Neuroscience of Learning
An Introduction to
Mind, Brain, Health, and Education

Section: Neurotransmitters
Harvard University Extension School (PSYCE-1609)
February 2, 2016
What did one neuron say to the other?
Excited to meet you!

What did one neuron say to the other?
Which of these is a neuron?
Which of these is a neuron?

All of them!

Bipolar (Interneuron)  Unipolar (Sensory Neuron)  Multipolar (Motoneuron)  Pyramidal Cell

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What is the neuron doctrine?
The Neuron Doctrine

Key tenet: Neurons are specialized brain cells that are not continuous, but contiguous (e.g., there is a gap/transmission barrier between neurons)
Neurons connect via a synapse
Where’s the synapse?
Where’s the synapse?
Name that anatomy...
Name that anatomy...

Axonal bouton = Pre-synaptic terminal
Name that anatomy...
Name that anatomy...

Dendrite = Post-synaptic terminal
Name that anatomy...
Name that anatomy...

Synaptic Vesicles
What’s inside synaptic vesicles?

Synaptic Vesicles
Neurotransmitters
Are we making new vesicles all the time?
Synaptic vesicles are constantly emptied, recycled, and refilled.
Where does all the NT go?
A lot of NTs are taken back into the vesicles for reuse

Some breakdown

Some diffuse
How do neurons “fire?”
Dendrites are “triggered” by a neighboring axon.
The cell body collects all the triggers from the dendrites.

Dendrites are “triggered” by a neighboring axon.

Triggering an Action Potential = Firing
Triggerring an Action Potential = Firing

- Dendrites are “triggered” by a neighboring axon
- The cell body collects all the triggers from the dendrites
- If enough input is collected, the cell body triggers the axon to transmit the signal to all connected neurons

Axon Hillock

If enough input is collected, the cell body triggers the axon to transmit the signal to all connected neurons.
How does summation happen? Why does it need to?
Because neurons receive both excitatory and inhibitory input

http://7e.biopsychology.com/vs03.html
What is the end result of a neuron firing?
What is the end result of a neuron firing?

Neurotransmitter release
Ionotropism: NT binds to the ion channel
Metabotropic: NT binding opens ion channels
How much is being released?

- All of the vesicles within a neuron contain about the same amount of NT
How much is being released?

• All of the vesicles within a neuron contain about the same amount of NT
• CNS synapses typically release one vesicle per action potential
How much is being released?

- All of the vesicles within a neuron contain about the same amount of NT
- CNS synapses typically release one vesicle per action potential
- Neuromuscular synapses release about 200 vesicles per action potential
How much is being released?

Why do muscles get more?
How much is being released?

Why do muscles get more?

As a fail-safe to make sure muscles can contract
Poll: What influences NT levels?
Neurotransmitters have different jobs

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Chemical Structure</th>
<th>Mechanism of Action</th>
<th>Location(s)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Acetylcholine (ACh)    | \(CH_3\)N\(CH_3\)CH\(=\)N\(CH_3\)CH\(=\)O\(CH_3\) | Primarily direct, through binding to chemically gated channels | CNS: Synapses throughout brain and spinal cord  
PNS: Neuromuscular junctions, neuroglandular junctions, and synapses in autonomic ganglia | Widespread in CNS and PNS; best known and most studied of the neurotransmitters                      |
| Norepinephrine (NE)    | \(NH_2\)CH\(=\)CH\(=\)OH | Indirect, through G proteins and second messengers         | CNS: Cerebral cortex, hypothalamus, brain stem, cerebellum, and spinal cord 
PNS: Most neuromuscular and neuroglandular junctions of sympathetic division of ANS | Involved in attention and consciousness, control of body temperature, and regulation of pituitary gland secretion |
| Epinephrine (E)        | \(CH_3\)NH\(CH_3\)CH\(=\)OH | Indirect: G proteins and second messengers                 | CNS: Thalamus, hypothalamus, midbrain, and spinal cord | Generally excitatory effect along autonomic pathways                                                |
| Serotonin              | \(NH_2\)CH\(=\)CH\(=\)O | Primarily indirect: G proteins and second messengers       | CNS: Hypothalamus, limbic system, cerebellum, spinal cord, and retina       | Important in emotional states, mood, and body temperature; several illicit hallucinogenic drugs, such as Ecstasy, target serotonin receptors |
| Glutamate              | \(\text{HOOC-CH}_2\text{-CH}_2\text{-CH}_3\text{-COOH}\) | Indirect: G proteins and second messengers Direct: opens calcium/sodium channels | CNS: Cerebral cortex and brain stem | Important in memory and learning; most important excitatory neurotransmitter in the brain        |
| Gamma-aminobutyric acid (GABA) | \(\text{NH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3\text{-COOH}\) | Direct or indirect (G proteins), depending on type of receptor | CNS: Cerebral cortex, cerebellum, interneurons throughout brain and spinal cord | Direct inhibitory effects: opens Cl\(^-\) channels; indirect effects: opens K\(^+\) channels and blocks entry of Ca\(^{2+}\) |

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What if blocking a certain neurotransmitter caused muscle paralysis? What would you guess about it’s function?
Botulism causes paralysis because it prevents the release of acetylcholine (necessary for muscle contraction)
Acetylcholine (excitatory)

• Stimulates muscle contraction
• Stimulates release of some hormones
• Helps regulate lots of things including:
  ▪ Wakefulness
  ▪ Attention/vigilance
  ▪ Anger
  ▪ Aggression
  ▪ Sexual drive
  ▪ Thirst
  ▪ Learning/memory
Acetylcholine (excitatory)

- Alcohol decreases acetylcholine transmission
What if blocking a certain neurotransmitter caused muscle spasms? What would you guess about it’s function?
Tetanus: GABA vesicles can’t release

Tetanus causes muscle spasm because it prevents the release of GABA which inhibits muscular contraction...the muscles never stop contracting.

GABA (inhibitory)

• Works throughout the brain to balance excitatory NTs
  o About 40% of neurons have GABA receptors
  o Most active inhibitory NT

• Synthesized from glutamate (the major excitatory NT)

• Essential for:
  o Motor control (refines movement)
  o Vision
  o Anxiety regulation
What would happen to GABA levels if glutamate levels decreased?
What would happen to GABA levels if glutamate levels decreased?

They would decrease
Neurotransmitters influence each other
If you alter the levels of one, the others will adjust in response.
If you alter the levels of one, the others will adjust in response.
If you alter the levels of one, the others will adjust in response.
Glutamate (excitatory)

- Works throughout the brain
- Involved in most cognitive functions, especially learning and memory
- Critical agent for long-term potentiation (Hebbian learning)
Glutamate (excitatory)

- Actions (at NMDA glutaminergic receptors) can be blocked by alcohol
Glutamate (excitatory)

• Actions (at NMDA glutaminergic receptors) can be blocked by alcohol

• St. John’s Wort can increase release
If you want to learn better, should you take lots of St. John’s Wort so you increase your glutamate levels?
Too much glutamate is a bad thing
Do genes influence NT levels?
Genes can influence NT levels/processing

- ADHD gene reduces dopamine release in dorsal striatum
- Gene associated with depression and suicide decreases noradrenergic transmission
- Adolescent binge drinking alters adult gene expression resulting in decreased cholinergic neuron density

Do lifestyle choices influence NT levels?
Lifestyle factors can influence NT levels

Nicotine blocks cholinergic receptors
Lifestyle factors can influence NT levels

• Exercise:
  o Attenuated dopamine depletion
  o Increased serotonin and Ach levels

• Enriched environment
  o Upregulates genes that balance NT activity

• Diet:
  o One-week of high-fat/low-carb diet decreased serotonin levels in the hypothalamus
  o Consuming fat/sugar combinations reduced dopamine signaling
  o Long-term consumption of low-protein/high-carb diet decreased dopaminergic receptor density

Valium? Inhibitory or Excitatory?
Valium? Inhibitory or Excitatory?

Inhibitory
GABA (inhibitory)

- Nature’s “valium-like” substance
- Drugs like valium, Ambien, Lunesta work by increasing the activation of GABAergic receptor sites

Benzodiazepines (like valium) are effective in treating anxiety
How might GABA influence sleep? ADHD?
GABA promotes sleep

**FIGURE 2.**
Sleep-promoting GABA system

GABA = γ-aminobutyric acid; Hy = hypothalamus; BF = basal forebrain; LDT = laterodorsal tegmental; PPT = pedunculopontine tegmental; TMN = tuberomammillary nucleus; VLPO = ventrolateral preoptic nucleus; LC = locus coeruleus; DRN = dorsal raphe nucleus.

GABA levels decreased in ADHD

Edden, Crocetti, Zhu, Gilbert & Mostofsky (2012)
Do we have any way to influence our GABA levels?
Increasing GABA

- Supplements not thought to cross BBB but may enter through enteric routes
- Animal data shows some benefits in sleep
What might happen if you increase GABA?

Neurotransmitter Mobile

- 5-HT
- NA
- DA
- ACh
- Glu
- GABA

Spring, 2016
Why is Calvin mad?

I'm in a very bad mood, so nobody'd better mess with me today, boy!!
Why is Calvin mad? He needs happy juice?

I'm in a *very* bad mood, so nobody'd better mess with me today, boy!!

http://www.achievetruehealth.com/winter-blues-low-serotonin-may-be-the-culprit/
The first date:

Do it better with dopamine!
Dopamine (excitatory & inhibitory)

• Involved in:
  o Reward center/positive reinforcement
Dopamine (excitatory & inhibitory)

• Involved in:
  o Reward center/positive reinforcement
  o Ability to experience pleasure/pain
Dopamine (excitatory & inhibitory)

• Involved in:
  o Reward center/positive reinforcement
  o Ability to experience pleasure/pain
  o Motivation
  o Emotional response (altered levels seen in depression)
  o Maintaining focus
    ▪ Stimulants/caffeine push dopamine into the synapse...result is increased focus (long-term, causes dopamine depletion)
  o Movement control
Dopamine errors

• Motor/movement disorders
• ADHD (low levels)
• Addictions (mild elevations)
• Paranoia (high levels)
• Schizophrenia (very high levels)
Do we want to increase dopamine levels?

Neurotransmitter Mobile
Cocaine increases dopamine levels

https://www.cnsforum.com/educationalresources/imagebank/substance_abuse/mao_cocaine
Cocaine causes short-term improvements but long-term deficits in cognition (attention, flexible thinking) ... why?
Long-term cocaine use induces plastic changes in the reward circuit (nucleus accumbens)
Can we legally influence our dopamine levels?
Can we legally influence our dopamine levels?
Exercise increases dopamine synthesis

D. Suto, K. Akiyama / Neurobiology of Disease 13 (2003) 1–14

- Exercise
  - Increase in acidity
  - Increase in parathyroid hormone activity
  - Increase in calcium level

- Bone
  - Stored calcium

- Brain
  - Activation of calcium/calmodulin-dependent protein kinase II
  - Increase in tyrosine hydroxylase activity
  - Increase in dopamine synthesis
  - Increase in dopamine level
  - Increase in calcium transport

Brain functions
- Production of refreshing feeling
- Regulation of receptivity to drugs or alcohol
- Regulation of locomotion and other behaviors
- Reduction in blood pressure
- Regulation of susceptibility to convulsions and improvement of symptoms in epilepsy
- Improvement of symptoms in Parkinson’s disease or senile dementia of the Lewy body type
- Regulation of others
Serotonin (inhibitory)

- Helps regulate:
  - Mood (balances excitatory NTs to create stable mood)
  - Hostility/aggression, arousal
  - Sleep (inhibits wakefulness)
Serotonin (inhibitory)

• Helps regulate:
  o Mood (balances excitatory NTs to create stable mood)
  o Hostility/aggression, arousal
  o Sleep (inhibits wakefulness)
  o Pain control
Serotonin (inhibitory)

• Helps regulate:
  o Mood (balances excitatory NTs to create stable mood)
  o Hostility/aggression, arousal
  o Sleep (inhibits wakefulness)
  o Pain control
  o Digestion
  o Sensory perception
  o Higher cognitive function
What happens if we don’t have the right serotonin level?
Serotonin (inhibitory)

- Imbalance can cause:
  - Depression
  - Insomnia
  - Decreased immune function
  - Carbohydrate cravings
Can we influence our serotonin levels?
Medications alter NT levels by interrupting neurotransmission.
Why are SSRIs preferred over valium for anxiety?

Neurotransmitter Mobile

- 5-HT
- DA
- NA
- ACh
- Glu
- GABA
Valium is temporary; SSRIs induce plastic changes

- Benzodiazepines cause immediate GABA-like actions
- SSRIs cause plastic changes to change overall NT balance
Can supplements help?

• Tryptophan supplement (serotonin precursor) altered serotonin levels and behavior in mice

• Vitamin D and omega-3s may modulate serotonin synthesis

Eat nuts, be happy?

12x happy
Increase Serotonin

Banana
boosts serotonin

Leafy Greens
boost Energy

Walnuts - Omega 3
brain nutrients

Smiling releases
happy hormones

Epson Salt
Calming

Oats
Eases Depression

Cayenne Peppers
Relieves Depression

Water Hydration
More Energy less stress

Green Smoothie
Energy boost, zap!

Almonds
Brain Food-Magnesium

Walking - clears mind
boosts serotonin

By: authenticatediscovery.com.au
Animal data shows an increase in serotonin levels with exercise
Take a Quiz: Excitatory vs. Inhibitory
• **Excitatory**
  - Glutamate
  - Acetylcholine
  - Norepinephrine (noradrenaline)
  - Epinephrine (adrenaline)
  - Dopamine

• **Inhibitory**
  - GABA (gamma-aminobutyric acid)
  - Serotonin
  - Dopamine
Neurotransmitters—the big picture

• Neurotransmitters (NTs) communicate information throughout the brain & body

• NTs tell your heart to beat, lungs to breath, stomach to digest

• NTs regulate mood, sleep, hunger, concentration, and more...lack of balance can cause adverse symptoms

• Genetic and lifestyle factors influence NT balance/levels/function

• NT levels are inter-related; you can’t alter one without altering the others
Neurotransmitters influence each other
Balance is key...remember the mobile
Questions?

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Complete the 3-2-1

https://canvas.harvard.edu/courses/8447/discussion_topics/90505
References


References, cont’d.