Introduction to Central Nervous System Pharmacology

C. B. Smith, M.D., Ph.D.
Types of neurons in CNS

- Unipolar neuron
- Pyramidal cell
- Bipolar neuron
- Multipolar neuron
Types of glial cells in CNS

- Microglial cell
- Oligodendrocyte
- Astrocyte
The Nerve Cell

- Mitochondria
- Synaptic vesicles
- Rough endoplasmic reticulum

Dendrites
Input of information and integration

Cell body
Cellular maintenance and information processing

Axon
Information transport

Nerve terminals
Output of information

Cartoon of neuron
Determinants of the Resting Membrane Potential

Extracellular

\[ \text{Cl}^- \quad \text{Na}^+ \quad \text{K}^+ \]

Intracellular

\[ \text{Cl}^- \quad \text{Na}^+ \quad \text{K}^+ \quad \text{Na}^+ \quad \text{K}^+ \quad 2\text{K}^+ \quad 3\text{Na}^+ \]

Intracellular passive fluxes (leak current)

Sodium channel (closed at rest)

Potassium channel (open at rest)

Sodium-potassium pump (3 for 2 exchange)
Voltage-dependent sodium channels in axonal membrane open

Sodium enters causing further depolarization

Sodium channels inactivate

Sodium channels become refractory

Voltage-dependent potassium channels open

Potassium leaves and membrane is repolarized

Potassium channels inactivate

Depolarization stimulus
Axonal Impulse Conduction

- Resting
- Refractory
- Open
- Resting

Depolarization blocked
Depolarization
Electrical and Chemical Synapses

Electrical Synapse

- Mitochondria
- Vesicles

Chemical Synapse

- Neurotransmitter
- Receptors
Types of Synaptic Connections in the CNS

- Dendrosomatic
- Dendrodendritic
- Axodendritic
- Axosomatic
- A xoaxonic
Types of Synaptic Connections in the CNS

Directed synapse

Nondirected synapse
Biogenic Amines

- Acetylcholine
- Dopamine
- Norepinephrine
- Epinephrine
- Histamine
- Serotonin
Amino Acids

- GABA
- Glutamate
- Glycine
- Aspartate
Nucleotides and Nucleosides

- Adenosine
- ATP
### Peptides

<table>
<thead>
<tr>
<th>Peptide</th>
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<tbody>
<tr>
<td>Angiotensin II</td>
<td>Bombesin</td>
<td>Bradykinin</td>
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<tr>
<td>Carnosine</td>
<td>Cholecystokinin</td>
<td>β-Endorphin</td>
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<tr>
<td>Enkephalins</td>
<td>Glucagon</td>
<td>Hypocretins</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neurotensin</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>Secretin</td>
<td>Somatostatin</td>
<td>Substance K</td>
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<tr>
<td>Substance P</td>
<td>Vasopressin</td>
<td>Neuropeptide Y</td>
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Adrenocorticotropic hormone  
Calcitonin gene-related peptide  
Corticotropin-releasing factor  
Luteinizing hormone-releasing hormone  
α-Melanocyte stimulating hormone  
Vasoactive intestinal peptide  
Thyrotropin-releasing hormone
Cotransmitters

Separate storage vesicles

Co-stored in same vesicles
## Coexistence of Neurotransmitters

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<tr>
<th>Transmitter</th>
<th>Co-transmitter</th>
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<td>Acetylcholine</td>
<td>Vasoactive intestinal peptide</td>
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<tr>
<td></td>
<td>Substance P</td>
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<tr>
<td>Vasopressin</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td></td>
<td>Dynorphin</td>
</tr>
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<td>Oxytocin</td>
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<tr>
<td>Peptide Co-transmitter</td>
<td>Transmitter</td>
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Models of nerve terminals

**Acetylcholine**
- Acetyl-CoA + choline → ACh
- ACh → choline + acetate

**Norepinephrine**
- Tyrosine (Tyr) → L-DOPA → DA → NE
- NE

**GABA**
- Glutamine → Glutamate → GABA
- GABA

**Peptide**
- Propeptide (from cell soma) → Peptide
- Diffusion and inactivation

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Potential Target for Released Transmitters
Types of Circuits

Hierarchical

Diffuse
Distribution of Noradrenergic Neurons in the Brain

Thalamus

Cingulate cortex

Neocortex

Hypothalamus

Olfactory bulb

Amygdala and hippocampus

A1, A2, A5, A7

Locus ceruleus

Cerebellar cortex

Tectum

Visceral cranial nuclei

Spinal cord
Types of Tolerance

Log dose

Response

Surmountable

Control

Insurmountable

Log dose
## Targets of Some CNS Drugs

<table>
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<th>Category</th>
<th>Targets</th>
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<tr>
<td>General Anesthetic Drugs</td>
<td>Membrane lipid cyclooxygenase</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
<td>Voltage-dependent sodium channels</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>L-Type voltage-dependent calcium channels</td>
</tr>
<tr>
<td></td>
<td>Opioid receptors</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>GABA receptors</td>
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<tr>
<td></td>
<td>Dopamine receptors</td>
</tr>
<tr>
<td>Opiate analgesics</td>
<td>Monoamine oxidase</td>
</tr>
<tr>
<td>Opiate antagonists</td>
<td>Norepinephrine reuptake</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Serotonin reuptake</td>
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<tr>
<td>Antipsychotic drugs</td>
<td>Dopamine reuptake</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Phosphatidylinositol breakdown</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Serotonin selective reuptake inhibitors</td>
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<tr>
<td>Amantadine</td>
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<tr>
<td>Lithium carbonate</td>
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Potency of Chlorpromazine at various sites in the CNS

High potency

-9

α₁-adrenergic receptors

H₁-histamine receptors

5HT₂-adrenergic receptors

Norepinephrine reuptake

D₂-dopamine receptors

Muscarinic cholinergic receptors

Serotonin reuptake

α₂-adrenergic receptors

Low potency

-4

Potency (log molar)

-8

-7

-6

-5