Lecture 4 (Jan 17th): SYNAPSES AND DRUGS

Lecture Outline

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
   - Ionotropic
   - Metabotropic

5) Synapses & Drugs
CONTROL (OPEN/CLOSE) OF ION CHANNELS

1) Voltage (i.e., Membrane Potential)-Gated (√) (last lecture)
2) Neurotransmitter-Gated (NT) (today’s lecture)
3) But for the SENSES, the input STARTS with a Stimulus e.g., Light, Sound or Touch “Stimulus-Gated”, 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”
- If depolarization gets to –55 mV -> Action Potential (AP)
- AP travels down axon
- Releases NT at axon terminals into synapse
- and repeat
Acetylcholine (Ach) = Acetate (met) + choline (diet)

**NEUROTRANSMITTER (NT) TYPES**

- **Monoamines**
  - Indoleamines: **Serotonin** (from Tryptophan in diet)
  - Catecholamines
    - Dopamine (DA)
    - Nor- (NE) Epinephrine
    - Epinephrine (EPI)

- **Amino Acids**
  - GABA
  - Glutamate

- **Peptides**
  - Endorphins
  - Substance P

Also, Purines and Gases (but don’t worry about)
A Day in the Life of a Neurotransmitter (NT)

1a Synthesis of neurotransmitters and vesicles
2 Transport of neurotransmitter
3 Action potential causes calcium to enter, releasing neurotransmitter
4 Neurotransmitter binds to receptor
5 Separation from receptors
6 The neurotransmitter needs to GO AWAY!
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 (in the synapse) to be *inactive*
      i) broken down by *enzymes*
         e.g., Acetylcholinesterase (ACh):
         ACh -> acetate + choline
         choline reabsorbed and added to acetate
    ii) converted to an *inactive* state by *enzymes*
         e.g., MAO (monoamine oxidase),
         converts Monoamines to inactive state
   c) NT will *float away* eventually, and get absorbed by Glial Cells
Back to the Effects of Neurotransmitter (NT)

$NT \rightarrow Binds \to \text{Receptor} \rightarrow$

*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, which opens up the ion channel to allow flow of ions across the membrane (*direction of flow?*)

FAST mechanism -> opens ion channels within 10 ms

SHORT duration -> left open for 10-20 ms (good for sensory and movement systems)
1) Ionotropic, **IONOPHORE** = Receptor + Ion Channel

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

**Why depolarizing?**

Na\(^+\): outside > inside
Na\(^+\): rushes IN (down concentration and electrical gradient)

e.g., **Glutamate** attaches to ionophores with Na\(^+\) channels = “excitatory” NT
1) Ionotropic, **IONOPHORE** = Receptor+Channel

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

**Why hyperpolarizing?**

**K**\(^+\) : inside > outside
K+ rushes OUT! Down the Concentration Gradient!

You can ignore this-\(\rightarrow\) **Concentration** Gradient is stronger than Electrical Gradient (last lecture)

Same hyperpolarizing story for ionophores with **Cl**\(^-\) channels
Cl- : outside > inside

If Cl- channels OPEN, Cl- rushes IN!

e.g., **GABA** attaches to ionophores with Cl\(^-\) channels = “**inhibitory**” NT
2) Metabotropic Receptor, “2nd messenger”

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

SLOW mechanism
opens ion 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 bind 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

Baba Ram Dass
Recreational (Medicinal?) Drugs
(not always clear if they are Agonists or Antagonists)

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

**Hallucinogenic “Psychedelic” Drugs (LSD, psilocybin, ayahuasca)**

*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? 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