CNS neurotransmitters

Éva Szőke
Neuronal interconnections in the CNS

Fig. 32.2 Simplified scheme of neuronal interconnections in the central nervous system. Neurons 1, 2 and 3 are shown releasing transmitters a, b and c, respectively, which may be excitatory or inhibitory. Boutons of neuron 1 terminate on neuron 2, but also on neuron 1 itself, and on presynaptic terminals of other neurons that make synaptic connections with neuron 1. Neuron 2 also feeds back on neuron 1 via interneuron 3. Transmitters (x and y) released by other neurons are also shown impinging on neuron 1. Even with such a simple network, the effects of drug-induced interference with specific transmitter systems can be difficult to predict.
The basic processes of synaptic transmission in the CNS

- four processes occur in relation to nerve transmission in CNS:

  - **Neurotransmitters** – are synthesized in presynaptic neurons and are released into synaptic cleft to rapidly stimulate or inhibit postsynaptic neurons, fast neurotransmitters operate through ligand-gated ion channels, slow neurotransmitters operate through G-protein-coupled receptors

  - **Neuromodulators** – are released by neurons and astrocytes to produce slower pre-or postsynaptic responses (eg. Carbon dioxide, locally released adenosine, some purines, peptides, prostaglandins, arachidonic acid metabolites and Nitric oxide)

  - **Neuromediators** – are second messengers that play crucial role in elicitation of postsynaptic responses produced by neurotransmitters (eg. cAMP, cGMP and inositol phosphate)

  - **Neurotropic factors** – are mainly released by CNS neurons, astrocytes and microglia and act longer than neuromodulators to regulate the growth and morphology of neurons and control long-term changes in brain (synaptic plasticity, remodeling, phenotype characteristics) mainly by affecting gene transcription by acting through tyrosine kinase-linked receptors (eg. Cytokines, chemokines, growth factors.)
Overview of synaptic transmission

- **Neurotransmitters** are chemical messengers that transmit signals from a neuron to a target cell across a synapse.

**Neurotransmitter - four criteria:**

1) Substance is *synthesized by presynaptic neuron*
2) Substance is *stored in the presynaptic ending and released in sufficient amount to elicit the change in the postsynaptic neuron or effector organ*
3) If the substance is *administered by exogenic way the reaction to its presence provokes the same reaction as its endogenous release*
4) The *specific mechanism which inhibits of this effective substance exists*
When a Neurotransmitter Binds: The Postsynaptic Potential

- Voltage change at receptor site – **postsynaptic potential (PSP)**
  - Not all-or-none
  - Changes the probability of the postsynaptic neuron firing
- Positive voltage shift – **excitatory PSP** (decreases the negativity of the inside of the neuron with respect to the outside)
- Negative voltage shift – **inhibitory PSP** (increases the negativity of the inside of the neuron)
### Table 48.1 Major Neurotransmitters

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Amino Acid Neurotransmitters

• Excitatory amino acids:
  Include:
  Glutamate
  Aspartate

• Inhibitory amino acids:
  Include:
  GABA (Gamma-Aminobutyric Acid)
  Glycine

-drugs which enhance inhibitory synaptic events mediated by GABA often
decrease opposing excitatory events mediated by glutamate and vice versa -
GABA and glycine are of particular interest to the neuropsychopharmacologist,
many commonly used drugs work by selectively affecting these two systems
Glutamate (Glutamic Acid) and Aspartate (Aspartic Acid)

- these two **excitatory amino acids** (EAAs) are widely distributed throughout the mammalian CNS
- their administration leads to **rapid depolarization** of neurons and an increase in **firing** rate
- they are stored in synaptic vesicles and released by Ca$^{2+}$-dependent exocytosis
- glutamate and aspartate re-enter the cell by a **Na$^+$-dependent transporter (EAAT)** driven by the high extracellular concentrations of Na$^+$ and the high intracellular concentrations of K$^+$, the entry is indirectly powered by the ATP-driven Na$^+$-K$^+$-ase (sodium pump) which creates the high ion concentration gradients
Transport of glutamate
There are two distinct classes of EAA receptors: ionotropic receptors (4 subunits) and metabotropic receptors. The ionotropic receptors (NMDA, AMPA, kainate) directly gate ion channels, while the metabotropic receptors are coupled to intracellular G proteins.
Glutamate receptors - NMDA receptors

1.) The best-characterized receptor is known as the **NMDA (N-methyl-D-aspartate) receptor (NMDAR)** (subunits: GluN1, GluN2A-D, GluN3A-B). They mediate slower excitatory transmission. They
- are directly blocked by Mg\(^{2+}\)
- are also permeable to Ca\(^{2+}\) and Na\(^{+}\).

**Polyamines (spermidine, spermine – allosteric)** facilitate opening (that is blocked by ifenprodil).

**Ketamine, memantine and phencyclidine** are selective blocking agents.

Activation of NMDAs requires **glycine** (allosteric modulator), **7-chlorokynurenic acid** blocks the glycine site.

- Compounds that block the NMDA receptor complex may attenuate the neuronal damage following anoxia, such as occurs during a **stroke**.
- Other potential therapeutic interests: **epilepsy, Alzheimer’s disease, drug dependence, depression.**
Glutamate receptors - AMPA and Kainate receptors

• 2) AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (AMPARs) (subunits: GluA1-4)
  also permeable to Ca\(^{2+}\) and Na\(^{+}\)
  they mediate faster excitatory transmission
  they enhance or reduce transmitter release
Perampanel: non-competitive AMPA receptor antagonist – antiepileptic drug

• 3) Kainate receptors (subunits: GluK1-5)
  kainate receptors are also ionotropic and functionally similar to AMPARs
  GluK1s have shown potential for treatment of pain, epilepsy, stroke and anxiety
Glutamate receptors – Metabotropic mGluRs

4) Metabotropic receptors

There are 8 known types of metabotropic receptors labelled as mGluR1-8 with large extracellular N-terminus domain. They are found presynaptically or postsynaptically, they increased the turnover of phosphatidylinositol (IP$_3$) and decreased cAMP. They modify responses through ionotropic GluRs.
Interconnection between the pathways for synthesis of EAAs and IAAs
γ-Aminobutyric Acid (GABA)

- is the major inhibitory neurotransmitter in the mammalian CNS (1950, Roberts and Frankel)
- is stored in synaptic vesicles and is released in a Ca\(^{2+}\)-dependent manner upon depolarization
- is primarily synthesized from glutamate by the enzyme L-glutamic acid-l decarboxylase (GAD); it can be transaminated with α-ketoglutarate by GABA-oxoglutarate transaminase (GABA-T)—GABA-T is inhibited by vigabatrine (anticonvulsant, epilepsy)
- reuptake occurs via highly specific transmembrane transporters (GAT) — inhibited by guvacine, nipecotic and tiagabine (epilepsy)
GABA receptors - \( \text{GABA}_A \)

Two types of GABA receptors have been identified in mammals, a \( \text{GABA}_A \) and a \( \text{GABA}_B \)-receptors.

The \( \text{GABA}_A \) receptor induces a shift in membrane permeability, primarily to chloride ions, causing hyperpolarization of the neuron.

- Pentamer structure (2α2β1γ) forms a pore.
- Binding sites: GABA, Benzodiazepine (indirect agonist) and alcohol (endogenous inverse agonist binds here), Barbiturate (indirect agonist), Steroid (indirect agonist), channel blocking drugs

- **Benzodiazepines:** sedative, anxiolytic and anticonvulsant – facilitate the action of GABA

Since GABA agonists have been shown to be anticonvulsants and GABA antagonists are convulsants, there is much interest in the role of GABA in epilepsy.
GABA receptors - $\text{GABA}_B$

- $\text{GABA}_B$ receptors are located pre- and postsynaptically
- G protein-coupled receptors, $G_i/G_q$ type, inhibit adenyl cyclase
- Inhibit voltage-gated $\text{Ca}^{2+}$ channels – reducing transmitter release
- Open $K^+$ channels – reducing postsynaptic excitability
- **Baclofen**: GABA analogue, selective, is used to treat spasticity and related motor disorders
GABAergic inhibition is seen at all levels of the CNS, including the hypothalamus, hippocampus, cerebral cortex and cerebellar cortex.
Glycine

• Glycine is another inhibitory neurotransmitter acting on its own receptor (structurally and functionally similar to GABA\textsubscript{A} receptor)

• whereas GABA is located primarily in the brain, glycine is found predominantly in the ventral horn of the spinal cord

• Glycine is removed from the extracellular space by two transporters GlyT1 and GlyT2 on astrocytes

• Strychnine: convulsant agent, appears to be a relatively specific antagonist of glycine

• Tetanus toxin: prevents glycine release from inhibitory interneurons
### Major neurotransmitters in the CNS

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Monoamines

- Catecholamines:
  - Derived from tyrosine
  - Include:
    - Dopamine
    - Noradrenalin
    - Adrenalin

- Indoleamine:
  - Derived from tryptophan
  - Include:
    - Serotonin

- Histamine
Dopamine

• is the most important of the biogenic amine neurotransmitters in CNS
• dopamine appears to be an inhibitory neurotransmitter
• plays an important role in the regulation of motor functions, initiation of behavioural patterns and modulation of visceral functions
• dopamine is particularly important in relation to neuropharmacology (Parkinson's disease, schizophrenia – hyperdopaminergic state, attention deficit disorder, substance abuse, endocrine disorders, fatigue, concentration difficulty, low motivation (anhedonia))

• several classes of drugs, notably the antipsychotics, interfere with dopaminergic transmission
Dopamine Synthesis

• The first step in the catecholamine synthesis is the hydroxylation of the tyrosine and the formation of L-DOPA. This reaction is catalysed by tyrosine hydroxylase. L-DOPA is converted into dopamine by the enzyme DOPA decarboxylase.

• Dopaminergic neurons lack dopamine β-hydroxylase, and thus do not produce noradrenaline.
Dopamine metabolism and reuptake

- dopamine is broken down into inactive metabolites by: **monoamine oxidase** (MAO-A and MAO-B), **catechol-O-methyl transferase** (COMT) and **aldehyde dehydrogenase** (ALDH) acting in sequence

- different breakdown pathways exist - the main product is homovanillic acid (HVA - excreted in the urine)

- the two primary metabolic routes that convert dopamine into HVA are:
  
  Dopamine $\rightarrow$ DOPAL $\rightarrow$ DOPAC (4-hydroxyphenylacetic acid) $\rightarrow$ HVA – catalyzed by MAO, ALDH, and COMT respectively

  Dopamine $\rightarrow$ 3-Methoxytyramine $\rightarrow$ HVA – catalyzed by COMT and MAO+ALDH respectively

- after the postsynaptic effects dopamine can be absorbed back into the presynaptic cell, via reuptake mediated either by the **dopamine transporter** or by the **plasma membrane monoamine transporter** - dopamine can either be broken down by a monoamine oxidase or repackaged into vesicles by vesicular monoamine transporter and released again
Dopamine receptors

- five dopamine receptors have been identified (D₁-D₅) which are all coupled to a G-protein regulating adenylate cyclase activity.

- they can be divided into two groups, depending on whether they activate AC and increase cAMP level via a Gs protein: D₁-receptor group (D₁, D₅)

- or inhibit it via a Gi protein and decrease cAMP, block certain calcium channels, and open certain potassium channels: D₂-receptor group (D₂, D₃, D₄)

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Dopamine receptors

- The density of various receptor subtypes differs in different areas of the CNS
- Cortical motor areas: rich in $D_2$
- Limbic system: rich in $D_3$-$D_4$ receptors
1. **Mesostriatal (or nigrostriatal) pathway:** 75% of the dopamine in brain. Neurons in the substantia nigra pars compacta (SNc) project to the dorsal striatum (*upward dashed blue arrows*); **motor control**-this is the pathway that degenerates in Parkinson disease.

2. **Tuberohypophyseal system:** is a group of short neurons running from the ventral hypothalamus to the median eminence and pituitary gland (*red arrows*). **Regulate secretions of pituitary gland**
3. **Mesolimbic pathway:** The third pathway projects from the ventral tegmentum to the mesolimbic forebrain, especially the nucleus accumbens and the amygdaloid nucleus.

4. **Mesocortical pathway:** whose cell bodies also lie in the VTA and which project via the medial forebrain bundle to the frontal cortex (*solid blue arrows*).

These pathways - **cognitive, reward and emotional behavior**
Mesocortical dopamine deficiency - ADHD
Mesolimbic dopamine deficiency – Schizophrenia
DOPAMINE RELATED DISEASES

Parkinson's Disease
- When striatum dopamine is depleted to 20% of the original level, symptoms of Parkinson's Disease appear

Treatment: Levodopa, Dopamine Receptor Agonists, Monoamine Oxidase Inhibitors (MAOIs) Catechol- O-Methyltransferase (COMT) inhibitors, Amantidine

Schizophrenia
- Schizophrenia is thought to be due to an overstimulation of D_2 receptors
  chlorpromazine: D_2 antagonist, alleviate the symptoms,
  amphetamine: increases D_2 stimulation, can induce psychotic symptoms resembling schizophrenia

Vomiting
Dopaminergic neurons can cause nausea and vomiting: all dopamine receptor agonists (e.g. bromocriptine) and drugs that increase dopamine release (e.g. levodopa) cause nausea and vomiting as side effects

Dopamine antagonists (e.g. phenothiazines, metoclopramide) have antiemetic activity (D2 receptors occur in the area of the medulla (chemoreceptor trigger zone) associated with the initiation of vomiting)
Noradrenaline

- the basic processes responsible for the synthesis, storage, release and reuptake of noradrenaline are the same in the brain as in the periphery and the same types of adrenoceptor are also found in pre- and postsynaptic locations in the brain
- the mammalian CNS contains both $\alpha$- and $\beta$-adrenoceptors
- noradrenergic neurons: in the nucleus locus coeruleus of the pons and in the reticular formation
- **Role:** affective disorders, in learning and memory and in sleep-wake cycle regulation
Noradrenalin Synthesis

- The third step in the catecholamine synthesis is the hydroxylation of the dopamine side chain and the formation of noradrenaline. This reaction is catalysed by dopamine beta-hydroxylase.
Noradrenalin metabolism

-the initial step in the breakdown can be catalyzed by either of the enzymes **monoamine oxidase** (MAO-A) or **COMT**, the principal end product is mainly **vanillylmandelic acid** and is excreted in the urine

-after the postsynaptic effects noradrenalin absorbs back into the presynaptic cell, via reuptake mediated either by the **noradrenalin transporter** or by the **vesicular monoamine transporter** - it can either be broken down by a monoamine oxidase or repackaged into vesicles by vesicular monoamine transporter and released again
The actions of noradrenaline

- are mainly inhibitory (β-receptors), but some are excitatory (α- or β-receptors)
- **Noradrenergic transmission**
  - controls wakefulness and alertness
  - regulates blood pressure
  - regulates response to stress
  - takes a part in the control of mood (functional deficiency contributing to depression)
Noradrenaline Pathways

- The principal centers for noradrenergic neurons are the **locus coeruleus** and the **caudal raphe nuclei**. The ascending nerves of the locus coeruleus project to the frontal cortex, thalamus, hypothalamus and limbic system (influence emotional behaviour).
- Noradrenaline is also transmitted from the **locus coeruleus** to the cerebellum.
- Nerves projecting from the **caudal raphe nuclei** ascend to the amygdala and descend to the **midbrain**.
Noradrenergic Drugs

**Psychotropic drugs** that act partly or mainly on noradrenergic transmission in the CNS include:

- Antidepressants
- Cocaine
- Amphetamine
- Antihypertensive drugs – clonidine, methyldopa
Monoamines Neurotransmitters

• Catecholamines:
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  Include:
    Dopamine
    Norepinephrine
    Epinephrine

• Indoleamine:
  Derived from tryptophan
  Includes:
    Serotonin

• Histamine
Serotonin

- in humans 10% of serotonin (5-hydroxytryptamine, or 5HT) occurs primarily in the platelets and brain

- tryptophan is initially hydroxylated to form 5-hydroxytryptophan, decarboxylation of the latter compound results in the formation of serotonin
- serotonin is initially oxidatively deaminated to form 5-hydroxyindoleacetaldehyde, and rapidly oxidized to the major metabolite 5-hydroxyindoleacetic acid and excreted in the urine

- serotonin is taken back into the initial neuron by an active reuptake mechanism to be released again
Serotonin pathways

- The most of the serotonin in the brain is in the brainstem, specifically in the raphe nuclei - these neurons control muscle activity.
- Considerable amounts are present in areas of the hypothalamus, the limbic system - regulate memory and mood.
- In frontal cortex - regulate cognition and memory and the pituitary gland.
14 distinct mammalian receptor subtypes for serotonin have been established, not all of which have been identified in the brain.

- **serotonin** is involved in the regulation of several aspects of behavior, including sleep, pain perception, depression, sexual activity, and aggressiveness.
- Serotonin also may be involved in temperature regulation and in the hypothalamic control of the release of pituitary hormones.
- Some of the most important antidepressant agents (SSRIs) are believed to prevent the reuptake of serotonin.
Histamine

- histamine occurs in the brain, particularly in certain hypothalamic neurons (axons run to all parts of the brain)
- histamine acts on four types of receptors ($H_{1-4}$)
- **Role:** regulation of food and water intake, thermoregulation, hormone release and sleep
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the discovery that Acetylcholine (Ach) was a transmitter in the peripheral nervous system formed the basis for the **theory of neurotransmission**

ACh was first identified in 1915 by Henry Hallett Dale for its actions on heart tissue, it was confirmed as a neurotransmitter by Otto Loewi (1936-Nobel prize)

ACh is an **excitatory** neurotransmitter containing a quaternary ammonium group

it is used in neuromuscular junctions of all vertebrates, all preganglionic neurons of the autonomous nervous system and all postganglionic parasympathetic neurons

in the CNS it modulates many cortical activities such as **arousal, sleep and memory consolidation**

ACh (among other neurotransmitters) is decreased in certain cognitive disorders, such as **Alzheimer’s disease**
Cholinergic signalling

- is mediate by two receptor types with several subtypes:

1) **Muscarinic receptors**
   - *metabotropic receptors* coupled to Gq proteins, which then regulate ion channel opening, the response of the postsynaptic neuron is relatively slow, **five subtypes** of muscarinic receptors have been identified, the *mAChRs* in the brain are predominantly of the M1 class
   - muscarinic receptors: mediate the main behavioural effects associated with Ach – effects on *arousal* and on *learning and short-therm memory*
   - muscarinic antagonists (e.g. scopolamine) cause amnesia

2) **Nicotinic receptors**
   - *ionotrophic receptors* opening cation channel permeable for sodium and potassium or calcium
   - *muscular type* found mostly in the *neuromuscular junction*
   - *neuronal type* found in all *postsynaptic terminals in autonomic ganglia*, in the CNS neuronal type receptors function as heteroreceptors for other systems (GABA, serotonin, glutamate, dopamine), they increase the permeability for calcium and increase the amount of released neurotransmitters
1. Neurons in the magnocellular forebrain nuclei send a diffuse projection to the brain - Degeneration of the nucleus basalis of Meynert (project to the cortex) – **Alzheimer’s, Dementia**

2. Septohippocampal projection – provides the main cholinergic input to the hippocampus – involved in **memory**

3. Short local interneurons in the striatum and nucleus accumbens – relation to **Parkinson’s disease and Huntington’s chorea**
Acetylcholine Drugs

- Acetylcholinesterase Inhibitors: Alzheimers disease
  Donepezil
  Tacrine
  Galantamine
  Rivastigmine

- Muscarinic Cholinergic Receptor Antagonists: Parkinson’s disease (tremor)
  Trihexyphenidyl and Benztropine
### Major neurotransmitters in the CNS

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Structure</th>
<th>Functional Class</th>
<th>Secretion Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td><img src="image" alt="Acetylcholine structure" /></td>
<td>Excitatory to vertebrate skeletal muscles; excitatory or inhibitory at other sites</td>
<td>CNS; PNS; vertebrate neuromuscular junction</td>
</tr>
<tr>
<td><strong>Biogenic Amines</strong></td>
<td></td>
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</tr>
<tr>
<td>Norepinephrine</td>
<td><img src="image" alt="Norepinephrine structure" /></td>
<td>Excitatory or inhibitory</td>
<td>CNS; PNS</td>
</tr>
<tr>
<td>Dopamine</td>
<td><img src="image" alt="Dopamine structure" /></td>
<td>Generally excitatory; may be inhibitory at some sites</td>
<td>CNS; PNS</td>
</tr>
<tr>
<td>Serotonin</td>
<td><img src="image" alt="Serotonin structure" /></td>
<td>Generally inhibitory</td>
<td>CNS</td>
</tr>
<tr>
<td><strong>Amino Acids</strong></td>
<td></td>
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</tr>
<tr>
<td>GABA (gamma aminobutyric acid)</td>
<td><img src="image" alt="GABA structure" /></td>
<td>Inhibitory</td>
<td>CNS; invertebrate neuromuscular junction</td>
</tr>
<tr>
<td>Glycine</td>
<td><img src="image" alt="Glycine structure" /></td>
<td>Inhibitory</td>
<td>CNS</td>
</tr>
<tr>
<td>Glutamate</td>
<td><img src="image" alt="Glutamate structure" /></td>
<td>Excitatory</td>
<td>CNS; invertebrate neuromuscular junction</td>
</tr>
<tr>
<td>Aspartate</td>
<td><img src="image" alt="Aspartate structure" /></td>
<td>Excitatory</td>
<td>CNS</td>
</tr>
<tr>
<td><strong>Neuropeptides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td><img src="image" alt="Substance P structure" /></td>
<td>Excitatory</td>
<td>CNS; PNS</td>
</tr>
<tr>
<td>Met-enkephalin (an endorphin)</td>
<td><img src="image" alt="Met-enkephalin structure" /></td>
<td>Generally inhibitory</td>
<td>CNS</td>
</tr>
</tbody>
</table>
**Neuropeptides as neurotransmitters**

- Large number of endogenous peptides are produced by neurons that appear to possess the essential characteristics of neurotransmitters
- Low concentration in brain (picomolar)
- Large vesicles, release is Ca$^{2+}$-dependent
- No reuptake – enzymatic cleavage
- Co-localized with other “traditional” transmitters
- Modulatory functions
- Mostly inhibitory
- Virtually all metabotropic
- Slow acting, long duration

**Examples:** opioid peptides, Substance P, vasopressin, oxytocin, NPY, AgRP, CCK
Opioid peptides

- include the endorphins, enkephalins and dynorphins
- the highest concentration of opioid receptors (µ, δ, κ) are found in the sensory, limbic and hypothalamic regions of the brain — and are particularly high in the amygdala and periaqueductal grey area
- play an important role in motivation, emotion, attachment behaviour, the response to stress and pain, and the control of food intake
- can modulate the action of the associated neurotransmitter (such as glutamate) which is being released from the same synapse
Substance P

- the first neuropeptide to be isolated and characterized is known as substance P
- it is an 11-amino acid peptide (undecapeptide) has been known for more than 60 years, its exact physiological role is still not clear
- Substance P occurs in high concentrations in neurons projecting into the substantia gelatinosa layer of the spinal cord from dorsal root ganglia, among many other areas of the brain
- Substance P can directly depolarize motor neurons in a manner analogous to that of other excitatory neurotransmitters
- it is probable that substance P is released from small unmyelinated nerve fibers in response to painful stimulation
- levels of substance P in the substantia nigra are markedly reduced in the neurological disease Huntington’s chorea
• also known as growth hormone-inhibiting hormone (GHIH) is a peptide hormone
• regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors $sst_1$-$sst_5$ (inhibits adenyl cyclase) and inhibition of the release of numerous secondary hormones,
• inhibits the release of growth hormone, thyroid-stimulating hormone, prolactin, insulin and glucagon secretion
• is released from small unmyelinated nerve fibers in response to painful stimulation – decreases neurogenic inflammation, has anti-inflammatory and analgesic effects
• in hypothalamus, arcuate nucleus, hippocampus and brainstem - role: sensory and motor functions, learning and memory, stress
Neuropeptid Y and Agouti-related protein (AgRP)

- **Neuropeptid Y (NPY)** is produced in the hypothalamus and hippocampus, specifically in the arcuate nucleus and dentate gyrus.
- **Role:** increasing food intake and storage of energy as fat, reducing anxiety and stress, reducing pain perception, affecting the circadian rhythm, reducing voluntary alcohol intake, lowering blood pressure.
- Neuropeptide Y has been identified as being synthesized in GABA-ergic inhibitory neurons.
- NPY exerts most of its effects through G-protein coupled receptor proteins, mainly Y1, Y2, Y4, and Y6.

- **Agouti-related protein (AgRP)** is synthesized only in NPY-containing cell bodies located in the ventromedial part of the arcuate nucleus in the hypothalamus, AgRP is co-expressed with NPY.
- **Role:** increase appetite and decrease metabolism, it is one of the most potent and long-lasting of appetite stimulators.
- inverse agonist of melanocortin receptors.
Cholecistokinin

- CCK is found extensively throughout the central nervous system, with high concentrations found in the **limbic system**
- elevated CCK levels causes increased **anxiety** - the site of the anxiety-inducing effects of CCK seems to be central with specific targets being the basolateral amygdala, hippocampus, hypothalamus, peraqueductal grey, and cortical regions
- the CCK tetrapeptide fragment CCK-4 (Trp-Met-Asp-Phe-NH2) causes **anxiety and panic attacks** (panicogenic effect) when administered to humans
- several studies have implicated CCK as a cause of **visual hallucinations in Parkinson’s disease**
- **CCK A and CCK B** (in the brain) **receptor**
Vasopressin and Oxytocin

- vasopressin and oxytocin, two nonapeptides, were the first peptide "neurohormones" to be considered
- they are stored in the neurohypophysis and released into the bloodstream upon an appropriate stimulus
- in the periphery, oxytocin stimulates the contraction of uterine smooth muscle and vasopressin (antidiuretic hormone) facilitates the reabsorption of water from the kidney tubules
- they both possess potent inhibitory actions on neuro-hypophyseal neurons
Thank you for your attention!