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Organization of the Nervous System

The central nervous system (CNS; brain, spinal cord) and peripheral nervous system (PNS) are composed of two main types of neural cells:

- Neurons
- Glial cells

Anatomy of a Neuron\(^{1–3}\)

Neurotransmitters: chemicals in the nervous system that transmit nerve impulses between neurons\(^3\)

Action potential: in neurophysiology, an electrical charge that moves through an axon\(^3\)

Various Types of Glia Cells in the Brain$^{1,2}$

Process of Electrical Neurotransmission$^{1–3}$

Information moves through the nervous system via two integrated forms of communication

- Electrical neurotransmission through action potentials (shown here)
- Chemical neurotransmission (detailed next)

Process of Chemical Neurotransmission\(^1,2\)

1. **Action potential**

2. **Neurotransmitters released**

3. **Neurotransmitters bind**

4. **Signal transduction**

5. **Neurotransmitters cleared**

Receptor: a protein molecule on a cell membrane that binds to a specific chemical, such as a neurotransmitter or drug, and produces a specific physiological effect.\(^3\)

Reuptake: a mechanism by which a neurotransmitter is taken back into the axon terminal that released it; the most common mechanism for removal and inactivation of neurotransmitters.\(^2\)

Diffusion: in regard to neurotransmission, a mechanism by which neurotransmitters drift out of the synaptic cleft.\(^2\)

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# Neurotransmitters and Receptors*

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor subtypes</th>
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<tbody>
<tr>
<td>Dopamine$^1$</td>
<td>Dopaminergic receptors (D$_{1-5}$ subtypes)</td>
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<tr>
<td>Serotonin$^2$</td>
<td>5-HT receptors (5-HT$<em>{1A-B}$, 5-HT$</em>{1D-F}$, 5-HT$<em>{2A-C}$, 5-HT$</em>{3-7}$ subtypes)</td>
</tr>
</tbody>
</table>
| Noradrenaline$^{1,3}$ | α-adrenergic receptors (α$_{1A, B, D}$, α$_{2A-C}$ subtypes)  
β-adrenergic receptors (β$_{1-3}$ subtypes) |
| Glutamate$^{1,4}$ | Ionotropic receptors: non-NMDA (AMPA, kainate), NMDA receptors  
Metabotropic receptors (mGluRs) |
| GABA$^1$         | GABA$_A$, GABA$_B$, and GABA$_C$ receptors |
| Acetylcholine$^1$| Cholinergic receptors: muscarinic receptors (M$_{1-5}$ subtypes),  
nicotinic receptors |
| Histamine$^1$    | Histaminic receptors (H$_{1-3}$ subtypes) |

5-HT, serotonin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; D, dopamine; GABA, gamma-aminobutyric acid; H, histamine; M, muscarinic; mGluRs, metabotropic glutamate receptors; NMDA, N-methyl-D-aspartate.

*Common targets for drugs; will be discussed in further detail in disease-specific modules.

Principles of Receptor Pharmacology

• Affinity:
  – How strongly does a molecule or drug bind to a specific receptor?\textsuperscript{1,2}
  – Typically discussed as high, moderate, or low based on Ki values (nM)\textsuperscript{3}

• Intrinsic activity\textsuperscript{1,2}:
  – Once bound, what is the effect of the drug at the specific receptor?
  – Determined by ability of molecule/drug to either stimulate a specific receptor (ie, an agonist) or inhibit an agonist from stimulating that receptor (ie, an antagonist)

• Receptor occupancy\textsuperscript{1}:
  – How many receptors are bound to by a molecule or drug at a particular dosage (% of receptors bound)?*

*More detail in section 201
Ki, inhibitory constant; nM, nanomolar.

Inhibition Constant, $K_i$ — How is it determined?\(^1, 2\)

$K_i$ is the concentration of competing ligand in a competition assay which would occupy 50% of the receptors if no radioligand were present.

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Concepts of Receptor Pharmacology — Binding Affinity

Affinity of drug at a receptor

• Strength of binding between a ligand (molecule or drug) and its target receptor

• Competitive binding experiments are used to investigate drug binding properties and affinities
  – Typically categorized as high, moderate, or low binding based on $K_i$ value (nM), the lower the $K_i$, the higher the binding affinity

$IC_{50}$, the concentration of a drug that is required for 50% inhibition in vitro; nM, nanoMolars (unit of quantity/concentration of a drug/molecule).

Concepts of Receptor Pharmacology — Intrinsic Activity

Intrinsic activity of drug at a receptor
- The physiologic effect a ligand elicits once bound to its receptor
- Ligand can partially or fully stimulate (agonism) or inhibit (antagonism) receptor activity

**Agonist**
- Full activation

**Partial agonist**
- Partial activation

**Antagonist**
- No activation

Summary

• The nervous system is organized into two main anatomical divisions: the CNS and the PNS\(^1\)
• Neurons are the basic nerve cells, which transmit messages throughout the nervous system\(^1\)
• Glia cells help support and protect neurons (see section 201)\(^2\)
• Neurons communicate with each other via transmission (electrical and chemical)\(^2,3\)
• Neurotransmitters are hypothesized to directly regulate human physiology and behaviour through neuronal communication\(^1\)
• These neurotransmitter signals are the pharmacologic targets of medications (see section 201)\(^3\)
• The pharmacological profile of a neurotransmitter (or receptor drug targets) can be described by binding affinity and intrinsic activity\(^4\)
