NEUROTRANSMITTERS, NEUROPEPTIDES AND THEIR RECEPTORS

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• Literature
• Siegel and Sapru, Essential Neuroscience, chapter 8
• Kandel, Schwartz and Jessel, Principles of Neural Science, chapter 12 (part)
BASICS OF CHEMICAL SIGNALIZATION

- Synthesis of the neurotransmitter
- Storage of the neurotransmitter into the vesicles
- Binding of the neurotransmitter for the receptors
- Inactivation of neurotransmitters
The transmission of information from one neuron to another

1. Synthesis of neurotransmitter and formation of vesicles
2. Transport of neurotransmitter down axon
3. Release of neurotransmitter
4. Interaction of neurotransmitter with receptor, exciting or inhibiting postsynaptic neuron
5. Separation of neurotransmitter molecules from receptors
6. Reuptake of neurotransmitter to be recycled
7. Vesicles without neurotransmitter transported back to cell body
Neurotransmitter:
- Molecule responsible for intercellular signalization
- Synthesized into the presinaptic neuron
- Released at a synapse (exocytosis)
- Binds to the receptors on the postsynaptic cell
- Elicits a specific response
- Neurotransmitters are electrically charged molecules.
- They are synthesized from the precursor, using the enzymes present in the cytosol.
- The presence of the main enzyme in the neuron can prove its neurotransmitter!
CRITERIA USED FOR IDENTIFYING NEUROTRANSMITTERS

A) PRESINAPTIC NEURON
1. The substance must be **PRESENT** in the nerve terminal
2. **ENZYMES** needed for its synthesis must be present
3. It must be released by **EGZOCYTOSIS** following depolarization

B) POSTSINAPTIC MEMBRANE
4. It should **MIMIC** the action of the endogenously released neurotransmitter when administered exogenously at or near synapse...
5. and activate same **INTRACELLULAR SIGNAL PATHWAYS**
6. There is a **MECHANISM OF INACTIVATION**

C) WHOLE MECHANISM
7. **AGONISTS AND ANTAGONISTS** evoke the same response
Neurotransmitter Criteria

The chemical must be produced within a neuron

The chemical must be found within a neuron.

When a neuron is stimulated (depolarized), a neuron must release the chemical.

When a chemical is released, it must act on a post-synaptic receptor and cause a biological effect.
After a chemical is released, it must be inactivated. Inactivation can be through a reuptake mechanism or by an enzyme that stops the action of the chemical.

If the chemical is applied on the post-synaptic membrane, it should have the same effect as when it is released by a neuron.
<table>
<thead>
<tr>
<th>Small-Molecule Neurotransmitters</th>
<th>Neuropeptides</th>
<th>Gaseous Neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Opioid peptides</td>
<td>Nitric oxide</td>
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<tr>
<td>Excitatory amino acids</td>
<td>β-endorphin</td>
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<tr>
<td>Glutamate</td>
<td>Methionine-enkephalin</td>
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<td>Aspartate</td>
<td>Leucine-enkephalin</td>
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<td>Inhibitory amino acids</td>
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<td>GABA</td>
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<td>Glycine</td>
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<td>Catecholamines</td>
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<tr>
<td>Dopamine</td>
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<td>Norepinephrine</td>
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<td>Epinephrine</td>
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<td>Indoleamine</td>
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<td>Serotonin (5-HT)</td>
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<tr>
<td>Imidazole amine</td>
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<td>Histamine</td>
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<td>Purines</td>
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<tr>
<td>ATP</td>
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<tr>
<td>Adenosine</td>
<td></td>
<td></td>
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</table>
Small Molecule Neurotransmitter Substances

Amines and ACh
- Norepinephrine (NE)
- Serotonin (5-HT)
- Histamine
- Dopamine (DA)
- Epinephrine
- Acetylcholine (ACh)

Amino Acids
- Gamma-aminobutyric acid (GABA)
- Glycine
- Glutamate
- Aspartate
Besides *classical neurotransmitters*, neurons can use *neuroactive peptides* for synaptic signalization.
• Neurotransmitters and neuropeptides have different characteristics and different criteria of identification.
Characteristics of classical neurotransmitters and neuropeptides

- **Neurotransmitters**
  - Medium to high concentration
  - Lower affinity binding for receptors
  - Small potency
  - High specificity
  - Medium speed synthesis
  - Small molecules (2-10 C atoms)
  - Mediators (excitatory or inhibitory)

- **Neuropeptides**
  - Very low concentration
  - High affinity binding for receptors
  - High potency
  - High specificity
  - Slow synthesis (in vitro)
  - Small to big molecules (2-100 C atoms)
  - Modulators
### Selected Bioactive Peptides

**Hypothalamic releasing factors**
- CRH: corticotropin releasing hormone
- GHRH: growth hormone releasing hormone
- GnRH: gonadotropin releasing hormone
- Somatostatin
- TRH: thyrotropin releasing hormone

**Pituitary hormones**
- ACTH: adrenocorticotropin hormone
- α-MSH: α-melanocyte stimulating hormone
- β-endorphin
- GH: growth hormone
- PRL: prolactin
- FSH: follicle stimulating hormone
- LH: luteinizing hormone
- TSH: thyrotropin [thyroid stimulating hormone]

**GI and brain peptides**
- CCK: cholecystokinin
- Gastrin
- GRP: gastrin releasing peptide
- Motilin
- Neurotensin
- Substance K; substance P (tachykinins)

**Circulating**
- Angiotensin
- Bradykinin

**Frog skin**
- Bombesin
- Caerulein
- Ranatensin

**Opiate peptides**
- β-endorphin
- Dynorphin
- Leu-enkephalin
- Met-enkephalin

**Neurohypophyseal peptides**
- Oxytocin
- Vasopressin

**Neuronal and endocrine**
- ANF: atrial natriuretic peptide
- CGRP: calcitonin gene-related peptide
- VIP: vasoactive intestinal peptide

**GI and pancreas**
- Glucagon
- PP: pancreatic polypeptide

**Neurons only?**
- Galanin
- Neuromedin K
- NPY: neuropeptide Y
- PYY: peptide YY

**Endocrine only?**
- Calcitonin
- Insulin
- Secretin
- Parathyroid hormone
Receptors

- Signalization (either mediated via neurotransmitters or neuropeptides) in chemical synapse depends on RECEPTORS located in the postsynaptic membrane.
- Receptors can be IONOTROPIC (ligand-gated receptors) or METABOTROPIC (G-protein coupled receptors).
• **Agonist** - mimics the function of endogenous ligand.

• **Antagonist** – binds for receptor and stops the function of the endogenous ligand. They are inhibitors or blockators. They can be competitive or non-competitive.
Receptors determine type and duration of the synaptic signalization

- Ionotropic
  - Ligand-gated receptors
  - Combine transmitter binding and channel function into one molecular entity.
  - Rapid (0.1 – 2 ms) and short-duration (≈20 ms) responses
  - Mediatary role
  - Excitatory (Na\(^+\) and K\(^+\) and sometimes Ca\(^{2+}\))
  - Inhibitory (Cl\(^-\))
  - Sumation of signals is needed to produce an action potential.
  - No voltage dependency except for glu-NMDA receptors
• Metabotropic
  • Slow signalization (100 ms – few sec; 10 000 x slower than ionotropic)
  • Long duration of responses (several minutes)
  • Modulatory role: presynaptic facilitation or inhibition
  • Effect depends on the concentration of the second messengers
  • Duration depends on the enzymes that inactivate second messengers
  • Second messengers stimulate enzymes (protein kinase A) which then phosphorylate appropriate ion channels.
**FIGURE 8-21** Mechanisms by which metabotropic receptors mediate responses to different transmitters. (A) Events that follow binding of acetylcholine to a muscarinic receptor. (B) Events that follow binding of norepinephrine to a β-adrenergic receptor. GTP = guanosine triphosphate; cAMP = cyclic adenosine monophosphate; EPSPs = excitatory postsynaptic potentials; Ca²⁺ = calcium; K⁺ = potassium; Cl⁻ = chloride.
<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Ionotropic Receptor</th>
<th>Metabotropic Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine (ACh)</td>
<td>Cholinergic nicotinic</td>
<td>Cholinergic muscarinic</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDA, AMPA, kainate</td>
<td>mGlu₁-mGlu₆</td>
</tr>
<tr>
<td>GABA</td>
<td>GABAₐ</td>
<td>GABAₐ</td>
</tr>
<tr>
<td>Glycine</td>
<td>Strychnine-sensitive glycine receptor</td>
<td>—</td>
</tr>
<tr>
<td>Dopamine</td>
<td>—</td>
<td>D₁-D₅</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>—</td>
<td>α- and β-adrenergic receptors</td>
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<tr>
<td>Epinephrine</td>
<td>—</td>
<td>α- and β-adrenergic receptors</td>
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<tr>
<td>Serotonin</td>
<td>5-HT₃</td>
<td>5-HT₁, 5-HT₂, 5-HT₄</td>
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<tr>
<td>Histamine</td>
<td>—</td>
<td>H₁, H₂, H₃</td>
</tr>
<tr>
<td>Adenosine</td>
<td>—</td>
<td>A₁-A₃</td>
</tr>
<tr>
<td>Opioid peptides</td>
<td>—</td>
<td>Mu, delta, kappa, ORL₁</td>
</tr>
</tbody>
</table>

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; GABA = gamma aminobutyric acid; NMDA = N-methyl-D-aspartic acid.
Ionotropic receptors can be excitatory or inhibitory

<table>
<thead>
<tr>
<th>Effect</th>
<th>Neurotransmitter</th>
<th>Receptor</th>
<th>Ions</th>
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<tbody>
<tr>
<td>Excitation</td>
<td>Acetylcholine</td>
<td>Nicotinic (nAChR)</td>
<td>Na⁺ and K⁺</td>
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<td>Glutamate</td>
<td>NMDA</td>
<td>Na⁺, K⁺ and Ca⁺</td>
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<tr>
<td></td>
<td>Glutamate</td>
<td>Non-NMDA</td>
<td>Na⁺ and K⁺</td>
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<td>Serotonin</td>
<td>5-HT₃</td>
<td>Na⁺ and K⁺</td>
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<tr>
<td>Inhibition</td>
<td>GABA</td>
<td>GABAₐ</td>
<td>Cl⁻</td>
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<tr>
<td></td>
<td>Glycine</td>
<td>Glycine Receptors</td>
<td>Cl⁻</td>
</tr>
</tbody>
</table>
Mechanisms of Regulation of Receptors

- Desensitization
- Down-Regulation
Desenzitization

- Prolonged exposure of a receptor to endogenous or exogenous agonist reduces the responsiviness of the receptor.
- NE + β adrenoreceptor → G-protein is stimulated
- cAMP is formed → protein kinaze A is stimulated
- β adrenoreceptor is phosphorylated and uncoupled from the G-protein
- The receptor no longer responds to the agonist
Down-Regulation

- When the number of receptors decreases.
- Receptors are internalized and sequestered inside the cell.
- Example: 5-HT receptors
INTERNALIZATION OF 5-HT rec (8-OH-DPAT)

Immunogold labeling of 5-HT$_{1A}$ receptors in dendrites from the NRD - Riad et al: Internalization of 5-HT$_{1A}$ receptors
INTERNALIZATION OF 5-HT recepors (fluoxetine)

- Immunogold labeling of 5-HT$_{1A}$ receptors in dendrites from the NRD- Riad et al: Internalization of 5-HT$_{1A}$ receptors
Glutamate

- Excitatory Amino Acid
- neurotransmitter of fast synaptic excitation
- Works through ionotropic and metabotropic receptors
  - IONOTROPIC glutamate receptors: NMDA, AMPA/kainate
  - NMDA receptors: Na\(^+\) gets into the cell to depolarize the membrane – fast synaptic transmission – EPSP
  - Ca\(^{2+}\) - second messenger: turns electrical signals into biochemical signals – long lasting synaptic effect
  - NMDA-receptor is VOLTAGE (partial depolarization) and LIGAND (glutamate) regulated ion channel.
Metabolism of glutamate

Synthesis

- Glutamate is synthesized in the brain by two processes.
- **1. Process**: glucose enters the neuron by facilitated diffusion and is metabolized via the Krebs (tricarboxylic acid) cycle
- α-oxoglutarate generated during the Krebs cycle is transaminated by α-oxoglutarate transaminase to form glutamate.
2. Process:
1. and 2. Nerve terminals and glial cells reuptake the glutamate released from the nerve terminals via glutamate transporters located in their cell membranes.
2. In the glia, glutamate is converted into glutamine by an enzyme, glutamine synthetase.
4. Glutamine is transported out of the glia into the neuronal terminal via glutamine transporters located in the glial and neuronal terminal membranes.
5. In the neuronal terminal, glutamine is converted into glutamate by an enzyme, glutaminase. Glutamate is taken up into the vesicles by active transport, stored.
• subsequently released by exocytosis. Released glutamate is then actively taken up by the glia and neuronal terminals via glutamate transporters (GLT-1 and EAAC1).

• In the neuronal terminal, it is repackaged into the vesicles for subsequent reuse. In the glia, it is converted into glutamine.
FIGURE 8-7  Steps involved in the synthesis and release of glutamate.
Glutamate receptors
**non-NMDA-receptor**
- activated by glutamate
- Na⁺ gets into the cell

**NMDA-receptor**
- Activated by potential and glutamate
- Role of Mg²⁺
- Na⁺ and Ca²⁺ get inside, K⁺ goes out
- Ca²⁺ - second messenger, important for LTP learning
- glycine
FIGURE 8-18 Components of an N-methyl-D-aspartic acid (NMDA) receptor. PCP = phencyclidine; 
Ca$^{2+}$ = calcium; Na$^+$ = sodium; K$^+$ = potassium; Mg$^{2+}$ = magnesium.
- METABOTROPIC glutamate receptors
- mGluR1 and mGluR5 activate phospholipase C (PLC) to activate PKC
- others inhibit adenylate cyklase and production of cAMP
- they block excitatory synaptic transmission
- multiple effects and characteristic
Metabotropic glutamate receptors

- Increase excitability
- Block excitatory synaptic transmission and occurrence of LTP
- Block voltage-gated Ca\textsuperscript{2+} channels
- Decrease excitotoxic effects mediated via NMDA receptors
GABA and Glycine - main inhibitory amino acid neurotransmitters (fast synaptic inhibition)

- **GABA** – synthesis and removal
  - 1. Glutamine is converted into glutamate by an enzyme, glutaminase.
  - 2. GABA is formed by α-decarboxylation of glutamate. This reaction is catalyzed by a cytosolic enzyme, *L-glutamic acid-1-decarboxylase* (GAD)
  - 3. Synthesized GABA is taken up into vesicles where it is stored.
  - 4. It is released into the synaptic cleft by exocytosis.
5. After its release, GABA is taken up into presynaptic terminal via GABA transporters and repackaged into vesicles for subsequent use.

6. GABA is also taken up into the glia via GABA transporters.

7. In glia, GABA is converted to glutamate by a mitochondrial enzyme, GABA transaminase (GABA-T).

8. Another enzyme, glutamine synthetase, converts glutamate into glutamine, which is then transported into the neighboring nerve terminals where it is processed to synthesize glutamate.
FIGURE 8-8  Steps involved in the synthesis and release of gamma aminobutyric acid (GABA).
Distribution of GABA and Glycine:

- GABA is found in high concentrations in the brain and spinal cord.
- is absent in peripheral nerves or peripheral tissues
- Glycine is found in the spinal cord, caudal (lower) parts of medulla and retina.
- Glycine hyperpolarizes neurons by opening chloride channels.
- hyperglycinemia, is devastating neonatal disease characterized by lethargy and mental retardation.
GABA and Glycine

- Bind to ionotrophic receptors (GABA_A i Glycine ) which are ligand-gated Cl- channels
- GABA also has a metabotropic receptors (GABA_B)
- Glycine works as a coactivator of glutamate NMDA-receptors.
GABA_\text{A} \text{ receptor}

- They consist of a combination of five subunits: two alpha, two beta, and one gamma.
- Each subunit has four transmembrane domains (TM1–TM4).
- Present on these receptors are major binding sites:
  - Benzodiazepines (diazepam [Valium]), barbiturates, steroids, anesthetics, picrotoxin
**GABA$_A$ receptor**

- Activation of the GABA receptor site by GABA agonists results in the opening of the chloride channel (Cl$^-$).
- Two molecules of GABA are needed.
- *Inhibitory postsynaptic potential (IPSP)* is formed.
Figure 8-19  Components of a gamma aminobutyric acid type A (GABAA) receptor. Cl\(^-\) = chloride.
FIG. 2. Structural model of the GABA<sub>A</sub>/benzodiazepine receptor-chloride (Cl⁻) ionophore complex. The cut-away view demonstrates targets for a variety of compounds that influence the receptor complex. No specific drug receptor location is implied.
GABA$_A$ receptor ANTAGONISTS

- Selective competitive antagonist BICUKULINE decreases frequency and duration of opened stage.
- PICROTOXINE – noncompetitive alosterick inhibitor – prevents the opening of the channel.
GABA_A receptor AGONISTS

- MUSCIMOL
- BENZODIAZEPINES – increase the frequency of the open stage (anxiolitics, antiepileptics, hypnotics, muscle relaxans)
- BARBITURATES – stimulate the effect of GABA on receptor, but can open Cl- channel with no GABA present (sedatives, hypnotics, anticonvulsives, anesthetics)
- PROGESTERONE – sedative; prolonges duration of the opening stage.
- GABA_B receptor: increases membrane permeability for K^+ (hyperpolarization), and decreases permeability for Ca^{2+} = development of slow IPSP
## Characteristics of GABA Receptors

<table>
<thead>
<tr>
<th>Category</th>
<th>GABA(_A) Receptor</th>
<th>GABA(_B) Receptor</th>
<th>GABA(_C) Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ligand-gated Channel</td>
<td>G-protein coupled receptor</td>
<td>Ligand-gated Channel</td>
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<tr>
<td>Subunits</td>
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<td>rho</td>
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<td>Baclofen</td>
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<td>Bicuculline, Picrotoxin</td>
<td>Phaclofen</td>
<td>TPMPA, Picrotoxin</td>
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<td>Desensitization</td>
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<td>Modulator</td>
<td>Benzodiazepines Barbiturates</td>
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<td>Zinc</td>
</tr>
</tbody>
</table>
• AGONISTS of Glycine receptors:
  • taurin, beta-alanin
• ANTAGONIST:
  • strihnin – source the plant *Strychinos nux vomica*; neurotoxin, evokes convulsions
Acetylcholine

- **Synthesis**

1. Glucose enters the nerve terminal by passive transport (facilitated diffusion).
2. **Glycolysis occurs in the neuronal cytoplasm, and pyruvate** (pyruvic acid) molecules are generated.
3. Pyruvate is transported into the mitochondria, and an **acetyl group** derived from pyruvic acid combines with **coenzyme-A** present in the mitochondria to form **acetylcoenzyme-A**, which is transported back into the cytoplasm.
• 4. Choline, the precursor for Ach, is actively transported into the neuronal terminal from the synaptic cleft via Na⁺ (sodium) and choline transporters.

• 5. Ach is synthesized in the cytoplasm of the nerve terminal from choline and acetylcoenzyme-A in the presence of an enzyme, choline acetyltransferase.

• 6. Ach is then transported into vesicles and stored there.

• 7. It is then released into the synaptic cleft by exocytosis and hydrolyzed by acetylcholinesterase.
FIGURE 8–5 Steps involved in the synthesis and release of acetylcholine. Na⁺ = sodium.
• **Removal**

• acetylcholinesterase is present on the outer surfaces of the nerve terminal (prejunctional site) and the effector cell (postjunctional site).

• This enzyme hydrolyses Ach in the junctional extracellular space; choline liberated in this reaction re-enters the nerve terminal and is again used for the synthesis of Ach.
- **Distribution**
- The basal forebrain constellation is located in the telencephalon, medial and ventral to the basal ganglia.
- The basal nucleus of Meynert provides cholinergic innervation to the entire neocortex, amygdala, hippocampus, and thalamus.
- The medial septal nuclei provide cholinergic innervation to the cerebral cortex, hippocampus, and amygdala.
The second constellation includes cholinergic neurons located in the **dorsolateral tegmentum of the pons** that project to the basal ganglia, thalamus, hypothalamus, medullary reticular formation, and deep cerebellar nuclei.

Ach is a neurotransmitter of neuromuscular synapse, preganglionic sympathetic and preganglionic and posganglionic parasympathetic neurons.
FIGURE 8-6  Major cholinergic cell groups. Note two major constellations of cholinergic neurons: cholinergic neurons located in the basal forebrain constellation, including the basal nucleus of Meynert, and cholinergic neurons located in the dorsolateral tegmentum of the pons.
Ach is a neurotransmitter of neuromuscular synapse, preganglionic sympathetic and postganglionic parasympathetic neurons.

CNS = central nervous system; Pre = preganglionic; Post = postganglionic; 
ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine; 
D = dopamine; M = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor; 
D_1 = dopaminergic receptor
Ach receptors

- Ionotrophic nicotinic (neuronal and muscular nAChR)
- Metabotropic muscarinic (M1 - M5)
  - M1 and M3 work through IP$_3$/DAG system and inactivate K$^+$ channels
  - M2, M4 and M5 inhibit adenyl cyclase (decrease intracellular concentration of cAMP) and activate K$^+$ channels.
• AGONIST of nicotinic acetylcholine receptor - NICOTINE
• ANTAGONIST of nicotinic rec: curare, α-bungarotoxin
• AGONIST of muscarinic receptors: muscarine
• ANTAGONIST of muscarinic receptors: atropine, scopolamine
• ireverzibile inhibitors: nerve toxins
• reverzibile inhibitors: neostigmin, fizostigmin
**Physiological and Clinical Considerations**

- regulation of forebrain activity during cycles of sleep and wakefulness
- Cholinergic neurons of the basal forebrain constellation are involved in learning and memory and have been implicated in *Alzheimer’s disease*.
- There is a dramatic loss of cholinergic neurons in the basal nucleus of Meynert and Ach in the cortex of these patients.
- treatment with donepezil (Aricept), an acetylcholinesterase inhibitor, is indicated for mild to moderate dementia in patients with Alzheimer’s disease.
Monoamine neurotransmitters

- **Catecholamines**: dopamine, norepinephrine, epinephrine; synthetised from *tyrosine*
- **Indoleamines**: serotonin (from triptofan) and histamine (from histidin)
- Monoamines are located in small and medium vesicles with dense core.
**Catecholamines:**
- dopamine
- norepinephrine
- epinephrine

synthetised from **tyrosine**
Dopamine: Synthesis and Removal

FIGURE 8.10 Steps involved in the synthesis and release of dopamine. COMT = catechol-O-methyltransferase.
Dopamine: Distribution

- Substantia nigra
- Ventral tegmental area
- The hypothalamic arcuate nucleus
Receptors

- **Dopamine** receptors D₁, D₅ activate adenilil cyklase – role in Parkinson’s disease; D₂, D₃, D₄ inhibit it – role in schizophrenia
- D₁ important in nigrostriatal projections (Parkinson’s disease)
- D₂ related to Schizophrenia

- **Serootonin** receptors 5-HT₁, 5-HT₂, 5-HT₃
  - Autoreceptors 5-HT₁₄ receptors on soma and dendrites of serotonergic neurons.
Physiological and Clinical Considerations

- *Parkinson’s Disease*
- “mask-like face”
- slowness of movement
- rigidity of the extremities and the neck
- tremors in the hands
- Dopaminergic neurons located in the substantia nigra are degenerated
- drug therapy: to replace the deficiency of the dopamine in the basal ganglia
- dopamine does not cross the blood-brain barrier - (L-DOPA (levodopa) is administered)
• **Psychotic Disorders**
  • schizophrenia
  • increased activity at dopaminergic synapses
• **Cocaine Drug Abuse**
  • blocks the reuptake of dopamine
  • Elevated levels of dopamine in certain brain circuits may be responsible for the euphoric effects of cocaine
  • Dopaminergic projections from the VTA to the limbic structures (nucleus accumbens), may be involved in emotional reinforcement and motivation.
Norepinephrine: Synthesis and Removal

**Figure 8-12** Steps involved in the synthesis and release of norepinephrine. COMT = catechol-O-methyltransferase.
• **Autoinhibition and Negative Feedback**

• Activation of presynaptic adrenergic receptors results in inhibition of the release of norepinephrine. This process is known as **autoinhibition**

• It is distinct from negative feedback in which synthesis of the transmitter (norepinephrine in this case) is blocked at its rate-limiting step (i.e., conversion of tyrosine to DOPA by tyrosine hydroxylase).
• **Distribution**

• **locus ceruleus** (also known as “A6 group of neurons”) that is located in the pons

• projections through the central tegmental tract and the medial forebrain bundle to the thalamus, hypothalamus, limbic forebrain structures (cingulate and parahippocampal gyri, hippocampal formation, and amygdaloid complex), and the cerebral cortex

• **Role in** sleep and wakefulness, attention, and feeding behaviors
- **Physiological and Clinical Considerations**
- neurotransmitter of postganglionic sympathetic nerve terminals.
- psychiatric disorders such as depression.
- tricyclic antidepressants (desimipramine) inhibit the reuptake of norepinephrine at the nerve terminals.
Norepinephrine receptors

- Norepinephrine receptors $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$
- all metabotropic
- $\alpha_1$ – through PLC on IP$_3$/DAG system
- $\alpha_2$ - inhibits adenylyl cyclase and lowers concentration of cAMP
- $\beta_1$ and $\beta_2$ activate adenylyl cyclase and increase concentration of cAMP
FIGURE 8–13  Steps involved in the synaptically released epinephrine. COMT = catechol-O-methyltransferase; PNMT = phenylethanolamine-N-methyltransferase.
Indoleamines: *Serotonin*

- **Synthesis and Removal**
- does not cross the blood-brain barrier
- brain cells must synthesize their own serotonin
- Tryptophan serves as a substrate for serotonin synthesis
FIGURE 8-14 Steps involved in the synthesis and release of serotonin. The distribution of some 5-HT receptors on different components of the serotonergic synapse is also shown. AC = adenyl cyclase; cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; Gi, Go, Gq = different G-proteins; IP3 = inositol triphosphate; 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}, 5-HT_{4} = different 5-HT receptors.
- **Distribution**
- Midline **raphe nuclei of the medulla, pons, and upper brainstem**
- Central nervous system - 1% of all serotonin
- Enterocromaphine cells of intestines contain about 90% of all serotonin
- Trombocytes – 2% of all serotonin
FIGURE 8–15  Major serotonin-containing neurons and their projections.
**Physiological and Clinical Considerations**

- Dorsal horn regulate the release of enkephalins, which inhibit pain sensation.
- Mediate affective processes, such as aggressive behavior and arousal.
- In the **pineal gland** is a precursor for the synthesis of **melatonin**, which is a **neurohormone** involved in regulating sleep patterns.
- plays an important role in depression.
- serotonin-specific reuptake inhibitors (SSRIs) are used in the treatment of depression, anxiety disorders, and some personality disorders - fluoxetine (Prozac)
- Sumatriptan (Imitrex) is a 5-HT_{1D} receptor agonist. It is a vasoconstrictor of intracranial arteries and has proved useful in treating migraine headaches.
• “Designer Drugs” of Abuse and Their Relationship With Serotonin.

• Ecstasy has been used as a recreational drug by young adults (“rave parties”)
Serotonin receptors

- $5HT_1$, $5HT_2$ and $5HT_3$
- $5HT_3$ are the only ionotropic
- $5HT_2$ works through phospholipase C na IP$_3$/DAG system
- $5HT_1$ inhibits adenylyl cyclase and lowers concentration of cAMP
<table>
<thead>
<tr>
<th>Receptor *</th>
<th>Distribution</th>
<th>Effector mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT(_{1A})</td>
<td>Hippocampus, amygdala, septum, entorhinal cortex, hypothalamus, raphe nuclei</td>
<td>Inhibition of adenylyl cyclase, opening of K(^+) channels</td>
</tr>
<tr>
<td>5-HT(_{1B})</td>
<td></td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT(_{1Da})</td>
<td>Not distinguishable from 5-HT(_{1Db})</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT(_{1Db})</td>
<td>Substantia nigra, basal ganglia, superior colliculus</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-htr(_{1E})</td>
<td>?</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-htr(_{1F})</td>
<td>Cerebral cortex, striatum, hippocampus, olfactory bulb</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT(_{2A})</td>
<td>Claustrom, cerebral cortex, olfactory tubercle, striatum, nucleus accumbens</td>
<td>Stimulation of phosphoinositide-specific phospholipase C (IP3/DAG), closing of K(^+) channels</td>
</tr>
<tr>
<td>5-HT(_{2B})</td>
<td>?</td>
<td>Stimulation of phosphoinositide-specific phospholipase C (IP3/DAG)</td>
</tr>
<tr>
<td>5-HT(_{2C})</td>
<td>Choroid plexus, globus pallidus, cerebral cortex, hypothalamus, septum, substantia nigra, spinal cord</td>
<td>Stimulation of phosphoinositide-specific phospholipase C (IP3/DAG)</td>
</tr>
</tbody>
</table>
# 5-HT receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Distribution</th>
<th>Effector mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Hippocampus, entorhinal cortex, amygdala, nucleus accumbens, solitary tract nerve, trigeminal nerve, motor nucleus of the dorsal vagal nerve, area postrema, spinal cord</td>
<td>Ligand-gated cation channel</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Hippocampus, striatum, olfactory tubercle, substantia nigra</td>
<td>Stimulation of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;5A&lt;/sub&gt;</td>
<td>?</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;5B&lt;/sub&gt;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;6&lt;/sub&gt;</td>
<td>?</td>
<td>Stimulation of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Cerebral cortex, septum, thalamus, hypothalamus, amygdala, superior colliculus</td>
<td>Stimulation of adenylyl cyclase</td>
</tr>
</tbody>
</table>

*Lower-case appellations are used in some cases because the functions mediated by these receptors in intact tissue are presently unknown.
Imidazole amines: *Histamine*

- **Synthesis and Removal**
- In the periphery, *histamine is synthesized* in mast cells.
- does not cross the blood-brain barrier
- Brain cells synthesize their own histamine from histidine, which enters the brain by active transport.
- Histamine is metabolized by two enzymes—histamine methyltransferase and diamine oxidase (histaminase)
• **Distribution.**
• hypothalamus
• **Physiological and Clinical Considerations**
• food and water intake
• thermoregulation and autonomic functions
Purines

- ATP (adenosine triphosphate) has been implicated as a neurotransmitter
- it is not stored in presynaptic vesicles and
- is not released in a Ca^{2+}-dependent manner.
NEUROACTIVE PEPTIDES:
Opioid Peptides

- β-endorphin
- Enkephalins
- Dynorphin
Physiological and Clinical Considerations

Intracerebroventricular injection of opioid peptides (e.g., β-endorphin) produces analgesia.

- no side-effects like addiction
- modulation of pain sensation
- regulating blood pressure, temperature, feeding, aggression, and sexual behavior.
Tachykinins: Substance P

- **Location**: The dorsal root ganglia projecting to the substantia gelatinosa of the spinal cord
- **Role**: nociceptors because they transmit information regarding tissue damage to the pain processing areas located in the CNS.
- Substance P has been implicated as one of the neurotransmitters in mediating pain sensation
a topical cream containing **capsaicin** has been used as an analgesic in the treatment of viral neuropathies, arthritic conditions

- Capsaicin, the pungent substance present in hot chili peppers, mediates its actions via vanilloid receptors, which are present exclusively on the membranes of primary afferent neurons
- With repeated applications, the vanilloid receptors may become desensitized, thus reducing pain sensations
- With prolonged use, capsaicin causes death of primary afferent neurons as a consequence of increased intracellular Ca2+ concentrations.
GASEOUS NEUROTRANSMITTERS

- Nitric oxide (NO)
- Carbon monoxide (CO)
- Physiological and Clinical Considerations
Thank you and Study Neuroscience!