Neuron types and Neurotransmitters

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Transmission of Receptor Information to the Brain

- the larger the nerve fiber diameter the faster the rate of transmission of the signal
- velocity of transmission can be as fast as 120 m/sec or as slow as 0.5 m/sec
- nerve fiber classification
  - type A - myelinated fibers of varying sizes, generally fast transmission speed
    - subdivided into α, β, δ, γ
  - type C - unmyelinated fibers, small with slow transmission speed
Types of Nerve Fiber
- Myelinated fibers –
  - Type A (types I, II and III)
    - A α
    - A β
    - A γ
    - A δ
- Unmyelinated Fibers –
  - Type C (type IV)
Structural Classification of Neurons

(a) Multipolar neuron
(b) Bipolar neuron
(c) Unipolar neuron

Figure 12.03 Tortora - PAP 12/e
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Neurotransmitters

- Chemical substances that function as synaptic transmitters
  1. Small molecules which act as rapidly acting transmitters
    - acetylcholine, norepinephrine, dopamine, serotonin, GABA, glycine, glutamate, NO
  2. Neuropeptides
    - more potent than small molecule transmitters, cause more prolonged actions
    - endorphins, enkephalins, VIP, ect.
    - hypothalamic releasing hormones
    - TRH, LHRH, ect.
    - pituitary peptides
    - ACTH, prolactin, vasopressin, ect.
Neurotransmitters

### Table 45-1

**Small-Molecule, Rapidly Acting Transmitters**

- Class I
  - Acetylcholine
- Class II: The Amines
  - Norepinephrine
  - Epinephrine
  - Dopamine
  - Serotonin
  - Histamine
- Class III: Amino Acids
  - Gamma-aminobutyric acid (GABA)
  - Glycine
  - Glutamate
  - Aspartate
- Class IV
  - Nitric oxide (NO)

### Table 45-2

**Neuropeptide, Slowly Acting Transmitters or Growth Factors**

- Hypothalamic-releasing hormones
  - Thyrotropin-releasing hormone
  - Luteinizing hormone-releasing hormone
  - Somatostatin (growth hormone inhibitory factor)
- Pituitary peptides
  - Adrenocorticotropic hormone (ACTH)
  - β-Endorphin
  - α-Melanocyte-stimulating hormone
  - Prolactin
  - Luteinizing hormone
  - Thyrotropin
  - Growth hormone
  - Vasopressin
  - Oxytocin
- Peptides that act on gut and brain
  - Leucine enkephalin
  - Methionine enkephalin
  - Substance P
  - Gastrin
  - Cholecystokinin
  - Vasoactive intestinal polypeptide (VIP)
  - Nerve growth factor
  - Brain-derived neurotropic factor
  - Neurotensin
  - Insulin
  - Glucagon
- From other tissues
  - Angiotensin II
  - Bradykinin
  - Carnosine
  - Sleep peptides
  - Calcitonin
Comparison between Small Molecules and Neuropeptides Neurotransmitters (NT)

- Small molecules NT are rapidly acting as compared to slowly acting neuropeptides
- Neuron has only one NT but may have one or more NP
- Small molecules NT have short lived action compared to prolonged time of action for neuropeptides
- Small molecules NT are excreted in larger amounts compared to smaller quantities of neuropeptide
- Small molecules NT vesicles are recycled but neuropeptide ones are not
- Neuropeptides are co-secreted with small molecules NT
- Neuropeptides are synthesized at the soma while small molecules could be formed at the presynaptic terminals
Removal of Neurotransmitter

- Diffusion
  - move down concentration gradient
- Enzymatic degradation
  - Acetylcholinesterase for (Ach), peptidases for neuropeptides
- Uptake by neurons or glia cells
  - neurotransmitter transporters
  - Prozac = serotonin reuptake inhibitor
Transmitter Inactivation: reuptake and enzymatic breakdown

Neurotransmitter can be recycled in presynaptic terminal or can be broken down by enzymes within the cell.
II Neurotransmitters and receptors
Basic Concepts of NT and receptor

Neurotransmitter: Endogenous signaling molecules that alter the behaviour of neurons or effector cells.

Neuroreceptor: Proteins on the cell membrane or in the cytoplasm that could bind with specific neurotransmitters and alter the behavior of neurons of effector cells.
• Vast array of molecules serve as neurotransmitters

• The properties of the transmitter do not determine its effects on the postsynaptic cells

• The properties of the receptor determine whether a transmitter is excitatory or inhibitory
A neurotransmitter must (classical definition)

- Be synthesized and released from neurons
- Be found at the presynaptic terminal
- Have same effect on target cell when applied externally
- Be blocked by same drugs that block synaptic transmission
- Be removed in a specific way
Agonist

A substance that mimics a specific neurotransmitter,
is able to attach to that neurotransmitter's receptor
and thereby produces the same action that the neurotransmitter usually produces.

Drugs are often designed as receptor agonists to treat a variety of diseases and disorders when the original chemical substance is missing or depleted.
**Antagonist**

Drugs that bind to but do not activate neuroreceptors, thereby blocking the actions of neurotransmitters or the neuroreceptor agonists.
• Same NT can bind to different -R
• different part of NT ~
Specificity of drugs

Drug A

NT

Drug B

Receptor A

Receptor B
Five key steps in neurotransmission

- Synthesis
- Storage
- Release
- Receptor Binding
- Inactivation
Synaptic vesicles

- Concentrate and protect transmitter
- Can be docked at active zone
- Differ for classical transmitters (small, clear-core) vs. neuropeptides (large, dense-core)
Neurotransmitter Co-existence (Dale principle)

Some neurons in both the PNS and CNS produce both a classical neurotransmitter (ACh or a catecholamine) and a polypeptide neurotransmitter.

They are contained in different synaptic vesicles that can be distinguished using the electron microscope.

The neuron can thus release either the classical neurotransmitter or the polypeptide neurotransmitter under different conditions.
Low-frequency stimulation

High-frequency stimulation

Small-molecule neurotransmitter in small clear-core vesicles

Localized increase in $\text{Ca}^{2+}$ concentration

Preferential release of small-molecule neurotransmitter

Neuropeptide in large dense-core vesicles

More diffuse increase in $\text{Ca}^{2+}$ concentration

Release of both types of transmitter
Receptors determine whether:

- Synapse is excitatory or inhibitory
  - NE is excitatory at some synapses, inhibitory at others

- Transmitter binding activates ion channel directly or indirectly.
  - Directly
    - ionotropic receptors
    - fast
  - Indirectly
    - metabotropic receptors
    - G-protein coupled
    - slow
Receptor Activation

• **Ionotropic channel**
  – directly controls channel
  – fast

• **Metabotropic channel**
  – second messenger systems
  – receptor indirectly controls channel
(1) Ionotropic Channels

Channel

NT neurotransmitter
Ionotropism Channels

Pore
Ionotropic Channels
Ionotropic Channels
Metabotropic Channels

- Receptor separate from channel
- G proteins
- 2nd messenger system
  - cAMP
  - other types
- Effects
  - Control channel
  - Alter properties of receptors
  - regulation of gene expression ~
G protein: direct control

- NT is 1st messenger
- G protein binds to channel
  - opens or closes
  - relatively fast ~
G protein: direct control
G protein: direct control
G protein: Protein Phosphorylation
G protein: Protein Phosphorylation

- R
- AC
- G
- GTP
- ATP
- cAMP
- PK
G protein: Protein Phosphorylation

- G protein
- GTP
- ATP
- cAMP
- PK
- Pore

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Transmitter Inactivation

- Reuptake by presynaptic terminal
- Uptake by glial cells
- Enzymatic degradation
- Presynaptic receptor
- Diffusion
- Combination of above
Summary of Synaptic Transmission

1. Transmitter is synthesized and then stored in vesicles.
2. An action potential invades the presynaptic terminal.
3. Depolarization of presynaptic terminal causes opening of voltage-gated Ca$^{2+}$ channels.
4. Influx of Ca$^{2+}$ through channels.
5. Ca$^{2+}$ causes vesicles to fuse with presynaptic membrane.
6. Transmitter is released into synaptic cleft via exocytosis.
7. Transmitter binds to receptor molecules in postsynaptic membrane.
8. Opening or closing of postsynaptic channels.
9. Postsynaptic current causes excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic cell.
10. Retrieval of vesicular membrane from plasma membrane.
Some Important Transmitters
(1) Acetylcholine (ACh) as NT
Acetylcholine Synthesis

\[
\text{choline} + \text{acetyl CoA} \rightarrow \text{ACh} + \text{CoA}
\]
Acetylcholinesterase (AChE)

- Enzyme that inactivates ACh.
  - Present on postsynaptic membrane or immediately outside the membrane.
- Prevents continued stimulation.
(a) Acetyl CoA + Choline \xrightarrow{Choline acetyltransferase (ChAT)} ACh + CoA

(b) ACh \xrightarrow{Acetylcholinesterase} CH₃C-OH + HOCH₂CH₂⁺N(CH₃)₃

Acetic acid + Choline
The Life Cycle of Ach

Presynaptic cell

ACh transporter

ACh

ChAT

Choline

Acetyl CoA

Na+

Choline transporter

ACh

Vesicle

ACh

AChE

ACh

Choline

Acetic acid

ACh receptors

Postsynaptic cell

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Ach - Distribution

**Peripheral N.S.**
- Excites somatic skeletal muscle (neuro-muscular junction)
- Autonomic NS
  - Ganglia
  - Parasympathetic NS--- Neuroeffector junction
  - Few sympathetic NS -- Neuroeffector junction

**Central N.S. - widespread**
- Hippocampus
- Hypothalamus ~
Ach Receptors

• ACh is both an excitatory and inhibitory NT, depending on organ involved.
  – Causes the opening of chemical gated ion channels.

• Nicotinic ACh receptors:
  – Found in autonomic ganglia (N₁) and skeletal muscle fibers (N₂).

• Muscarinic ACh receptors:
  – Found in the plasma membrane of smooth and cardiac muscle cells, and in cells of particular glands.
Acetylcholine Neurotransmission

“Nicotinic” subtype Receptor:
- Membrane Channel for Na\(^+\) and K\(^+\)
- Opens on ligand binding
- Depolarization of target (neuron, muscle)
- Stimulated by Nicotine, etc.
- Blocked by Curare, etc.
- Motor endplate (somatic) (N\(_2\)),
- all autonomic ganglia, hormone producing cells of adrenal medulla (N\(_1\))
“Muscarinic” subtype Receptor: $M_1$

- Use of signal transduction system
  - Phospholipase C, IP$_3$, DAG, cytosolic Ca$^{++}$
  - Effect on target: cell specific (heart $\downarrow$, smooth muscle intestine $\uparrow$)
- Blocked by Atropine, etc.
- All parasympathetic target organs
- Some *sympathetic* targets (endocrine sweat glands, skeletal muscle blood vessels - dilation)
Acetylcholine Neurotransmission

• “Muscarinic” subtype: M₂
  – Use of signal transduction system
    • via G-proteins, opens K⁺ channels, decrease in cAMP levels
  – Effect on target: cell specific
  – CNS
  – Stimulated by ?
  – Blocked by Atropine, etc.
Cholinergic Agonists

• Direct
  – Muscarine
  – Nicotine

• Indirect
  – AChE Inhibitors ~
Cholinergic Antagonists

- Direct
  - Nicotinic - Curare
  - Muscarinic - Atropine
Ligand-Operated ACh Channels

N Receptor
G Protein-Operated ACh Channel

M receptor
(2) Monoamines as NT
Monoamines

- **Catecholamines** –
  - Dopamine - DA
  - Norepinephrine - NE
  - Epinephrine - E

- **Indolamines** –
  - Serotonin - 5-HT
Synthesis of Monoamine NT

Tyrosine

$\text{tyrosine hydroxylase}$

L-Dopa

$dopa\ decarboxylase$

Dopaminergic Neurons

Dopamine

$\text{dopamine} \beta -$ hydroxylase

Norepinephrine

phenylethanolamine-$N$-methyltransferase

Epinephrine

Adrenal Glands
Mechanism of Action ($\beta$ receptor)
Norepinephrine (NE) as NT

• NT in both PNS and CNS.

• PNS:
  – Smooth muscles, cardiac muscle and glands.
    • Increase in blood pressure, constriction of arteries.

• CNS:
  – General behavior.
Adrenergic Receptors

\[
\begin{align*}
\alpha_1 & : \alpha_{1a}, \alpha_{1b}, \alpha_{1d} \\
G_{q/11} & : \text{increase } [Ca^{2+}]_i \\
\alpha_2 & : \alpha_{2a}, \alpha_{2b}, \alpha_{2c} \\
G_i & : \text{inhibit adenylyl cyclase} \\
\beta & : \beta_1, \beta_2, \beta_3 \\
G_s & : \text{stimulate adenylyl cyclase}
\end{align*}
\]
Adrenergic Neurotransmission

\( \alpha_1 \) Receptor

- Stimulated by NE, E,
- blood vessels of skin, mucosa, abdominal viscera, kidneys, salivary glands
- vasoconstriction, sphincter constriction, pupil dilation
Adrenergic Neurotransmission

$\alpha_2$ Receptor

- stimulated by, NE, E, ….
- Membrane of adrenergic axon terminals (pre-synaptic receptors), platelets
- inhibition of NE release (autoreceptor),
- promotes blood clotting, pancreas decreased insulin secretion
Adrenergic Neurotransmission

\( \beta_1 \) receptor
- stimulated by E, ….
- Mainly heart muscle cells,
- increased heart rate and strength
Adrenergic Neurotransmission

• $\beta_2$ receptor
  – stimulated by E..
  – Lungs, most other sympathetic organs, blood vessels serving the heart (coronary vessels),
  – dilation of bronchioles & blood vessels (coronary vessels), relaxation of smooth muscle in GI tract and pregnant uterus
Adrenergic Neurotransmission

- $\beta_3$ receptor
  - stimulated by E, ....
  - Adipose tissue,
  - stimulation of lipolysis
(3) Amino Acids as NT

- Glutamate acid and aspartate acid:
  - Excitatory Amino Acid (EAA)
- Gamma-amino-butyric acid (GABA) and glycine:
  - Inhibitory AA
(4) Polypeptides as NT

- **CCK:**
  - Promote satiety following meals.
- **Substance P:**
  - Major NT in sensations of pain.
Nitric Oxide (NO)
- Exerts its effects by stimulation of cGMP.
- Involved in memory and learning.
- Smooth muscle relaxation.

Carbon monoxide (CO):
- Stimulate production of cGMP within neurons.
- Promotes odor adaptation in olfactory neurons.
- May be involved in neuroendocrine regulation in hypothalamus.
THANK YOU