Metabolism of neurotransmitters

Synthesis, degradation, receptors and role in diseases and pharmacology

Josef Fontana
Introduction to neurotransmission systems

Metabolism of neurotransmitters:

- amino acids: 1) excitatory: glutamate, aspartate; 2) inhibitory: GABA, glycine
- acetylcholine
- monoamines: 1) catecholamines: NA, dopamine; 2) serotonin, (melatonin)
- peptides
- other: purines, gases, endocannabinoids
Introduction to neurotransmission systems
Introduction to neurotransmission systems

\[ I/V \]

- **Neurotransmitter (NT):** a substance **released by the neuron** to the **concrete target cell** where **induces specific response**
- **Targets:** another **neural cell** or **organs** (especially **glands** and **muscles**)
- Difference from the endocrine signalling: **neurotransmission targeted to the cells in the close neighbourhood of the neuron** releasing NT to:
  - synaptic cleft
  - vicinity of so called **varicosities (buttons en passant)** in the autonomic NS
- Difference between neurotransmission and paracrine signalling: **NT doesn’t effects** only **to target cells** but **to the releasing neuron too**
  - modulation of another neurotransmitter release
Introduction to neurotransmission systems II/V

- **NT binding to receptor** is just **temporary** and lasts from just a few milliseconds to minutes.
- **Provoked changes last for a while too or persist for days or weeks**
- Immediate impact is usually caused by **ionotropic receptors**:  
  - work as **ion channels** (or are linked to them)  
  - **change of the MP** – threshold of depolarisation – action potential
- Long term changes mediated by **metabotropic receptors**:  
  - activate intracellular signal cascades **via G-protein** – change in the gene expression or change of preexisting enzymes (e.g. phosphorylation/dephosphorylation)
Introduction to neurotransmission systems III/V

• The concept of neurotransmission as the only intercellular communication of a one neuron to another one or to some organ is not completely right.

• Some **glial cells**, astrocytes in the most, are able to **synthesize the neurotransmitter** and are able to release it to their target cells as they are able to **express receptors** on their membrane.
Introduction to neurotransmission systems V/V

• Only precursors of neurotransmitters can cross the blood-brain barrier (BBB) to the central nervous system and not pure neurotransmitters
  • role in treatment of some neurological diseases

• Synthesis of the majority of neurotransmitters takes place at the synaptic ending
  • CAVE! peptides produced in the soma
Groups of neurotransmitters

• By the chemical point of view neurotransmitters aren’t unified group of substances, their structure is very variable - two large groups:

• 1) Big molecules
  • peptides: beta-endorphins, leu-enkephalins, substance P
  • endogenous cannabinoids

• 2) Small molecules
  • amino acids: glutamate, aspartate or glycine
  • amino acids derivatives: GABA, catecholamines – noradrenaline and dopamine, serotonine
  • acetylcholine
  • other: purines (ATP, ADP, adenosine), gases (NO)
Metabolism of neurotransmitters

Glutamate
Glutamate

• The main excitatory neurotransmitter in the CNS (40 %)
• It is distributed so widely that it is impossible to talk about individual centres or projections
• Plays an indispensable role in the synaptic plasticity, i.e. the removal of old, unused synapses, potentiation of others and the formation of new synapses.
• Alter interneuronal connections virtually on a minute by minute scale
• Neurobiological process behind memory retention and learning
Synthesis and inactivation of glutamate –
cycle neuron-astrocyte I/III

• Glutamate essentially never penetrates from blood into
  the brain - under normal conditions glutamate is only
  transported from the CNS into blood

• Glutamate transporters EAAT1 and EAAT2 (Excitatory
  Amino Acid Transporter) keep low Glu concentration

• Cycle neuron-astrocyte: a close cooperation between
  neurons and astrocytes is therefore essential for the
  production of glutamate and GABA
Synthesis and inactivation of glutamate – cycle neuron-astrocyte II/III

• Most glutamate is produced in neurons from glutamine (*glutaminase*) or alpha-KG (*glutamate dehydrogenase*)

• **Gln** formed in astrocytes and transported into neurons

• Upon release into the synaptic cleft only a small portion of glutamate is re-uptaken into the presynaptic neuron

• Most of it is transported via **EAAT1** and **EAAT2** into astrocytes

• Glutamate is transformed into glutamine inside an astrocyte (requires ATP and ammonia, catalysed by glutamine synthetase)

• **Gln** is exported into neurons hence completing the cycle
Synthesis and inactivation of glutamate – cycle neuron-astrocyte III/III

• Some diseases such as liver failure may cause an elevation of blood ammonia levels

• Ammonia easily crosses the blood-brain barrier

• Reacts with glutamate – conversion to glutamine (consuming ATP)

• If there is too much of ammonia:
  • neuronal ATP may be depleted
  • time two major neurotransmitter systems are be dysregulated – Glu and GABA

• Liver encephalopathy
Glutamate receptors

• Several types of glutamate receptors categorised according to their specific pharmacological agonists:
  • 1) AMPA receptors
  • 2) NMDA receptors
  • 3) Kainate receptors
  • 4) Metabotropic receptors (mGluR1-8)
1) AMPA-receptors (AMPARs)

- Ligand: \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
- Ligand-gated ion channels, i.e. ionotropic receptors
- Their opening allows the \textit{influx of calcium} and \textit{sodium} and the \textit{efflux of potassium}
- Closes soon after opening
2) NMDA-receptors (NMDARs)

- Ligand: **N-Methyl-D-aspartate**; L-aspartate, L-glycine a D-serine (serine racemase in glial cells and neurons)
- Also **ionotropic receptors** increasing the permeability for **Ca$$^{2+}$$, Na$$^+$$ and K$$^+$$
- The opening of NMDA receptors requires in addition to a conformational change the removal of a **magnesium ion**, which blocks the pore
- Mg$$^{2+}$$ leaves the channel only if the membrane is sufficiently depolarised (e.g. via AMPARs), which alteration of the electric field repulses the cation
- NMDARs allow a **Ca influx** sufficient for the activation of Ca-dependent enzymes, which can then regulate properties of the postsynaptic neuron
- These processes are very important for **synaptic plasticity**
Glutamate receptors

• 3) Kainate receptors
   • also **ionotropic** and functionally similar to AMPARs

• 4) Metabotropic receptors (mGluR1-8)
   • 8 types
   • e.g. on presynaptic neurons, where they attenuate their activity
Metabolism of neurotransmitters

GABA
GABA

• **Gamma-aminobutyric acid (GABA)** is the **main inhibitory neurotransmitter** in the CNS

• Similar to glutamate its distribution is diffuse and a distinct neurotransmitter system cannot be identified
Synthesis and inactivation of GABA – cycle neuron-astrocyte I/II

• GABA-shunt

• Synthesised by the decarboxylation of glutamate: glutamate decarboxylase

• Precursor is glutamine transported from astrocytes

• Glutamine is converted inside a neuron to glutamate (glutaminase), which is then decarboxylated to GABA
Synthesis and inactivation of GABA – cycle neuron-astrocyte II/II

- GABA is mainly taken up by astrocytes and converted back to glutamine
- The gamma-amino group of GABA is first transaminated to give an aldehyde group thus forming succinate semialdehyde (GABA transaminase)
- Succinate semialdehyde is oxidised to succinate - enters the TCA cycle
- Formation of 2-oxoglutarate - (trans)aminated to glutamate
- Amidation to glutamine using ammonia and ATP - Gln is then exported - cycle closes
GABA receptors

• 3 types of GABA receptors:
  • 1) GABA_A
  • 2) GABA_B
  • 3) GABA_C
GABA\textsubscript{A}-receptor

- **Ionotropic receptor** allowing the transport of **chloride anions**
- Its opening leads to an influx of chlorides into the cytosol and hence to a **lowering of the membrane potential**
- Forms a **supramolecular receptor complex**, which in addition to GABA binds **benzodiazepines, barbiturates, corticosteroids and alcohol**
- All these binding sites affect the opening of the central pore and all act to inhibit the neuron either directly via opening the pore or indirectly by potentiating the binding of GABA
GABA$_B$-receptor

- Metabotropic receptor coupled to a $G_i$-protein inhibiting adenylate cyclase
- Decrease in cAMP levels changes membrane protein phosphorylation – an increase in $K^+$ permeability (membrane hyperpolarisation) and a decreased activity of calcium channels
- Result: decreased amount of NT released by the neuron
$\text{GABA}_C$-receptor (GABA$_A$-rho receptor)

- **Ionotropic receptor** connected to a **chloride channel**

- In contrast to GABA$_A$ receptors they open more slowly and remain open for a longer period of time
Metabolism of neurotransmitters

Acetylcholine
Acetylcholine

- Acetylcholine (ACh) is the only neurotransmitter containing a quaternary ammonium group
- Neurotransmitter used in:
  - 1) neuromuscular junctions
  - 2) preganglionic neurons of the autonomous nervous system
  - 3) all postganglionic parasympathetic neurons
  - 4) CNS
- Modulates many cortical activities such as \textit{arousal, sleep} and \textit{memory consolidation}
Synthesis and inactivation of acetylcholine I/II

• An ester of choline and acetic acid
• Transfer of the acetyl group from acetyl-CoA to choline (choline acetyltransferase)
• CNS receives all its choline from the blood
• Choline is mostly synthesised in the liver by a triple methylation of ethanolamine, S-adenosylmethionine (SAM) is the donor of methyl groups
• Ethanolamine is produced by a decarboxylation of serine
Synthesis and inactivation of acetylcholine

- Cholinergic signal is terminated by the acetylcholine esterase (AChE) bound to the postsynaptic membrane.
- Products: choline (taken up by the presynaptic neuron and recycled) and acetate.
- AChE is not entirely specific for ACh, it hydrolyses other choline esters also.
Receptors for acetylcholine

• Cholinergic signalling in the nervous system is mediated by two types of receptor with several subtypes:

  • 1) Muscarinic receptors

  • 2) Nicotinic receptors
1) Muscarinic receptors

- **Metabotropic receptors** coupled to G-proteins, which regulate ion channel opening
- Response of the postsynaptic neuron is thus relatively slow
- Five subtypes
a) $M_1$ receptors

- So called **neuronal** receptors
- In high density in the CNS, particularly in the **hippocampus** and **cortex**
- Mediates an **excitatory response** via a $G_q$-protein starting a signalling cascade leading to a **decreased permeability for $K^+$**
- Decrease in their function or density is one of the causes of **dementia**
b) M₂ receptors

• **Cardiac receptors**
  • Expressed in cardiomyocytes and neuronal tissues

• **Inhibitory response via a Gᵢ-protein that activates K⁺ channels** (via its β-γ subunit dimer) thus causing **membrane hyperpolarization**

• This is the mechanism by which the vagus nerve exerts its **negative chronotropic effect on the sinoatrial node** and the **negative dromotropic effect on the atrioventricular node**

• **CNS**: on presynaptic neurons mediating negative feedback inhibition in the cortex and the hippocampal formation
c) $M_3$ receptors

- Receptors of **glands** and **smooth muscles**
  - cholinergic stimulation of exocrine glands and the contraction of smooth muscles in the GIT and other organs
- Coupled with a $G_q$-**protein**: increases intracellular $Ca^{2+}$ concentration via the activation of phospholipase C (formation of $IP_3$ and DAG)
- CNS: relatively low density - induce a **strong emetic effect**
d) M₄ receptors

• Mechanisms of action is similar to M₂ receptors: Gᵢ-protein activating K⁺ channels
• Found mainly in the striatum, where they function mainly as regulatory autoreceptors on cholinergic neurons - the same role as M₂-receptors in the hippocampus and other cortical regions
e) $M_5$ receptors

- Similar to $M_1$ and $M_3$ receptors, $M_5$ receptors are coupled with a $G_q$-protein.
2) Nicotinic receptors

• **Ionotropic receptors**

• **Opening of cation channel** permeable for $\text{Na}^+$ and $\text{K}^+$, in some subtypes also for $\text{Ca}^{2+}$

• Basic division:
  • **muscular type** ($N_M$ receptor): present in the **neuromuscular junction**
  • **neuronal type** ($N_N$ rec.): in postsynaptic terminals in **autonomic ganglia** and **CNS**

• In the CNS $N_M$ receptors act as heteroreceptors for other systems (GABA, serotonin, glutamate, dopamine) – increase the permeability for calcium and increase the amount of released NT
Acetylcholine in the brain

• Mainly in the **basal nucleus of Meynert** and in septal nuclei
• Projections into the **cortex** and the **hippocampus**: activation of certain cortical areas and in short term memory consolidation
  • neurons of the basal nucleus and medial septum damaged in **Alzheimer’s disease**
• Cholinergic neurons found in the tegmentum of the brainstem also – send projections into the cerebellum, hypothalamus and lower portions of the CNS: affect arousal, sleep cycle and are important for the initiation of the REM sleep phase
• Cholinergic interneurons in the striatum: form a part of the basal ganglia circuit - play a role in the regulation of posture, movement initiation and selection of appropriate movement patterns
Clinical role I/II

• Acetylcholine esterase inhibitors:
  • 1) Treatment of diseases such as Alzheimer’s disease or myasthenia gravis
  • 2) Highly toxic substances such as extremely effective organophosphates
    • form a strong covalent bond with the OH group of the serine residue in the active site of the enzyme, which lasts for weeks
    • insecticides and highly toxic nerve gases (sarin, tabun and VX)
Clinical role II/II

• **M-receptor blockers** = **atropine** (parasympatholytic drug)

• **N-receptor blockers** = **curare** (derivatives = muscle relaxants)
Metabolism of neurotransmitters

Catecholamines as neurotransmitters
Catecholamines as neurotransmitters

- Norepinephrine/noradrenaline (NE/NA), epinephrine/adrenaline (Adr) and dopamine (DA)
- All are derived from the aromatic amino acid L-tyrosine (or from phenylalanine via tyrosine)
- Their structure contains a catechol ring – benzene ring with two hydroxyl groups – with a side chain containing an amino group
Synthesis and inactivation of catecholamines I/II

• Conversion of tyrosine to adrenaline follows these steps:
  • 1) Ring hydroxylation
  • 2) Decarboxylation – formation of dopamine
  • 3) Side chain hydroxylation – formation of noradrenaline
  • 4) N-methylation – formation of adrenaline
Tyrosine → Tyrosine hydroxylase → DOPA → DOPA decarboxylase → Dopamine

Dopamine → Dopamin β-hydroxylase → Norepinephrine → N-methyltransferase → Epinephrine
Synthesis and inactivation of catecholamines II/II

• Catecholamine signalling is terminated by the re-uptake of the neurotransmitter and subsequent intracellular inactivation

• Two enzymes catalysing:
  • 1) Catechol-O-methyltransferase (COMT)
  • 2) Monoamine oxidase (MAO)
Norepinephrine \rightarrow \text{COMT} \rightarrow \text{Vanillylmandelic acid}
Clinical role

- **MAO inhibitors** (MAOI, iMAO) are used to treat depression
- **Vanillylmandelic acid** is excreted mainly in the urine and its excretion can be used to estimate the production of catecholamines in the body
  - used when an **adrenal medulla tumor** (pheochromocytoma) is suspected
Metabolism of neurotransmitters

Noradrenergic system
Noradrenergic system

- Regulates the activity of other neurotransmitter systems
- Noradrenergic pathways increase or decrease the excitability of target areas depending on the receptors expressed
- Regulation of both, the excitatory function of glutamate and the inhibitory function of GABA
Adrenergic receptors

- **Four subtypes** of adrenergic receptors in the CNS: $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$
- $\beta_3$-rec. increasing lipolysis in the peripheral tissues
- **NA** binds with higher affinity to $\alpha$-receptors
- **Adrenaline** binds to $\alpha$- and $\beta$-receptors with the same affinity
Alpha-adrenergic receptors

• 1) $\alpha_1$ receptor (coupled with $G_q$-protein)
  • Present in postsynaptic neurons, mediates excitatory effects of noradrenaline

• 2) $\alpha_2$ receptor (coupled with $G_i$-protein)
  • Present mainly in presynaptic terminals – mediates inhibitory effects
  • Feedback inhibition of NA release in the synapse
Beta-adrenergic receptors

• All are coupled with $G_s$-protein
• 1) $\beta_1$ receptor
  • Neuronal receptor with excitatory effects
• 2) $\beta_2$ receptor
  • In the CNS mainly expressed in glial cells
Location of NA neurons

• In the brainstem, particularly in the locus coeruleus (group A6), tegmentum and the reticular formation of the medulla and pons (groups A1, A2, A5, A7)

• Axons project virtually to all CNS regions

• Modulates the excitability of other projection systems and regulates attention, arousal, sleep cycle and response to stress

• Projections into association cortical areas influence emotional behaviour
Metabolism of neurotransmitters

Dopaminergic system
Dopaminergic system

- Regulation of motor functions, initiation of behavioural patterns and modulation of visceral functions

- Dopaminergic neurons can be found in the mesencephalon and hypothalamus

- From a functional point of view several distinct dopaminergic projections are described
# Projections of dopaminergic system

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Dopaminergic receptors

• **Five types of dopamine receptors:** $D_{1-5}$
• **All coupled to G-protein** – affect **adenylate cyclase**:
  • 1) stimulate adenylate cyclase via $G_s$: $D_1$ and $D_5$
  • 2) inhibit adenylate cyclase via $G_i$: $D_2$, $D_3$ and $D_4$
• **CNS structures differ in density and proportion of receptors:**
  • motor cortical areas are rich in $D_2$
  • limbic systém is rich in $D_3$ and $D_4$ receptors
• **Adr and NA are partial agonists of dopamine receptors**
Clinical role I/II

- **Schizophrenia** is at least partly caused by an excessive activity of the mesolimbic system and a deficient activity of the mesocortical system.

- **Antipsychotics:** typical (D-rec. blockers) and atypical
  - AE: parkinsonism, hyperprolactinemia

- **Parkinson's disease:** loss of DA neurons in the **substantia nigra**
  - therapy: L-DOPA
Clinical role II/II

• **Cocaine and amphetamines: blockers of DA and NA reuptake (DAT inhibition)** + amphetamine increases release of NT

• DA is the major NT of the **reward system** (mesolimbic) - DAT blockade leads to an increase in the amount of DA at the target structures (nc. accumbens) – intensive positive feelings

• **Symptoms**: euphoria, exaggerated mood, stimulate the cardiovascular system, psychological dependence
Mechanism of Cocaine Based DAT block: Cocaine binds DAT and slows transport.

Mechanism of Amphetamine Based DAT block: Amphetamine induces MAPK/PKC to phosphorylate DAT. Phosphorylation slows transport and triggers internalization of DAT.
Metabolism of neurotransmitters

Serotoninergic system
Serotoninergic system

• The name serotonin points to its discovery as the substance in the serum, which affects smooth muscle tone

• Similar role in the CNS as the noradrenergic system: regulates a range of functions and modulates the activity of other projection systems
  • often innervates the same structures as noradrenergic afferents

• Raphe nuclei of the reticular formation: rostral part with ascendent projections and a caudal part with descendent projections

• Functions:
  • fear/aggression, mood, sleep and sexual behavior
  • appetite/vomiting, regulation of body temperature
Synthesis and inactivation of serotonin I/II

• Serotonin is derived from L-tryptophan, chemically it is 5-hydroxytryptamine
• Two-step synthesis:
  • 1) Tryptophan hydroxylation
  • 2) Decarboxylation
L-Tryptophan → 5-Hydroxy-L-tryptophan (5-HTP) → Serotonin (5-HT)

O₃, Tetrahydrobiopterine → L-Tryptophan-5-monoxygenase (TPH)

Hydroxytetrahydrobiopterine → 5-Hydroxytryptophan decarboxylase

Pyridoxal phosphate → Aromatic L-amino acid decarboxylase
Synthesis and inactivation of serotonin II/II

• Serotonergic neurotransmission is terminated by the **reuptake** of serotonin and its subsequent **intracellular metabolism**

• **Monoamine oxidase** (MAO) and aldehyde dehydrogenase (see catecholamine inactivation)

• **Product**: 5-*hydroxyindoleacetic acid* (5-HIAA)
  • excreted in urine conjugated with glucuronic acid
  • diagnostic marker for **neuroendocrine tumours secreting serotonin** (formerly **carcinoid**)


Serotonin (5-HT)

\[
\begin{align*}
\text{O}_2, \text{H}_2\text{O} & \quad \text{Monoamine oxidase (MAO),} \\
\text{NH}_3, \text{H}_2\text{O}_2 & \quad \text{Aldehyde dehydrogenase}
\end{align*}
\]

5-Hydroxyindoleacetic acid (5-HIAA)
Clinical role I/II

• **Specific serotonin re-uptake inhibitors (SSRI)** increase the activity of the serotonergic system and are used to treat patients with unipolar **depression**

• AE: decrease libido and cause food intake disorders, usually hyperphagia
Serotoninergic receptors

• Seven types: 5-HT_{1-7}R

• Inhibitory and excitatory actions:
  • 5-HT_1: coupled with G_i-protein
  • 5-HT_2: coupled with G_q-protein
  • 5-HT_3: cation channel

• The effect of serotonin depends on their localisation and the types of receptors expressed
Clinical role II/II

• **LSD** (lysergic acid diethylamide): *agonist of 5-HT\(_1\) and 5-HT\(_2\) receptors, produces pure hallucinations*
  • **high efficiency** (1 \(\mu\)g/kg)
  • originally developed as a potential drug in the laboratories of the pharmaceutical company Sandoz (1938) by **Albert Hoffman**

• **Antagonists of 5-HT\(_3\) receptor**, called *setrons* (e.g., ondansetron) *inhibit nausea and vomiting* (e.g., in chemotherapy)
Melatonin

• **Serotonin** starts another metabolic pathway leading to the **hormone** melatonin

• Amino group of serotonin is first acetylated - N-acetylserotonin

• Methylation on the indole hydroxyl group to form melatonin

• **Regulation of sleep**
Melatonin biosynthesis

Melatonin is important in regulating sleep.
Metabolism of neurotransmitters

Glycinergic system
Glycinergic system

• **Inhibitory neurotransmitter** - at a high density in the **spinal gray matter**: the main neurotransmitter of **inhibitory interneurons**

• Produced from **serine**

• **Ionotropic receptor** coupled to a **Cl⁻ channel** causing **membrane hyperpolarization**

• **Modulator of NMDA receptor activity**: excitatory effects via facilitating the activity of the glutamatergic system

• **Strychnine** is a **blocker of the glycine receptor**
  • by inhibiting inhibitory interneurons in the spinal gray matter it causes **uncoordinated spread** of stimulation causing **muscle spasm**
  • **strong bitter taste**, it is one of the most bitter substances
Metabolism of neurotransmitters

Histaminergic system
Histaminergic system

• As a neurotransmitter it regulates **sleep**, arousal and hormone secretion in the hypothalamo-pituitary system

• Formed by a **decarboxylation of histidine** (histidine **decarboxylase**)

• Histamine is **degraded by two enzymes**:
  • **histamine N-methyltransferase** (HMT/HNMT, cofactor **SAM**)
    preferential pathway in CNS
  • **diamine oxidase**: does not occur in the CNS, oxidative deamination

• Three subtypes of histamine receptors
Histidine decarboxylase
Histamine receptors I/II

• 1) H₁ receptors
  • in the hypothalamus and mamillary bodies, smooth muscle and endothelium of blood vessels
  • their effect is excitation: coupled with G_q-protein – a reduction in membrane permeability for K⁺ - depolarization
  • sleep / wake, vasodilation, bronchoconstriction and itching
  • blockers of H₁-rec. – antihistaminic drugs reduce symptoms of allergies
    • CAVE! and cause fatigue
Histamine receptors II/II

2) H$_2$ receptors
   - metabotropic receptors coupled to a $G_s$-protein
   - cortical neurons, glial cells, endothelium of cerebral capillaries and gastric glands
   - rise of gastric secretion
   - H$_2$ blockers: treatment of excess production of gastric HCl

3) H$_3$ receptors
   - on presynaptic terminals: autoreceptors that limit further release of Hist
   - heteroreceptors on noradrenergic, dopaminergic and cholinergic neurons, where they inhibit the release of the respective neurotransmitter
Metabolism of neurotransmitters

Peptide neurotransmitters
Peptide neurotransmitters I/II

• Synthesised on ribosomes in the neuronal body – axonal transport to the synaptic terminal
• Large precursor molecule is spliced into smaller neuropeptides
• Pro-opiomelanocortin (POMC, 241 AA) is which is cleaved to:
  • 1) β-endorphin
  • 2) MSH (melanocyte stimulating hormone)
  • 3) ACTH (adrenocorticotropic hormone)
• Removal from the synaptic cleft: usually degradation, not reuptake
Peptide neurotransmitters II/II

• Group of peptide neurotransmitters is large (more than 50 members):
  • 1) Opioid peptides: enkephalins, endorphins and dynorphin
  • 2) Substance P
  • 3) Neuropeptide Y
  • 4) Somatostatin
  • 5) Cholecystokinin
Opioid substance of the brain and opiates

- **Opioid receptors**: $\mu$, $\kappa$ and $\sigma$ - $G_i$-protein $\rightarrow \downarrow$ AC $\rightarrow \downarrow$ cAMP
- Opioids – endogenous substances having morphine-like action:
  - enkephalins – pentapeptides
  - endorphins and dynorphin – polypeptides ($\beta$-endorphin has 31 AK)
- **Morphine** – plant alkaloid, "mimicking" natural opioids
- A feeling of **physical well-being** - "good mood hormones"; analgesia, sedation $\times$ suppression of the respiratory center – **very strong addiction** (physical and mental)
- Secretion of opioids increases during **physical work** and **sport**
- Antagonist: **naloxone**
Metabolism of neurotransmitters

Endocannabinoids
Endocannabinoids I/II

- **Anandamide** (arachidonoylethanolamide, AEA): amide of **ethanolamine** and **arachidonic acid**
- Specific type of signaling - **retrograde neurotransmission**:
  - synthesized in the postsynaptic neuron
  - diffuses into the presynaptic neuron, where it modulates neurotransmitter release
Cannabinoid receptors

• Two basic types:

  1) CB₁ receptors
     • present mostly in the CNS, coupled to a G-protein
     • presynaptically on GABAergic neurons - inhibit the release of GABA into the synapse
     • agonists have orexigenic effects and stimulate the reward system

  2) CB₂ receptors
     • PNS, hematopoietic and immune cells: pain relief and immune response

• Exogenous ligands: tetrahydrocannabinol (THC)
Endocannabinoids II/II

• The structure of anandamide was described in 1992 by the Czech chemist Lumír Ondřej Hanus and the American pharmacologist William Anthony Devane at Hebrew University in Jerusalem.

• Its name is derived from the Sanskrit word ananda meaning bliss.