters!

Opioids

function & pharmacology - see S20, S21 p.

**pro-opiomelanocortin (POMC)** – common precursor for:

ACTH, β-LPH, MSH, β-endorphin, Met-enkephalin

* skirtinguose neuronuose, veikiant skirtingiems skaldantiems enzimams, gaunami skirtingi POMC produktai.
* POMC gausiai randamas hipofizėje, hypothalamus ir kitose CNS dalyse, o taip pat plaučiuose, GI trakte, placentoje.

Opioid peptides (substances that bind to opioid receptors):

* 1. **Enkephalins** (Leu-enkephalin, Met-enkephalin)
	2. **β-Endorphin**
	3. **Dynorphins**
	4. **Neoendorphins** (α and β)
	5. **Endomorphins** (1 and 2)
* opioid peptides have number of different precursors; each has ***prepro form*** and ***pro form*** from which signal peptide has been cleaved.

**opioid receptors**

|  |  |
| --- | --- |
| **μ1-2 receptor** (site of morphine action): supraspinal analgesia (μ1), euphoria (physical dependence), sedation, respiratory depression (μ2), GI motility↓, miosis, GH and prolactin secretion↑.**κ1-3 receptor**: spinal analgesia, dysphoria, sedation, diuresis, miosis.**δ1-2 receptor**: analgesia. | D:\Viktoro\Neuroscience\A. Neuroscience Basics\A3-5. Neuron, Synapsis, Neurochemistry\00. Pictures\Opioid receptors ligand affinity.gif |

* all three are serpentine receptors **coupled to Gq protein** (↓ cAMP).

**μ receptors** increase K+ conductance (→ hyperpolarization).

**κ** and **δ receptors** close Ca2+ channels (→ transmitter release↓).

**σ receptor**: dysphoria, psychotomimetic effects (hallucinations), pupil dilation, respiratory & vasomotor stimulation.

* less specific – also binds nonopioids (e.g. phencyclidine).

**ε receptor**: catatonia.

Receptor distribution:

1. **CNS** (μ receptors in brain, κ receptors in spinal cord):

***limbic system*** (esp. amygdala): emotional behavior;

***hypothalamus***: neuroendocrine secretion;

***medial thalamus***: deep pain (poorly localized, emotionally influenced);

***brain*** ***stem***: respiration, cough, nausea & vomiting (without unpleasant sensation), BP maintenance, pupillary diameter, stomach secretion control;

***substantia gelatinosa***: attenuation of afferent painful stimuli.

1. **PNS** (δ receptors): attenuation of painful stimuli.
2. **GI tract**: motility↓
3. **Immune cells**

**Endogenous opioids**

**endorphins (“endogenous morphins”)**

* neuropeptides that bind to same receptors that bind exogenous opiates.
* found in many parts of body.

**enkephalins** – pentapeptide endorphins.

* found in many parts of brain and GI tract.
* bind to pain-related receptors (nonaddicting analgesics) – presynaptically inhibit pain transmission by substance P.
* pagal amino rūgštį 5-oje pozicijoje:
1. **Leu-enkephalin**
2. **Met-enkephalin**

**dynorphins** - group of seven peptides with similar amino acid sequences.

* geographically coexist with enkephalins.

Substance P & other tachykinins

**Tachykinins** (differ at amino terminal end but have in common carboxyl terminal sequence of Phe-X-Gly-Leu-Met-NH2, where X is Val, His, Lys, or Phe):

|  |  |  |
| --- | --- | --- |
| **Gene** | **Polypeptide tachykinin** | **Receptors** |
| **SP/NKA (substance P/neurokinin A)** | Substance PNeurokinin ANeuropeptide KNeuropeptide αNeurokinin A (3-10) | Substance P (NK-1)Neuropeptide K (NK-2) |
| **NKB (neurokinin B)** | Neurokinin B | Neurokinin B (NK-3) |

Substance P

* substance P receptor is **G protein-coupled** (↑ IP3 and DAG).
* substance P is **primary transmitter for pain** in dorsal roots (i.e. first synapse in pathway for slow pain):



* **enkephalins** vykdo presinaptinę inhibiciją – blokuoja substance P išsiskyrimą ir skausmo perdavimą.
* kaip veikia serotonerginiai bulbospinaliniai skausmą slopinantys aksonai nežinoma (inhibicinės sinapsės in substantia gelatinosa?).
* substance P randama ir **žarnyne** bei **uždegimo židiniuose** – ***viena iš stipriausiai lygiuosius raumenis veikiančių medžiagų*** (dilation of blood vessels, contraction of intestine).
* substance P is probable mediator of local **axon reflex** (upon injection into skin, it causes redness and swelling) – ***neurogenic inflammation***.

fosaprepitant (Emend®) – when administered IV is rapidly converted to aprepitant - selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors – strong **antiemetic**.

* crosses BBB (effective in central emesis).
* augments antiemetic activity of ondansetron and dexamethasone.
* indicated in combination with other antiemetic agents for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly *emetogenic cancer chemotherapy* (incl. high-dose cisplatin).

Cannabinoids

* two receptors (CB1, CB2) have high affinity for *exogenous* **Δ9-tetrahydrocannabinol (THC, dronabinol)** - psychoactive ingredient in marijuana (derived from hemp plant, *Cannabis sativa*).
* hashish is made from plant resin - contains more psychoactive cannabinoids.
* THC accumulates in body fat, metabolized in liver.
* mild tolerance and mild psychologic dependence occur with continued frequent use. see Psy23 p.

**CB1 receptor**

* *endogenous* ligand for receptor is **anandamide** (derivative of arachidonic acid):



**CB2 receptor**

* *endogenous* ligand **palmitoylethanolamide (PEA)**; physiologic role of this compound is unsettled (acts peripherally to augment analgesic effects of anandamide).

Marijuana effects (immediately after smoking; maximal effects take about 20 minutes; effects largely disappear by 3 hours):

* 1. euphoria, relaxation (high) → drowsiness, calmness, sexual arousal↑, dream states, analgesia.
	2. enhancement of sensory activity, distortion of time and space.
	3. decreased muscle strength, impaired short-term memory, mental activity, coordination and highly skilled motor activity (such as driving car).
	4. appetite↑, xerostomia, reddening of conjunctiva! (no change in pupils!)
	5. tachycardia, postural hypotension.
	6. high doses → toxic psychosis with hallucinations, delusions (e.g. schizophrenia exacerbation).

N.B. seizures do not occur!!!

* some report increased suspiciousness, paranoia, and aggressiveness; others become quite withdrawn socially.
* fatal overdose has not been documented!
* treatment of intoxication: reassurance in quiet setting (!!!), diazepam; for acute psychotic state – haloperidol.

Medical use: severe emesis caused by chemotherapy, appetite enhancement in AIDS patients.

Gases

* act by *diffusion* (rather than being secreted in packets at synapses and binding to receptor sites on membranes).
* **relax smooth muscles**.
* involved in memory.

NO

Not to be confused with "laughing gas" nitrous oxide (N2O)!!!

* sintezuojamas iš **Arg** by **NO synthase, type 1**. see 1317 p. (cardiovascular)
* not stored – i.e. synthesized when needed.
* ***retrograde neurotransmitter*** – released from postsynaptic cells, activates presynaptic potentials.
* crosses cell membranes with ease and binds directly to **guanylyl cyclase** → cGMP↑.
* *very short-lived*: NO → nitrite → nitrate → urine.
* NO is **strong smooth muscle relaxant** (e.g. in enteric NS, pulmonary vasculature).
* klinikinis pritaikymas: *nėščiųjų toksikozės* gydymas, *plautinės hipertenzijos* gydymas.

CO

* susidaro **hemo** katabolizmo metu. see 822 p. (biochemistry)
* like NO, activates **guanylyl cyclase**.

Transmitters of Motor System

* **LMN (lower motor neuron)** in ***spinal cord*** uses acetylcholine.
* **internuncial pool of inhibitory neurons** in ***spinal cord*** use GABA and glycine (Renshaw cell).
* **UMN (upper motor neurons)** of ***cerebral cortex*** use glutamate (this includes all motor outputs from cerebral cortex – corticospinal, corticobulbar tracts, inputs to rubrospinal and tectospinal systems, etc).
* output neurons in ***basal ganglia*** and ***cerebellum*** use GABA.

basal ganglia transmitters – see A102 (2) p.

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