Lecture 4 (Oct 10th) SYNAPSES AND DRUGS

Lecture Outline

Finish up from last lecture

1) Types of Ion Channels
   - VOLTAGE-gated
   - NEUROTRANSMITTER-gated
   - STIMULUS-gated

2) Neurotransmitter (NT) Types

3) A Day in the Life of a NT

4) Two Main Types of NT-gated RECEPTORS (learn on your own)
   - Ionotropic
   - Metabotropic

5) Synapses & Drugs

We might not get through it all today (usually there are a lot of Qs :-) which is why you will learn part 4 on your own
Nodes of Ranvier / Saltatory Conduction

Action Potential JUMPS from Ion Channel to Ion Channel at the Nodes of Ranvier
Nodes of Ranvier / Saltatory Conduction

What goes wrong in Multiple Sclerosis (MS)?

1) Early in development, when no myelin yet

2) Later, you develop myelin, and the ion channels underneath the myelin go away

3) MS: myelin gets destroyed by own immune system
CONTROL (OPEN/CLOSE) OF ION CHANNELS

1) **Voltage (i.e., Membrane Potential)** \( \sqrt{ } \) (last lecture)
2) **Neurotransmitter (NT)** (today’s lecture)
3) But for the **SENSES**, the input **starts** with a **Stimulus** e.g., Light, Sound or Touch (later in course)

**General Overview of “Excitatory” NT Actions:**

- NT binds to receptors on neuron’s dendrites
- -> **Opens “Neurotransmitter-GATED” Ion Channels**
- -> If those “Neurotransmitter-GATED” channels are Na\(^+\) channels,
- -> **Depolarization**, which then **opens “Voltage-Gated Na\(^+\) channels”**
  (and, opens Voltage-Gated K\(^+\) channels more than they were open at rest)
- -> If depolarization gets to \(-55 \text{ mV}\) -> **Action Potential (AP)**
- -> **AP travels down axon**
- -> **Releases NT at axon terminals into synapse**
- -> and repeat
Also, Purines and Gases (but don’t worry about)
The neurotransmitter needs to GO AWAY!

A Day in the Life of a Neurotransmitter (NT)
6) The NT needs to go away!
   a) NT is *re-absorbed* by the presynaptic terminals, i.e., *recycled*
      e.g., Monoamines
   b) NT is altered by *enzymes* (in the synapse) to be *inactive*.
      i) NT *broken down* (into its parts) by enzymes
         e.g., Acetylcholinesterase (ACh):
            ACh -> acetate + choline
            choline reabsorbed and added to acetate
      ii) NT converted to an *nonfunctional* state by enzymes
         e.g., MAO (monoamine oxidase),
            converts Monoamines to nonfunctional state
   c) NT will *float away* eventually, and get absorbed by Glial Cells
Back to the Effects of Neurotransmitter (NT)

**NT -> Binds to Receptor -> Opens (Fairly) Specific Ion Channels (e.g., Na\(^+\), K\(^+\))**

1) Ionotropic Receptor: *Direct* action on ion channels

2) Metabotropic Receptor: *Indirect* action on ion channels

1) Ionotropic, **IONOPHORE** = Receptor + Ion Channel

* NT causes a change in configuration of ionophore

* Depolarizing **NT** -> *binds to ionophores with Na\(^+\) channels and opens them* (not the same channels as the voltage-gated ones!)

**Why depolarizing?**

ANSWER: Na\(^+\): rushes IN (down concentration and electrical gradient)

e.g., Glutamate = “excitatory” NT
1) Ionotropic, **IONOPHORE** = Receptor+Channel

- Hyperpolarizing **NT** -> binds to ionophores with **K⁺** channels and opens them (not the same channels as the voltage-gated ones!).

Why hyperpolarizing?

ANSWER: **K⁺** rushes OUT! Down the Concentration Gradient!

... remember.. Concentration Gradient is stronger than the Electrical Gradient (*last lecture*)

Same Hyperpolarizing Story for ionophores with **Cl⁻** channels

**Cl⁻**: outside > inside (new info)

If **Cl⁻** channels open, **Cl⁻** rushes IN!

e.g., **GABA** attaches to ionophores with **Cl⁻** channels = “**inhibitory**” **NT**

FAST mechanism -> opens channels within 10 ms

SHORT duration -> left open for 10-20 ms

(good for sensory and movement systems)
2) Metabotropic Receptor, “2nd messenger”

Opens/closes a (fairly) specific Ion Channel type... indirectly!

SLOW mechanism
opens channels within 30 ms

LONG duration
left open for seconds or longer
MAJOR RECEPTOR TYPES
(named for the NT that binds to it, or the DRUG that binds to it, no standard rule)

**Acetylcholine (Ach) Receptor:**
- ~4 Nicotinic Receptor Types (Ionotropic)
- ~5 Muscarinic Receptor Types (Metabotropic)
(of course, this receptor binds Ach too!)

**In PNS:** at Neural-Muscular Junction
- Nicotinic (skeletal muscle, e.g., bicep)
- Muscarinic (smooth muscle, e.g., uterus)

**In CNS:** Both Nicotinic and Muscarinic Exist

**Norepinephrine (NE):** 2 main receptor types
- Alpha Receptors
- Beta Receptors

**Dopamine (DA):** ~6 Receptors

**Serotonin:** ~14 Receptors
What is a DRUG?

A medicine or other substance that has a physiological effect when ingested or otherwise introduced into the body

Psychoactive drug: any substance that changes brain function and results in altered perception, mood or consciousness

Medicinal vs. Recreational
How Psychoactive Drugs Affect Neurons

**Agonist:** mimics or increases the effect of a neurotransmitter system

**Antagonist:** blocks or decreases the effect of a neurotransmitter system

5 ways to be an **AGONIST:**

1) Drug Stimulates Receptor: Mimics NT
   - e.g., Nicotine attaches to *Nicotinic Ach* receptor
     (and has roughly same effect)
   - e.g., XANAX (*Benzodiazepine*) attaches to *GABA* receptor

2) Drug stimulates release of more NT
   - e.g., Amphetamines -> NE
     -> DA

3) Drug blocks re-absorption of NT at the synapse
   - e.g., Amphetamines & Cocaine (& Ritalin)
     Cocaine blocks the re-absorption of DA
     “Crashing” (depletion, because NT “floats away”)

4) Drug acts as a precursor for the NT
   e.g., **L-DOPA** synthesizes to DA (Parkinson’s)

5) Drug inactivates enzyme that breaks down NT:
   e.g., **Physostigmine** inhibits *Acetylcholinesterase*
   **Iproniazid** inhibits *Monoamine Oxidase*
4 ways to be an **ANTAGONIST:**

1) Drug blocks receptor
   - e.g., **Curare** attaches to *Acetylcholine (Ach) receptor*, and keeps Ach from binding to receptor - > **muscle paralysis**

2) Drug inhibits NT release
   - e.g., Clostridium botulinum (bacteria) releases **botulin toxin** - > inhibits *release of Ach* - > **muscle paralysis** (called “botulism”)

3) Drug inactivates synthetic enzyme
   - e.g., AMPT blocks enzyme that converts *tyrosine* - > **DOPA**

4) Drug makes the synaptic vesicles inside the neuron “leaky”
   - e.g., **reserpine**: *monoamine vesicles*
Recreational (Medicinal?) Drugs

Timothy Leary & Richard Alpert (Harvard 1960s): “Tune in, turn on, and drop out”

Consciousness-expanding drugs
Recreational (Medicinal?) Drugs
(not always clear if they are Agonists or Antagonists)

Alcohol:  works on many systems: Glutamate, GABA, DA, endorphin

Hallucinogenic “Psychodelic” Drugs (LSD, psilocybin, mescaline)

Serotonin system. Agonist??
creates hallucinations, dream-like state
Raphe nuclei in brainstem (sleep and dreams)
  Used medicinally for PTSD, terminal death, etc

Other Serotonin-Related (Agonist) Drugs

PROZAC (depression) -> prevents re-absorption
St. John’s Wort for Depression (more natural?)
  - social phobias, schizo, bulimia, autism

Opiates (Heroin, Morphine, Methadone)

endorphin receptor AGONISTS
used as “pain-killers” (more later in course)
produce “euphoria”
Marijuana (THC and other cannabinoids, from Cannabis plant) acts on cannabinoid receptors (numerous in the brain especially in HIPPOCAMPUS). Agonist or Antagonist? dissolve in body FATS intensified sensory experience, time slows down used clinically for pain, nausea, glaucoma, migraines brings awareness to the “present moment”

“Overdosing”: shutting down the medullary respiratory center

Barbiturates and Opiates -> Yes
Marijuana -> NO

Ondine’s Curse