Pharmacology of the Central Nervous System (CNS)

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Classification of the vertebrate nervous system

- The vertebrate nervous system (VNS)
  - Peripheral Nervous System (PNS)
    - Motor Component
    - Sensory Component
      - Visceral
      - Somatic
      - Nerves
      - Receptor
  - Central Nervous System (CNS)
    - Brain
      - Brainstem
      - Medulla
      - Pons
      - Midbrain
      - Diencephalon
      - C. Hemispheres
    - Spinal Cord
      - Forebrain
      - Cerebellum
(A) A lateral view (B) ventral view (C) Diagram of several spinal cord segments, showing the relationship of the spinal cord to the bony canal in which it lies.
The major components of the nervous system and their functional relationships. (A) Digital 3-D reconstruction of the human body. (B) Diagram of the major components of the central and peripheral nervous systems and their functional relationships. Stimuli from the environment convey information to processing circuits within the brain and spinal cord, which in turn interpret their significance and send signals to peripheral effectors that move the body and adjust the workings of its internal organs.
(A) At left, a ventral view of the brainstem showing the locations of the cranial nerves as they enter or exit the midbrain, pons and medulla. Exclusively sensory nerves are indicated in yellow, motor nerves in blue, and mixed sensory/motor nerves in green. At right, the territories included in each of the brainstem subdivisions (midbrain, violet; pons, green; medulla, pink) are indicated.
(B) view of the dorsal surface of the brainstem showing the location of the brainstem cranial nerve nuclei that are either the target or the source of the cranial nerves.
Direct and indirect pathways from the motor cortex to the lateral (A) and medial (B) gray matter of the spinal cord.
Transverse sections through the brainstem and spinal cord. The location of the cranial nerve nuclei, ascending, and descending tracts is indicated in each representative section.
(A) Major features apparent after bisecting the brain in this plane. (B) The lobes of the brain seen from its medial surface. (C) An enlarged view of the diencephalon and brainstem in this view.
Internal structures of the brain seen in coronal section. (A) This plane of section runs through the basal ganglia (term). (B) A somewhat more posterior plane of section that includes the thalamus. (C) A transparent view of the basal ganglia showing the approximate location of the sections in (A) and (B).
Examples of the rich variety of nerve cell morphologies found in the human nervous system (the human brain is estimated to contain 100 billion neurons and several times as many supporting cells)
A typical vertebrate neuron. The arrows indicate the direction in which signals are conveyed. The single axon conducts signals away from the cell body, while the multiple dendrites receive signals from the axons of other neurons. The nerve terminals end on the dendrites or cell body of other neurons or on other cell types, such as muscle or gland cells.
Chemical mediators in the CNS

**Neurotransmitters** are released by presynaptic terminals and produce rapid excitatory or inhibitory responses in postsynaptic neurons. They are broadly divided into;
- Fast neurotransmitters, operating through ligand-gated ion channels (e.g. glutamate, GABA).
- Slow neurotransmitters and neuromodulators, operating mainly through G-protein coupled receptors (e.g. dopamine, neuropeptides).

**Neuromodulators** are released by neurons, and produce slower pre- or postsynaptic responses, mediated mainly by G-protein-coupled receptors.

**Neurotrophic factors** are released mainly by non-neuronal cells and act on tyrosine-kinase-linked receptors which regulate the growth and morphology of neurons as well as their functional properties.

The same agent (e.g. glutamate, 5-HT, ACh) may act through both ligand-gated channels and G-protein-coupled receptors.

The neuromodulators NO and arachinodic acid metabolites, may be produced by non neuronal cells as well as neurons.
Signaling by neurotransmitter release at a synapse The arrival of a nerve impulse at the terminus of the neuron signals the fusion of synaptic vesicles with the plasma membrane, resulting in the release of neurotransmitter from the presynaptic cell into the synaptic cleft. The neurotransmitter binds to receptors and opens ligand-gated ion channels in the target cell plasma membrane.
Some neurotransmitters in **CNS**, classified according to their chemical structure

<table>
<thead>
<tr>
<th>Substance</th>
<th>Locations</th>
<th>Receptors</th>
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<tbody>
<tr>
<td>Acetylcholine</td>
<td>Many parts of brain</td>
<td>N, M&lt;sub&gt;1-5&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Amines</strong>;</td>
<td></td>
<td></td>
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<tr>
<td>Dopamine</td>
<td>Hypothalamus, limbic system, &amp; parts of neocortex</td>
<td>D&lt;sub&gt;1&lt;/sub&gt;, D&lt;sub&gt;2&lt;/sub&gt; family</td>
</tr>
<tr>
<td>NE</td>
<td>C. cortex, hypothalamus, brain stem, cerebellum &amp; sp. cord</td>
<td>α&lt;sub&gt;1&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, β&lt;sub&gt;1-3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Hypothalamus, limbic system, cerebellum &amp; sp. Cord</td>
<td>5-HT&lt;sub&gt;1A-F&lt;/sub&gt;, 5-HT&lt;sub&gt;2-7&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Excitatory A a;</strong></td>
<td></td>
<td></td>
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<tr>
<td>Glutamate</td>
<td>C. Cortex &amp; brain stem</td>
<td>NMDA, AMPA, Kainate, Metabotropic</td>
</tr>
<tr>
<td>Aspartate</td>
<td>Sp. Cord &amp; other parts of CNS</td>
<td>NMDA, AMPA, Kainate, Metabotropic</td>
</tr>
<tr>
<td><strong>Inhibitory A a;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>Neurons mediating direct inhibition</td>
<td>Glycine receptor resembles GABA&lt;sub&gt;A&lt;/sub&gt;</td>
</tr>
<tr>
<td>GABA</td>
<td>Neurons mediating presynaptic inhibition</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;, GABA&lt;sub&gt;B&lt;/sub&gt;</td>
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</tbody>
</table>
Four classes of ligand-triggered cell-surface receptors. Common ligands for each receptor type are listed in parentheses. (a) G protein linked receptors. Binding of ligand (maroon) triggers activation of a G protein, which then binds to and activates an enzyme that catalyzes synthesis of a specific second messenger. (b) Ion-channel receptors. A conformational change triggered by ligand binding opens the channel for ion flow. (c) Tyrosine kinase linked receptors. Ligand binding causes formation of a homodimer or heterodimer, triggering the binding and activation of a cytosolic protein-tyrosine kinase. The activated kinase phosphorylates tyrosines in the receptor; substrate proteins then bind to these phosphotyrosine residues and are phosphorylated. (d) Receptors with intrinsic ligand-triggered enzymatic activity in the cytosolic domain. Some activated receptors are monomers with guanine cyclase activity and can generate the second messenger cGMP (left). The receptors for many growth factors have intrinsic protein-tyrosine kinase activity (right). Ligand binding to most such receptor tyrosine kinase (RTKs) causes formation of an activated homodimer, which phosphorylates several residues in its own cytosolic domain as well as certain substrate proteins.
(a) **G protein-coupled receptors** (epinephrine, glucagon, serotonin)

- **Exterior**
  - Ligand

- **Plasma membrane**
  - **R** (Receptor protein)
  - **G** (Inactive G signal-transducing protein)
  - **E** (Inactive effector enzyme (adenylyl cyclase, phospholipase c, or others))

- **Cytosol**
  - **G** (Activated form of G protein)
  - **E'** (Active effector generates "second messengers" (cAMP; inositol 1,4,5-triphosphate; 1,2-diacylglycerol))
Structure and function of metabotropic receptors. (A) The transmembrane architecture of metabotropic receptors. These monomeric proteins contain seven transmembrane domains. Portions of domains II, III, VI, and VII make up the neurotransmitter-binding region. G-proteins bind to both the loop between domains V and VI and to portions of the C-terminal region. (B) Subunits of metabotropic receptors.
The general architecture of ligand-gated receptors. (A) One of the subunits of a complete receptor. The long N-terminal region forms the ligand-binding site, while the remainder of the protein spans the membrane either four times (left) or three times (right). (B) Assembly of either four or five subunits into a complete receptor. (C) A diversity of subunits come together to form functional ionotropic neurotransmitter receptors.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Distribution</th>
<th>Effector mechanism</th>
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<tbody>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</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-HT1Da</td>
<td>Not distinguishable from 5-HT1Db</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT1Db</td>
<td>Substantia nigra, basal ganglia, superior colliculus</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-ht1E</td>
<td>?</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-ht1F</td>
<td>Cerebral cortex, striatum, hippocampus, olfactory bulb</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>Claustrum, cerebral cortex, olfactory tubercle, striatum, nucleus accumbens</td>
<td>Stimulation of phosphoinositide-specific phospholipase C, closing of K+ channels</td>
</tr>
<tr>
<td>5-HT2B</td>
<td>?</td>
<td>Stimulation of phosphoinositide-specific phospholipase C</td>
</tr>
<tr>
<td>5-HT2C</td>
<td>Choroid plexus, globus pallidus, cerebral cortex, hypothalamus, septum, substantia nigra, spinal cord</td>
<td>Stimulation of phosphoinositide-specific phospholipase C</td>
</tr>
<tr>
<td>5-HT3</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-HT4</td>
<td>Hippocampus, striatum, olfactory tubercle, substantia nigra</td>
<td>Stimulation of adenylyl cyclase</td>
</tr>
<tr>
<td>5-ht5A</td>
<td>?</td>
<td>Inhibition of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT5B</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>5-ht6</td>
<td>?</td>
<td>Stimulation of adenylyl cyclase</td>
</tr>
<tr>
<td>5-HT7</td>
<td>Cerebral cortex, septum, thalamus, hypothalamus, amygdala, superior colliculus</td>
<td>Stimulation of adenylyl cyclase</td>
</tr>
</tbody>
</table>
Classification of Psychotropic drugs

1. **Anxiolytics and sedative-hypnotics;** drugs that cause sleep and reduce anxiety.

2. **Anesthetics agents;** drugs used as an adjunct to surgical procedures in order to render the patient unaware of and unresponsive to, painful stimulation.

3. **Narcotic analgesics;** drugs with morphine-like action.

4. **Anti-epileptic drugs;** drugs used to treat the epilepsy.

5. **Anti-psychotic drugs (neroleptic drugs);** drugs that are effective in relieving the symptoms of schizophrenic illness.

6. **Anti-depressant drugs;** drugs that alleviate the symptoms of depressive illness.

7. **Anti-parkinsonian drugs;** drugs used to treat the Parkinsonism.

8. **Cognition enhancers (nootropic drugs);** drugs that improve memory and cognitive performance.

9. **Convulsants and respiratory stimulants (Analeptics);** agents intended to reverse marked CNS depression, usually from an overdose of barbiturate or other depressant drugs.

10. **Psychotomimetic drugs;** drugs that cause disturbance of perception (visual) and of behaviour in ways that cannot be simply characterised as sedative or stimulant effects.

11. **Psychomotor stimulants;** drugs that cause wakefulness and euphoria.
Physiological changes during the various sleep states in a typical 8-hour period of sleep.

Periods of non-REM sleep (I-IV) are characterized by decreases in muscle tone, heart rate, breathing, and blood pressure. Periods of REM sleep, in contrast, are characterized by increases in blood pressure, and heart rate to levels almost as high as those found in the awake state. The duration of REM sleep increases from 10 minutes in the first cycle to up to 50 minutes in the final cycle; note that slow-wave (stage IV) sleep is attained only in the first two cycles.
**Benzodiazepines:** increase the frequency of channel opening in response to GABA (Benzodiazepine receptors are heterogeneous with respect to affinity for certain ligands).

**Barbiturates:** increase the mean channel open time and Cl⁻ flux.

**General anesthetics;** including barbiturates, volatile gases, steroids 3a,5a-pregnan-3a-ol-20-one (THPROG), and alcohols, enhance GABA-mediated Cl conductance.

**Picrotoxin:** decrease the mean channel open time.
Serotonin receptors ($5\text{-HT}_{1A-F}$, $5\text{-HT}_{2-7}$)

Drugs that act as agonists are indicated by solid-line arrows, whereas antagonists or inhibitors are shown with broken-line arrows. The $5\text{-HT}$ 1A receptor acts as both the somatodendritic autoreceptor (inhibitory receptors) and a postsynaptic receptor. Anxiolytic drugs, such as buspirone, are agonists at this receptor, thus reducing the release of excitatory mediators.
1. Drug therapy of anxiety should be accompanied by psychotherapy and relaxation techniques.
2. Drug therapy of insomnia should be started only when other methods fail (bathing, exercise, ……).
3. Start by small dose, short time to avoid drug abuse.
4. Gradual withdrawal to avoid withdrawal syndrome (convulsion and rebound insomnia).
5. Short acting hypnotic is better (less hangover).
6. Long acting anxiolytic is better (less residual anxiety).
7. Potent BZDs are preferred in Panic attacks (alprazolam, clonazepam).
8. Doses should be reduced in old and in hepatic patients to avoid toxicity.