203 Winter 2013 Lecture 7 - Chapter 2
Electrical - Chemical Message

\[ \text{So What Happens After the AP?} \]
...the continuing saga...
Basic principle of synaptic transmission

- Action potential
- Transmitter release
- Activation of receptors
- Inactivation mechanisms
Synapse

(20 nm = 1 billionth of M)
Axodendritic Synapse
Axosomatic Synapse
Axoaxonic Synapse
1. Postsynaptic Neuron
2. Presynaptic Neuron
3. Vesicle with Neurotransmitter (NT) Molecules
4. Mitochondrion (for energy production from glucose)
5. Synaptic Cleft
6. Neurotransmitter (NT) Molecules
7. Postsynaptic Membrane (with NT receptors)
8. Cisterna (membrane recycled to new vesicles)
DNA makes RNA makes protein

In higher organisms, the hereditary material, DNA, is located in the cell nucleus. The DNA in one human cell contains about 100,000 genes, located on 46 chromosomes. A chromosome pair and the DNA molecule, a long double-stranded helix, are shown to the right and below.

The genetic information in the DNA is stored as a sequence of bases (or nucleotides). The bases are stacked in between the two strands which wind around each other. The order of the bases determines the genetic information. When a gene is activated, the DNA strands separate and one of them serves as a template for copying a messenger RNA (mRNA) as shown on the right.

The letters represent the bases adenine (A), thymine (T), guanine (G) and cystosine (C). In the double helix, A always pairs with T, and C with G. In the mRNA, thymine is replaced by uracil (U).

A stretch of three bases in the mRNA determines the position of a particular amino acid in the growing protein molecule. The mRNA, containing the information for a particular protein, is transported from the nucleus to the cytoplasm, where protein synthesis takes place. Amino acids are joined together as pearls on a string. There are 20 different amino acids. Their order in the protein molecule determines its structure and function. Proteins may serve e.g., as enzymes, hormones or structural components of a cell.

The final protein molecule may consist of several hundred amino acids linked together according to the instructions encoded in the mRNA.
Dale's Law:
neuron produces and releases only one type of neurotransmitter...

co-release:  
GABA/Glycine  
Acetylcholine/glutamate  
Dopamine/ glutamate

Receptors too!  CB1/D2 receptors
Can any chemical be a NEUROTRANSMITTERS? NO

Criteria for a Substance to be called a Neurotransmitter

1. It is synthesized in the neuron - present in the terminal

2. It must be released in response to presynaptic depolarization - $Ca^{2+}$ mediated release

3. Specific receptors must be present in the postsynaptic cell

4. A specific mechanism exists for removing it from its site of action (synaptic cleft)
RECEPTOR Binding Site

Chemical attaches to binding site

LIGAND = NT

Artificial Ligands

DRUGS
RECEPTORS

- Membrane proteins that have extra-cellular binding site
Class of proteins ("serpentine") → Transmembrane structure to span the membrane 7 times (80%)
The Fate of the Neurotransmitter?

1. Reuptake
2. Degradation by enzyme

Synapse
Also, Diffusion: the neurotransmitter drifts away, out of the synaptic cleft where it can no longer act on a receptor.

Ex: Enzymatic degradation

AcetylCholine $\rightarrow$ AcetylCholinesterase
Acetate + Choline

Ex: Reuptake: 5HT, DA & Norepi
Reuptake:
Transport systems
The Life Cycle of a Neurotransmitter

1. Synthesis
2. Storage
3. Release
4. Diffusion across the synaptic cleft
5. Binding
6. Release
7. Inactivation by enzyme - reuptake

The Life Cycle

1. Conception
2. 9 months
3. Birth
4. Move out
5. Marriage
6. Divorce
7. Death???
   reincarnation
2 BASIC TYPES OF RECEPTORS

Direct → IONOTROPIC (ligand activated)

FAST RESPONSE - SHORT LIVED RESPONSE
EPSP & IPSP (Na+/K+)

Indirect → METABOTROPIC
(G-PROTEIN COUPLED RECEPTOR)

SLOWER RESPONSE - LONGER LASTING RESPONSE
More of these
Can either cause a channel to open or trigger 2nd messenger
IONOTROPIC
(LIGAND BINDING RECEPTOR)

METABOTROPIC
(G-PROTEIN COUPLED RECEPTOR)
Class of proteins ("serpentine") → Transmembrane structure to span the membrane 7 times (80%)
Neurotransmitter

Diagram showing the interaction of neurotransmitter with receptor, leading to activation of G protein, adenyl cyclase, production of cAMP, CREB binding to DNA, and cAMP response element.
Autoreceptors
• located on presynaptic cell
• feedback loop
• sensitive only to NT released by the presynaptic cell

http://www.mc.../pha824ar/PHA824ar.html
The Life Cycle of a Neurotransmitter

1. Synthesis *
2. Storage
3. Release
4. Diffusion across the synaptic cleft
5. Binding **
6. Release
7. Inactivation by enzyme - reuptake **

Most Effects of Drugs Occur at One of These Steps

Drugs can either decrease (antagonist) or increase (agonist) the effects of a neurotransmitter.
**General Classification of Drug Action**

**Agonist**: Drug that facilitates the effect of a particular Neurotransmitter

Drug that binds to a receptor and activates it, producing a pharmacological response

**Antagonist**: Drug that attenuates the effect of a Particular NT (agonist)...HOW?
Affinity

How efficiently a drug binds to the target receptor

**High Affinity** = binds tightly produces effects at low doses

**Low Affinity** = binds weakly, produces effects with high doses
2 Basic Types of Antagonist

**Competitive**: binds reversibly to the same receptor site as the agonist...occupies the site without activating it

**Noncompetitive** (irreversible): binds irreversibly to region of the receptor in common with the agonist (can be drug or NT) but occupies the site without activating it
**Competitive Binding**

*Antagonist*

**Noncompetitive Binding**

- Binds reversibly
- Can overcome the antagonist
- [ ] of agonist (Drug)

**Allosteric**

- Binds irreversibly
- Antagonist...
Meet the big boys...well the small molecules...

**NEUROTRANSMITTERS**

**Simple Amino Acids**
- Glutamate
- Aspartate
- Glycine
- GABA

**Monoamines**
- Acetylcholine
- Dopamine
- Epinephrine
- Norepinephrine
- Serotonin

**Catecholamines**

**Indolamines**
- Serotonin

**Acetylcholine**
- Acetylcholine

**Soluble Gases**
- Nitric oxide
- Carbon monoxide

**Neuropeptides**
- Endorphins, hormones…

**Small molecule (4 classes)**
Otto Loewi (1903-1961)

- Born in Germany, American Citizen
- 1920 - Discovered 1st NT
- “Dreamed” the experiment
- Acetylcholine → “vagus substance”
- 1936 - Nobel Prize
"The night before Easter Sunday, I woke, turned on the light and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. The next night at three o'clock, the idea returned. It was the design of an experiment to determine whether or not the hypothesis of chemical transmission that I had uttered seventeen years ago was correct. I got up immediately and went to the laboratory and performed the simple experiment."

...The experiment worked
The Experiment: Test the hypothesis of chemical transmission

- Stimulate Vagus Nerve in Frog $\rightarrow$ decrease in HB
  - take fluid from donor heart
  - place recipient heart in fluid
  - decrease in HB

most "intuitive" discoveries are associated with earlier hypotheses buried deep in the unconscious mind
Acetylcholine

*enzyme degradation (acetylcholinesterase) (MSF) *mostly excitatory

Acetylcholine (Cholinergic) - CNS (Efferents) Sympathetic & Parasympathetic Pre ganglion

Cholinergic synapses:
- Hippocampus - Learning & Memory

- Parasympathetic Viscera → target organ

- All motor neurons → Excites skeletal muscle/BUT inhibits heart muscle → nerve gas blocks AChE → death → atropine (antagonist: receptor blocker [M]) Ach

- Curare: blocks ACh in skeletal muscles [N]→ paralysis
Major Cell Bodies Sites

Cholinergic Projections

interneurons

Learning & memory

PGO Spiking

ACETYLCHOLINE (CHOLINERGIC) PROJECTION SYSTEM IN THE BRAIN
Where do your NTs come from?
Biosynthetic Pathway for Acetylcholine

Choline (diet) + Acetic Acid (BD of lipids) → choline acetyl transferase (ChAT) → Acetylcholine

Cauliflower, Milk, Lecithin (egg yolks, liver, soybeans, butter, peanuts)

Synthesized in terminal button
Simple Amino Acids

- Glutamate*
- Aspartate
- Glycine
- GABA*
**Glutamate**

**Glutamate - (Glutaminergic) - CNS**
*reuptake - glia (Astrocyte)*
*excitatory (opens Na+ channels)*

**Glutaminergic synapses:**
- All over the place!!! Originate in the brain (neocortex, hippocampus)
- Most abundant NT in brain = over 50% of synapses
- Especially important for LTP - memory - hippocampus
- Most important for normal brain function (neural injury)

MNDA, AMPA, Kainate Receptors
Biosynthetic Pathway for Glutamate

Glutamine (amino acid)

Glutaminase

Glutamate

- Does not cross the BBB: synthesized in the brain
- Glutamine synthesized in astrocytes (glia)
Glutamate - Possible malfunctions in transmission

Too much of it

Excessive excitation
(*Excitotoxicity*)

Too little of it

Deficient excitation
GABA (discovered in 1950)

Gama-aminobutyric Acid - (Gabaergic) - CNS
*reuptake
*inhibitory - Opens K+ & Cl- channels = hyperpolarization

GABAergic synapses:
- widespread in the brain
- excitation in the brain must be balanced with inhibition
- Don't have it = too much brain activity
- Anti-seizure drugs
- Block Gaba (Bicuculline) = convulsions & death
- Anxiety (too much activity) → Valium

GABA_A & GABA_B Receptors
Biosynthetic Pathway for γ-aminobutyric acid (GABA)

Glutamate

\[ \text{glutamic acid decarboxylase} + \text{cofactor: pyridoxal phosphate} \]

GABA

- Most abundant inhibitory NT = over 1/3 of synapses release
- Cofactor: Vitamin B₆ deficiencies = seizures in infants
Monoamines

Catecholamines

Indolamines

Dopamine
Epinephrine
Norepinephrine

Serotonin
First isolated in 1933 in gut → “enteramine”
- 1947 - blood plates → serotonin

Serotonin (Serotonergic)
* **reuptake (transport system)**
* **excitatory** (opens Na+ channels) and inhibitory

Serotonergic synapses:
- Widely distributed throughout the brain
  * Limbic system (mood & emotion): depression
  * Reticular activating system (RAS-raphe nucleus): arousal / sleep-wakefulness cycle
  * Eating Disorders

5HT(1, 2, 3, 4 & 5) receptors
Serotonergic Projections

Projections to the telencephalon & diencephalon

Sleep, mood

Arousal, mood
Biosynthetic Pathway for Serotonin

Tryptophan (amino acid from diet) → tryptophan hydroxylase → 5-Hydroxytryptophan → aromatic-L-amino acid decarboxylase → 5-Hydroxytryptamine (5HT - Serotonin) → serotonin-N-acetyl transferase (NAT) → N-Acetylserotonin → Hydroxyindole-O-methyltransferase → Melatonin (Neurohormone)
Dopamine

Dopamine - (Dopaminergic) - CNS
*reuptake (Transport system)
*excitatory & inhibitory

Dopaminergic synapses:
- Striatum: Motor behavior (PD)
- Nucleus Accumbens: Reward-Pleasure
- Mesolimbic/mesocortical: affect, emotions, motivation (Schizophrenia)
- Hypothalamus: Release of hormones

D1, D2, D3, D4, D5 Receptors

Arvid Carlsson
• Nobel Prize (2000)
BIOSYNTHETIC PATHWAY FOR DOPAMINE

PHENYLALANINE

PHENYLALANINE HYDROXYLASE

TYROSINE

TYROSINE HYDROXYLASE

3,4-DYHYDROXYPHENYLALANINE (L-DOPA)

AROMATIC-L-AMINO ACID DECARBOXYLASE

DOPAMINE (DIHYDROXYPHENYL-ETHYLAMINE)
Biosynthetic Pathway for Dopamine, Norepinephrine & Epinephrine

Phenylalanine (amino acid from diet) → *phenylalanine hydroxylase
  Tyrosine → tyrosine hydroxylase (RLS)
  3,4 Dihydroxyphenylalanine (L-DOPA) → aromatic-L-Amino Acid decarboxylase
  Dopamine → dopamine β decarboxylase
  Norepinephrine → Phenylethanol-amine N-methyl-transferase
  Epinephrine

* Phenylketonuria (PKU)
Dopaminergic Projections

- Motor
- Reward/pleasure
- Thought
- Schizophrenia
- Mesolimbic pathway
- Mesocortical pathway
- Hormones

DOPAMINE PROJECTION SYSTEM IN THE BRAIN