• Understanding neurotransmitters and their actions is helping us understand psychoactive drugs.
• Virtually all psychoactive drugs act at synapses affecting one or more of the steps we just listed.

2 Categories of Drug Actions

A drug which mimics or somehow increases the effects of a neurotransmitter is called an AGONIST.

A drug which blocks or somehow decreases the effects of a neurotransmitter is called an ANTAGONIST.

Drug Actions

• AGONIST examples:
  - Narcotic pain relievers fit and activate opiate receptors mimicking the action of normal endorphin.
  - Nicotine fits into & stimulates ACh receptor sites, arousing the cortex like ACh.

• ANTAGONIST examples:
  - Haldol blocks DA receptors in schizos
  - Naloxone blocks opiate receptors
  - Atropine blocks muscarinic ACh receptors & curare or botox block nicotinic ACh receptors

• For example, the first drug we’ll encounter in our discussion of Parkinson’s disease, L-dopa, affects the first step (synthesis of neurotransmitter).
• L-dopa is a “precursor” or ingredient DA neurons can use to make DA.

Recall the Basal Ganglia p. 361

• Functions:
  - Learning movement sequences performed as a unit.
  - Initiating those motor programs when needed
  - Inhibiting undesired movements

Caudate + putamen also known as the “striatum”
Basal Ganglia or “Striatum”

Parkinson’s Disease (362-364)

• About 1-2/100 of those over 60 have PD (about 1,000,000 total in US)
• Symptoms: Difficulty initiating movements, slow movements, loss of balance reflexes, muscle rigidity & tremors-at-rest
• Reduction in movement is also seen in lack of facial expression & blinking; shuffling walk without associated arm movements; soft, halting, monotone voice; slow blinks; small writing; feeling stuck or frozen
• Also cognitive slowing & depression in many

What’s Happening in Brain?

• Progressive loss of DA cells in substantia nigra which normally send DA messages to basal ganglia
• We all gradually lose neurons but those with PD may have accelerated loss (70% or more gone)

Substantia nigra of midbrain contains the cell bodies of DA neurons whose axons go to the basal ganglia & other forebrain areas

PD vs normal SN

Normal # of DA cells vs PD
Possible Causes

- Early Parkinson's disease – strong genetic link
- (see next slide)
- Environmental toxin of some sort (herbicides, pesticides): IA, MN, ND, SD, & NEB have highest rates in US! Those working with pesticides in California have 3x the risk of PD than the general public.
- Other toxins (carbon monoxide, industrial) also linked to increased risk.

Possible Causes continued

- Head injury may be associated with up to 11 fold increase in risk & earlier age of onset.
- 1 concussive loss of consciousness → 32% increase in risk, several losses of consciousness → 174% increase in risk
- Caffeine or nicotine use may decrease your risk significantly! It appears the neurotransmitter effects of these drugs decrease the impact of neurotoxin exposure.

PD Concordance in Twins

- Early Onset (16 pairs)
  - MZ 100% (4 pairs)
  - DZ 16%
- Late-Onset (161 pairs studied)
  - MZ 13%
  - DZ 16%
- This suggests strong genetic influence in the rare cases of early PD but relatively weak genetic influences on regular PD

Treatments

- Increase DA production with L-dopa
  - Problems: L-dopa induced side effects as dose goes up & loss of effectiveness over time
  - http://www.youtube.com/watch?v=31d2j0h66I
- Stimulate DA receptors with DA agonists that fit the DA receptors

When Drug Therapy Fails

- When drug effectiveness declines, experimental options include:
  - Deep brain stimulation to block hyperactivity in this system
    - http://www.youtube.com/watch?v=dBhuH9P_8BI
  - DBS means that surgical treatments like pallidotomy ; thalamotomy (ichael J. Fox's surgery) are less often used.
  - DBS also decreases impulse control problems of PD patients
  - Experimental: Transplant of DA producing cells into brain
Parkinson's Disease

- Another abnormality: Lewy Bodies (abnormal clumps of proteins in neurons)
- May precede the development of PD symptoms
- Lewy bodies found in lower brain stem in REM behavior disorder — 2/3's of those patients develop PD within 10 yrs
- Also sometimes seen in Alzheimer’s disease


Cell Membrane

- Double layer of fat (lipid) molecules keeps out most chemicals.
- For example, the cell membrane generally does not let IONS pass freely through it.
- What is an ion? An electrically charged atom or group of atoms.
- Ions to know:
  - Sodium       Na+
  - Potassium     K+
  - Chloride     Cl-
  - Calcium     Ca++

Neuron’s Cell Membrane

- Double layer of lipid (fat) molecules with large proteins stuck in it.
- Only certain things can freely pass thru the membrane (“selectively permeable” or “semi-permeable”)
- 2 or 3 examples of these proteins coming up

Neuron’s Ion Balance

- If you count the +’s inside the neuron (brown) versus outside the neuron (beige) — many more +’s outside.
Neuron’s Ion Balance

- A difference in charge means there is the potential for charges to flow ("membrane potential").

Membrane proteins serve special functions. Some act as channels that regulate the flow of charged ions that are the basis for the neuron’s electrical messages.

The Sodium/Potassium Pump

- The ion difference between the inside & outside is also maintained by "pumps" built into cell membrane, which actively pump Na+ out and K+ in.

Polarization

- Because of the ion difference, the inside of neuron is more negative compared to outside of neuron.

- Neuron at rest is "polarized" - difference in charge of inside vs. outside is like the - and + poles of a battery. There is "potential" for current flow between them.

I can use microelectrodes to measure the difference in charge between the inside and outside of the neuron.
Neuron at Rest

Because there are fewer positive charges inside:

The Result: Resting Potential

- Inside of neuron at rest is -70 mV more negative than outside of neuron
- This is known as the resting potential.
- This difference in charge depends on the
  1. Semi-permeable membrane and
  2. the Na+/K+ pumps

Hillock = Beginning of Axon

Changes in the Neuron’s Charge

- For a neuron to send a message or “nerve impulse” down its axon, its inside charge must get more +. This is called “depolarization”.
- Depolarization is what excites neurons.
- If neuron gets more negatively charged (“hyperpolarization”), firing of a message is inhibited.
Let’s Look at the Axon

Changes in the Axon’s Potential
• lots of ion channels in axon
  • these channels usually closed at rest
• What is it that opens the channels in an axon?
  • Axon contains “voltage-activated” Na+ channels
    which open when soma is sufficiently “excited” (depolarized).
• The critical voltage is known as the “threshold” ~15mV more positive

A Na+ Channel
• Opening of the axon’s Na+ channels is “voltage activated”
• The particular voltage that is necessary to open the axon’s Na+ channels is that neuron’s “threshold”
• Example: the neuron may need to get 20mV more positive for the axon’s Na channels to open.

Sufficient Depolarization to Trigger Opening of Axon’s Na+ Channels

The Action Potential or Nerve Impulse
• If sufficient exciting input is coming in to the neuron’s dendrites & soma to reach threshold, Na+ channels at axon hillock open, & so much Na+ enters that that spot becomes positively charged! (e.g. +30mV)
• This is enough + voltage to trigger the opening of the next Na+ channel, and the process is repeated all the way down the axon.
• This “action potential” thus is self-perpetuating & stays the same size as it travels down the axon, because the opening of each successive Na+ channel renews the positive charge.

Think about things you can electronically open/activate – a sufficient electrical signal will trigger opening

http://www.youtube.com/watch?v=M_R6IGrMxl8 domino example
The Action Potential or Nerve Impulse - a moving zone of positive charge

Nerve impulse is “all or none”. Stronger stimuli produce more impulses not bigger impulses.

A stronger stimulus does not produce larger action potentials. A stronger stimulus may trigger several successive action potentials, but they will all be the same size (or voltage).

Hey, this doesn’t look like our “typical neuron”!
In a Myelinated Neuron: 
Saltatory Conduction

- A different kind of voltage activated ion channel is involved in neurotransmitter release

Chemical Transmission
- Arrival of action potential voltage at presynaptic terminals opens Ca++ channels.
- Ca++ entering the terminal triggers chemical release ("exocytosis") by synaptic vesicles
- Neurotransmitter molecules bind to post-synaptic receptors, triggering a change in the next cell
- WHAT KIND OF CHANGES?

Now Let’s Look at How Messages Affect Dendrites
Ionotropic Receptors

- Some neurotransmitter receptors are located on ion channel proteins. When the transmitter binds to the receptor, the ion channel opens. These are chemically-activated *channels.
- * also known as transmitter-activated or ligand-activated channels
- Glutamate, GABA and ACh often bind to ionotropic receptors.

Ionotropic Receptor Effects: Quick But Brief

- Ion flow starts almost immediately and continues ~ 20 msec until the molecule of transmitter detaches.
- The ion flow changes the local charge of the dendrite or soma.

Another Ion You Should Know: Cl⁻ (more on outside of neuron)

Post-Synaptic Potentials

- If transmitter opened Na⁺ channels, the dendrite will depolarize (an excitatory post-synaptic potential or “EPSP”).
- If it opened Cl⁻ or K⁺ channels, the dendrite will hyperpolarize (an inhibitory post-synaptic potential or “IPSP”).
- These are “graded” potentials (graded = variable in size) that dissipate as they travel towards soma – like ripples of charge.
- Sum total of EPSPs & IPSPs must reach threshold for action potential to occur in axon
Summation

• The electrical effects of chemical transmissions occurring close together in time can add together.
  • Temporal summation – additive effects of transmissions occurring at the same synapse several times close together
  • Spatial summation – effects of different synapses on a neuron’s dendrites & soma add together

Summation of Inputs

• Some neurotransmitter receptors are NOT located on ion channel proteins.

Metabotropic Receptors

• Receptors which, when activated, trigger a sequence of metabolic reactions. Receptor is associated with a “G-protein” rather than an ion channel
• Reactions are triggered via a “second messenger” & are slower, more lasting, more distant & more varied than ionotropic effects.
• May:
  • Affect transmitter or receptors
  • Affect ion channels
  • Turn on part of the genome!

• Metabotropic Actions
  • https://www.youtube.com/watch?v=NB7YfAvez3o

Neurons can’t send messages if the ion channels don’t work

• Local anesthetics like Novacain prevent Na+ channels from opening. Also the neurotoxin tetrodotoxin found in pufferfish (fugu) & several other marine species.
• General anesthetic gases open K+ channels too much, so axon can’t reach threshold
• Scorpion venom holds Na+ channels open and K+ channels closed
• African tarantula venom blocks Ca++ channels