Introduction to the Central Nervous System and Neurotransmitter Pathways

The Toll of Selected Brain and Nervous System Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Cases</th>
<th>Costs/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing Loss</td>
<td>28 million</td>
<td>$56 Billion</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>4.5 million</td>
<td>$100 Billion</td>
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<tr>
<td>All Depressive Disorders</td>
<td>20.5 million</td>
<td>$44 Billion</td>
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<tr>
<td>Stroke</td>
<td>4.7 million</td>
<td>$51 Billion</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2 million</td>
<td>$32.5 Billion</td>
</tr>
<tr>
<td>Traumatic Head Injury</td>
<td>5 million</td>
<td>$56.3 Billion</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>1 million</td>
<td>$5.6 Billion</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>30,000</td>
<td>$2 Billion</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>2.5 million</td>
<td>$9.5 Billion</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>250,000</td>
<td>$10 Billion</td>
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</tbody>
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From Brain Facts (Society for Neuroscience 2004), estimates provided by NIH and voluntary organizations

1. Organization of the CNS
2. The Neuron
3. Neurotransmitters
1. **Organization of vertebrate CNS**

- Brain is bathed in about 150 mL of CerebroSpinal Fluid (CSF) secreted by the Choroid Plexus
- 500 mL CSF secreted daily and circulates through the 4 ventricles, around spinal cord into the subarachnoid space. (Brain has no lymphatic system)
- Surrounded by the meninges
- Encased in the skull
A. **The Forebrain**: Associated with the highest level intellectual functions such as thinking, planning, problem solving and speech

**Cerebral cortex**
- Largest part of the brain – 90%
- Two hemispheres: Right and Left
  - Left: controls right side of body (analytical thinking, problem solving, language)
  - Right: controls left side of body (artistic expression and spatial relationships)
- A convoluted plate of cells forming the brain surface divided into four sections: frontal, temporal (sides), parietal (upper) occipital (back)
The Limbic System - the “emotional brain”

• An assembly of regions: the **amygdala, hippocampal formation**, septum, olfactory nuclei, basal ganglia and selected nuclei of the **diencephalon**

• Important structures are innervated by noradrenergic neurons

• Helps regulate emotion, memory and certain aspects of movement

Functions such as vision, hearing, speech are distributed in selected regions, some regions are associated with more than one function
Diencephalon

The thalamus acts as a relay station for almost all sensory information coming from the periphery to the brain.

The hypothalamus serves as the principal integrating region for internal regulatory systems.

- Receives information from the autonomic nervous system and regulates the body (e.g. temperature, sleep, circadian and sexual cycles) via nerves and the pituitary.

B. The Midbrain and Hindbrain

Midbrain

- Coordinates visual and auditory input from sense organs

Hindbrain / Brainstem

- Medulla controls heart rate, respiration and blood pressure
- Pons contains fibres that link cerebral cortex with spinal cord and cerebellum. Controls sleep, awakening and dream impulses.
- Hindbrain also controls body temperature, simple reflexes (coughing, sneezing) and digestion.
Cerebellum

- Coordinates movement, posture, sense of balance.

Reticular Activating System / Reticular Formation

- A diffuse network of neurons in medulla, pons and midbrain
- Major monoamine oxidase containing neurons are found here
- Essential for sleep, arousal, wakefulness
- Coordinates reflex acts: swallowing, vomiting, respiration and those involving the cardiovascular system
C. **Spinal cord**

- Receives sensory information from, and sends motor information to the trunk, limbs and many of the organs

- Autonomic reflexes can be elicited within local segments

D. **Blood-Brain Barrier**

- The tight seal of cells that lines the blood vessels in the brain is known as the blood-brain barrier.
- Endothelial cells are the principle anatomic site of the blood-brain barrier, characterized by tight junctions, they are distinct from general (systemic) capillaries. Glial cells also wrap around the capillaries.
- Entry into brain is achieved by: (1) diffusion of lipid soluble substances, (2) Active/ATP-dependent transport.
Entry is inhibited by:

1) Physical barrier composed of endothelial cells with tight junctions
2) Active efflux pumps in the endothelial cells, commonly known as the ATP binding cassette (ABC) transporters:
   - ABCB1/MDR1 gene encodes P-glycoprotein
   - ABCC1/multidrug resistance-associated protein 1 (MRP1)

**Imaging Techniques**

**Positron emission tomography** (PET) – based on detection of trace amounts of radioisotopes following injection into the blood stream

**Magnetic Resonance Imaging** (MRI) – exposure to a strong magnetic field causes protons of the body’s hydrogen atoms to line up. Hydrogen nuclei are knocked out of alignment by exposure to a pulse of radio waves, this leads to a detectable signal as they fall back into alignment.
2. **The Neuron**

- Basic working unit of the CNS
- Consists of a cell body, dendrites and axon
- Highly specialized, designed to transmit information to other neurons, muscle or gland cells
- Support cells (Glia) outnumber neurons by more than 10 to 1 in the mammalian brain

![Neuron Diagram](image)

**Neuronal signaling**

- Neurons communicate with each other at **synapses**
- Synaptic connections are complex in the CNS (relative to ANS)
• Cell body and dendrites are covered in synapses formed by connections with the ends of the axons of other neurons

![Diagram of a neuron showing cell body, dendrites, and synaptic connections.](image)

• Neurons signal by transmitting electrical signals (*action potentials*) along their axons (.0.1 mm to 3 m)

• Action potentials are initiated at the initial segment of the axon and are conducted down the axon at rates of 1 – 100m / sec

• Many axons are insulated by a myelin sheath to increase the speed of transmission (many are not insulated)

• The myelin sheath is interrupted by the nodes of Ranvier ( uninsulted regions where the action potential regenerates)
Electrical signals flow in **one** direction (action potential is propagated unidirectionally) and make **specific** connections with postsynaptic target cells (i.e. networks are not random)

- At the end of the axon, voltage changes trigger the release of **neurotransmitters**
- Drug selectivity is based on the fact that different neuronal pathways utilize different neurotransmitters
- It has been estimated that one neuron communicates with 1000 others!
• **The neuronal cytoskeleton** is highly specialized.

• Excitatory neurons contain an electron dense postsynaptic density (PSD) that is enriched with receptors plus proteins that anchor and cluster receptors for optimal signal transduction.

• These organized structures occur at the level of the dendritic spine (“door knob” shaped extrusions that occur along the length of glutamatergic neurons.

• Physical changes at the level of the dendritic spines are thought to represent the basis of learning and memory (**synaptic plasticity**).
3. **Neurotransmitters**

A neurotransmitter has to fulfill the following criteria:

1. Synthesized in the neuron
2. Present in the presynaptic cleft and released in amounts sufficient to exert a defined action on the postsynaptic neuron or effector organ
3. When administered exogenously (as a drug) it will mimic the action of the endogenous transmitter
4. A specific mechanism exists to remove it from its site of action the synaptic cleft).
Several classes of neurotransmitters are used for signaling

- **Small molecules** (NE, DA, SER, Ach)
- **Neuroactive peptides** (short polymers of amino acids e.g. opioids)
- **Amino Acids**

- All classes are contained in presynaptic vesicles
- Vesicles may store more than one neurotransmitter (cotransmission)

* neuronal NO important neurotransmitter in the CNS

A second classification is based on speed of neurotransmission;

- **FAST-ACTING NEUROTRANSMITTERS**
  - Speeds of around one millisecond – target for the neurotransmitter is a LIGAND-GATED ION CHANNEL
  - Excitatory (glutamate)
  - Inhibitory (GABA)

- **SLOW–ACTING NEUROTRANSMITTERS**
  - At least one hundred times slower (100s millisecs to minutes)
  - Biogenic Amines
  - Peptides
  - Amino Acids
  - Second messengers - Protein Kinases – Protein Phosphatases
  - Slow acting neurotransmitters modulate Fast-acting neurotransmitters
3.1 Acetylcholine (ACh)

- First compound to be identified pharmacologically as a neurotransmitter
- Motor neurons are cholinergic and therefore ACh is the neurotransmitter at all **vertebrate neuromuscular junctions**
- In the **ANS**, ACh is the neurotransmitter for all **preganglionic neurons** and **parasympathetic postganglionic neurons**
- **CNS circuits** are implicated in: attention, learning, memory, arousal
- Exposure to irreversible AChE inhibitors is lethal

**(A) Cholinergic pathways**

Identified by histochemical staining techniques & receptor autoradiography these can be divided into two basic schemes:

1. **Local circuit cells:** those which are morphologically arrayed wholly within the neuronal structure in which they are found
2. **Projection neurons:** those that connect two or more different regions
Two important projections are in the **basal forebrain cholinergic complex**

- **sep** medial septal nucleus
- **bas** nucleus basilis

- These pathways send projections to hippocampus (septohippocampal pathway) & cortex
- Critical for cognition, learning, memory & association in the cerebral cortex
- A primary neurochemical deficit in **Alzheimer’s Disease** is loss of cholinergic pathways from the nucleus basilis to the cerebral cortex
- ACh content in the brain of Alzheimer’s patients at postmortem is profoundly reduced
- Explains the focus on cholinergic agents in the treatment of cognitive deficits in Alzheimer’s patients
- Projections from medial septal nucleus to hippocampus important for generation & maintenance of short term memory
- Muscarinic receptor antagonists disrupt short term memory e.g. scopolamine and atropine

**(B) Central cholinergic synapse**

1) *de novo* **Enzymatic synthesis**
2) Transport into vesicles and storage
3) Release
4) Pre and Postsynaptic receptors
5) **Enzymatic degredation** - acetylcholinesterase
6) **Reuptake** – via a high-affinity **choline transporter** (CHT) – cytoplasmic synthesis depends on acute reuptake
CHT

- Homologous to Na\(^+\)-dependent glucose transporter rather than other neurotransmitter transporters
- 12 transmembrane domains, intracellular N and C terminals
- Sensitive to hemicholinium-3
- CHT +/- and CHT -/- mice are deficient in cholinergic neurotransmission and die within one hour of birth
(C) Cholinergic receptors
Fall into two classes: (1) muscarinic (G-protein coupled)
   (2) nicotinic (ligand-gated ion channels)

Another general way to classify receptors is according to location at the synapse: pre and postsynaptic receptors.

Presynaptic cholinergic receptors regulate release of ACh in an inhibitory manner (negative feedback)

Postsynaptic cholinergic receptors can be muscarinic or nicotinic.

1. Muscarinic receptors
   • High density in brain
   • G protein coupled
   • 7 transmembrane domains
   • Multiple receptor subtypes (M_1 neural / M_2 / M_3 / M_4 / M_5)

2. Nicotinic receptors
   • Ligand-gated ion channels
   • Multiple homologous subunits oriented around a central cation channel, each subunit has 4 transmembrane domains
   • 5 subunits make 1 receptor
   • Muscle-type receptor (α_1)_2β_1γδ; Ganglion type (α_3)_2 (α_4)_3
   • Neuronal nicotinic ACh receptor subtypes are:
     (α_4)_2 (α_2)_3

     1) Pre and postsynaptic excitation
     2) Increased cation permeability (Na^+, K^+)
        • Neuronal subtype responsible for high-affinity binding of nicotine - known pathological significance is addiction to tobacco
        • Nicotine is a CNS stimulant - produces a desynchronization of the cerebral cortex
1) Pre and postsynaptic **excitation**

2) **Increased cation permeability (Ca\(^{2+}\))**

- Homomeric
- Only nicotinic receptor subunit known to bind alpha-bungarotoxin in mammalian brain
- Thought to play a unique role in synaptic plasticity. Nicotine improves cognitive performance in working memory tasks (alpha 7 and alpha 4 beta 2 are present in hippocampus and amygdala)
- Genetic linkage in schizophrenic families also supports a role for the alpha 7 subunit with linkage at the alpha 7 locus on chromosome 15.
- Nicotinic alpha 7 agonists being developed for treatment of Schizophrenia and Alzheimer's