Ch. 4 part 1. Neurons, Neurotransmitters, & Cell Communication

***Numbers here don't necessarily match up with slide number in powerpoint*.**

1. Objectives:

1. Review different types of neurons and neuron anatomy.
2. Understand how neurons communicate. -neurotransmitter signaling & action potentials
3. Learn types & functions of neurotransmitters.
4. Become familiar with influence of disease & drugs on neurotransmitter signaling.

2. Different Types of Neurons *[Review of Anatomy – go over QUICKLY]*

i. Neurons = functional unit of nervous system

a) Sensory neurons (afferent neurons) = pick up sensory info. & transmit up spinal cord to CNS

b) Motor neurons (efferent neurons) = transmit motor command from CNS (motor cortex) to muscle cells or glands

c) interneurons - relay info from motor OR sensory neurons in spinal cord.

3. Diagram of diff types of neurons (emphasize diff between way info travels)

4. **Neuroglial (glial) cells =** Helper cells that help neurons function, repair themselves, and communicate. They are the majority of neural cells (outnumber other neurons 10 : 1!)

CNS: > **astrocytes** = form blood brain barrier, take up and release neurotransmitters.
> microglia = cells that are macrophages of brain & spinal cord. Seek out & destroy invaders
> **ependymal cells** = cells that produce cerebral spinal fluid, within brain ventricles, that bathes & cushions brain.
> Oligodendrocytes = make myelin sheath around axon of neurons.

PNS: **> schwaan cells** = cells that produce the myelin sheath around neuron axons
> **satellite cells** = cover neurons of the PNS. Play a role in chronic pain. They increase in number w/ nerve damage.

5. Anatomy of a Neuron *[Review of Anatomy – Go over QUICKLY]*

Cell body *= beginning of a neuron, contains nucleus*

dendrites = projections from the cell body that receive signal from previous neuron or cell.

axon = elongated tube that transports signal to end of neuron.
- Signal moves faster along thicker axon (↓ resistance)
- axon lengths vary few mm to 3 ft long (e.g. those from sacral spinal cord to feet!)

myelin sheath = insulating wrapping around axon that speeds signal transduction.
(e.g. myelinated axon = signal moves 100 meters/sec or 225 mph1 , …… unmyelinated axon = 0.5 meters/sec!)

Nodes of Ranvier = Gaps between myelin sheaths called, signal jumps from node to node in "***saltatory conduction***"

synaptic knobs = end points of a neuron that communicate with neuron or effector.

6. **Multiple Sclerosis (see clinical app online)**

Autoimmune attack on myelin sheaths which creates multiple scars (scleroses) on the axons. Slows transmission of APs, especially in motor neurons (movement)

7. **Secretory vesicles** = sacs in synaptic knobs containing neurotransmitters, which are released when AP reaches them.
neurotransmitter = chemical signal that crosses synapse, binds to receptor on adjoining neuron OR effector cell.
synapse = open space between 2 communicating neurons OR between motor neuron and effector cell.
pre-synaptic neuron = neuron before synapse
post-synaptic neuron (or muscle or gland cell) = after synapse

8. Review slide

9. How Neurons Communicate

Neurotransmitter signaling = a chemical released from a neuron binds to receptor on target cell membrane, which:

1) Opens Na+ or Ca+2 channel in cell. Ions floods into cell causing AP (or depolarization, EPSP, or stimulation).
2) opens K+ or Cl- channel in cell, causing inhibition of cell (or repolarization or IPSP).

10. Steps from neurotransmitter release to cell AP *(Click image to show video embedded in powerpoint)*

1) Neurotransmitter released from vesicles of presynaptic neuron into synapse
2) Neurotrans. binds to receptor on postsynaptic cell & opens ion channel (usually Na+ channel)
3) Na+ floods into cell causing AP (depolarization).

11. Neurotransmitter binding to receptor opens ion channel. What kind of ion channel determines what happens to cell.

A) Cause an AP - **Excitatory postsynaptic potential (EPSP)** IF Na+ or Ca+ channel opened.
- EPSP can have a **graded potential** (depends on amount of neurotrans.):
  > the more neurotransmitter released = greater cell response
  > the less neurotransmitter released = less cell response
- EPSP can produce **summation** (depends on frequency of neurotrans. stim.)
  > greater frequency = greater cell response
  > lower frequency = less cell response

Ex. ↑ heart rate with epinephrine binding to its receptor on heart pacemaker cells.
ASK "What is the receptor on heart for epinephrine?" ANS = β1 adrenergic
When receptor bound it opens Na+ andCa+2 channels in pacemaker cells causing EPSP.

12. B) Inhibits an AP **– Inhibitory postsynaptic potential or IPSP** IF K+ or Cl- channel opened.
Ex. ↓ heart rate when ACh binds to its receptor on heart pacemaker cells.
ASK "What is the receptor on heart for ACh?" ANS = muscarinic cholinergic
When receptor bound it opens K+ channels in pacemaker cells causing IPSP.

13. **How Neurotransmitters Are Regulated:**

1) Type of receptor they bind to

A) nicotinic (ion-gated) receptor = found on skeletal muscles for voluntary control of movement
B) muscarinic receptor = found on cardiac and smooth muscle, and gland cells under autonomic control

2) Removal systems for neurotransmitters (there are 4)

14. A) Nicotinic Receptor – for voluntary (somatic) control of skeletal muscles.

> For ACh stimulation of skeletal muscles (called **nicotinic cholinergic receptor**)

> Receptor binding opens Na+ channels to open.

> Na+ floods into cells causing AP (muscle contracts, causes EPSP)

15. **B) Muscarinic Receptors – for autonomic regulation of cardiac & smooth muscle, and glands.**

> Receptor binding activates an enzyme, then G-protein, which opens ion channel

> If Na+ and Ca+2 channel opens = EPSP (cell stimulated)
K+ or Cl- channel opens = IPSP (cell inhibited)

> For ACh, norepinephrine, epinephrine
If for ACh – receptor called **muscarinic cholinergic receptor**
If for epinephrine (adrenaline) – receptor called **adrenergic receptor** (there are several kinds)

Slides 16 – 18: ASK the student what kind of response cell will have (EPSP or IPSP) by looking at what ion channel is opened.

16. EX. Of nicotinic cholinergic receptor. ***ANS = EPSP (Na+ channels opened, Na+ entering cell)***

17. Ex. Of muscarinic adrenergic receptor. ***ANS = EPSP (Na+ channels opened, Na+ entering cell)***

18. Ex. Of muscarinic receptor for GABA. ***ANS = IPSP (Cl- channel opened, Cl- entering cell)***

19. **Table on ACh and its receptors.** Effects of ACh & its receptor on skeletal muscle, cardiac & smooth muscle, & glands.

>Somatic motor neuron – releases ACh, which binds to **nicotinic cholinergic receptor** on skeletal muscle.
ASK: "What kind of ion channel is opened?" ANS = Na+ channel, and muscle has an EPSP to contract

> Motor neuron from parasympathetic regulation (rest & digest system)
Releases ACh, which binds to **muscarinic cholinergic receptor** on cardiac & smooth muscle & gland cells.
Can open up diff ion channels, <u>depending</u> on what makes sense during rest & digest
- Heart rate slows down during parasympathetic control (an IPSP) – K+ channels opened
- Bronchiole smooth muscle constricts during parasympathetic control (EPSP) – Na+ & Ca+2 channel opened
- GI smooth muscle constricts (peristalsis ↑) during parasympathetic – Na+ & Ca+2 channels open
- GI gland secretions ↑ during parasympathetic – Na+ channels open

20. **Examples of ACh binding to either nicotinic or muscarinic cholinergic receptors**:

> Left side = ACh and nicotinic cholinergic receptor on skeletal muscles for voluntary (somatic) control
- Receptor binding opens Na+ channels, Na+ enters cell
- Muscle has an AP (EPSP) and contracts

> Right side = ACh and muscarinic cholinergic receptor during parasympathetic regulation
- ACh binding to receptor on **heart muscl**e (pacemaker cells)
- receptor binding opens K+ channel, K+ leaves cell
- Heart muscle is inhibited (IPSP) & heart rate ↓

- ACh binding to receptor on GI smooth muscle or gland cells
- receptor binding opens Na+ and Ca+2 channels, which enter cells
- GI smooth muscle stimulated to contract (EPSP), get ↑ peristalsis & gland secretion

21. **Neurotransmitter Removal Systems** (very important in nursing – pharmacology!)
Neurotransmitters in synapse with cells produces powerful effect, so regulation of them is very important.
Neurotransmitters staying longer than needed in synapse than needed causes problems.

4 Systems:

i) Diffusion = neurotransmitter simply diffuses out of synapse.

ii) Enzyme breakdown = an enzyme breaks down neurotransmitter in synapse (into small inactive parts) **** VERY COMMON removal system.***

Ex. ACh-E stands for acetylcholinesterase = enzyme that breaks down ACh in synapse

Ex. MAO stands for monoamine oxidase = enzyme that breaks down monoamine neurotransmitters in synapse (ex of monoamine neurotrans are dopamine, serotonin, & epinephrine)

iii) Glial removal = neurotransmitter removed by astrocytes in CNS

iv) Reuptake = presynaptic neuron takes back neurotransmitter from synapse. ***ALSO COMMON removal system***
(This is how most serotonin gets removed from synapse)

Nursing application:

Depression & anxiety often involve low serotonin levels.
Common pharmacological treatment of anxiety & depression are SSRIs.
ASK: What are SSRI's (like Prozac, Lexapro, Citalopram)? ***ANS = selective serotonin reuptake inhibitors***
They work by inhibiting reuptake of serotonin, so serotonin builds up in synapse.

22. Figure of ACh-E breaking down ACh in synapse.

23. Click image to go to YouTube video showing (quality not best, but it works)

24. Review slide

25. **Types of Neurotransmitter Based on What They Made From**
Choline-derived = ACh found in CNS & is always stimulatory
ACh in PNS can be stimulatory or inhibitory (depends)
Review of Ch 6!
ASK: "Is ACh stimulatory or inhibitory with cardiac muscle? ANS = inhibitory (↓ heart rate)
"Is ACh stim. Or inhibitory with GI smooth muscle? ANS = stimulatory (↑ peristalsis)
Monoamine-derived = norepinephrine, epinephrine, dopamine, & serotonin
Norepinephrine, dopamine, & serotonin is in CNS – always stimulatory
Epinephrine in PNS for autonomic sympathetic regulation of body during fight/flight
Can be stimulatory or inhibitory – depends…
ASK: "Is epineph stim. or inhibitory with heart muscle? ANS = Stimulatory (↑ heart rate)
"Is epineph stim. or inhibitory with GI smooth muscle?" ANS = inhibitory (↓ peristalsis)
"Is epineph stim. or inhibitory with bronchiole smooth muscle?" ANS = inhibitory (bronchodilation)
"Is epineph stim. or inhibitory artery smooth muscle going to GI? ANS = stimulatory (vasoconstrict)

Interesting point to bring up: most of serotonin receptors (90%) found in GI tract & only 10% found in CNS (thus low serotonin in brain associated with various problems like anxiety & depression.

Other amino acid-derived neurotrans = Glutamate (stimulatory in CNS), Glycine & GABA (both inhibitory)

Gas-derived = nitric oxide

26. **I. Acetylcholine** [***Review from Ch 6 and earlier in Ch 4]***

> Found in both CNS & PNSP

> can be both stimulatory & inhibitory

> removed from synapses by acetylcholinesterase (ACh-E)

Involves 2 types cholinergic receptors:

1) Nicotinic cholinergic

- for voluntary control of skeletal muscles
- ACh released and causes EPSP by opening _____ ***(ASK "What ion channels?" ANS = Na+ channels)***
- causes skeletal muscles to contract

27. **2) Muscarinic cholinergic**

- for autonomic parasympathetic regulation of body during rest/digest
- causes diff effects:

IPSPs in cardiac muscle when K+ channels open (↓ heart rate)

EPSPs in GI smooth muscle & glands when Na+ and Ca+2 channels open (↑ peristalsis)

28. **Agonist** = substance that can increase the levels or activity of a neurotransmitter, or stimulate its receptor.
Antagonist = substance that can decrease the levels/activity of a neurotransmitter, or block its receptor (blocker)

29. **When enzymes <u>can't</u> break down ACh (causes problems)**

A) Acetylcholinesterase inhibitor (ACh-EI)

- prevents acetylcholinesterase (ACh-E) from breaking down ACh
- ACh builds up in synapse and keeps acting on receptors & can cause **cholinergic syndrome**

QUES: "Is ACh-EI an ACh Agonist or Antagonist?" ANS = Agonist

Ex. 1. Organophosphate pesticides act as ACh-EI

> Malathion – used for mosquito control

> Carbamate – general insecticide

> Chlorpyrifos – Used in flea & tick meds until banned in US in 2001.

30. **Ex. 2. Pyrethrins** (Non-organophosphate pesticide)

> can be used to repel fleas / ticks in dogs BUT NOT cats!

> in cats pyrethrins act as ACh-EI and cause cholinergic syndrome

31. **Ex. 3. Sarin gas (nerve gas)** – is an ACh-EI & used as biological weapon
(see clinical app online)

32. **Clinical presentation of someone with cholinergic syndrome – such as a farmer exposed to pesticides in agriculture (use mnemonic): DUMBBELSS**

D = diarrhea – too much ACH = too much GI peristalsis

U = urination

M = miosis (constricted pupils)

B = Bradycardia and other B = Bronchoconstriction

E = emesis (vomiting)

L = lacrimation (tearing)

S = salivation and other S = sweating (from skeletal muscle seizures)

33. **Treatment for cholinergic syndrome from ACh-EI exposure**

> Antidote = give **Protopam or 2 PAM** (brand name) (**Pralidoxime** active ingredient) - it stops phosphorylation of the enzyme ACh-E, so it can work again. While wait for 2-PAM to work, treat symptoms.

> <u>Treat symptoms</u> (while wait for 2 PAM to cure)

Atropine (see clinical app online)

- ACh antagonist (blocker) – blocks ACh muscarininc cholinergic receptors on heart (bring HR back up) and GI smooth muscles (slows GI activity including salivation), and bronchioles (opens them up again)

Valium (benzodiazepine) – see clinical app online

- Stimulates GABA which inhibits muscle activity (stop seizures)

QUES: "Is Valium a GABA agonist or antagonist?" ANS = agonist

34. **Toxins that are ACh Agonists**

A) **Tetanus** = toxin produced by ***Clostridium tetani*** bacteria.

- found in deep puncture wounds (can get from rusty metal)
- is an **ACh agonist &** causes muscle tetany (**hypertonia**)
- also cause lock jaw (trismus)
- also is a **Glycine and GABA antagonist** (prevents muscle relaxation)
- Prevent with tetanus vaccine (every 10 yrs)
- if no vaccination or out of date – give shot of tetanus antitoxin (lab created antibodies that inactivate the toxin in your body.

35. **Toxins that are ACh Antagonists (see clinical app online)**

A) **Botulism** = toxin produced by ***Clostridium botulinum*** bacteria

- get from contaminated canned food or bad Botox
- Prevents ACh from leaving presynaptic vesicles (never gets into synapse)
- Causes flaccid paralysis or **hypotonia**

B) Paralytic shellfish poisoning (see online)

- Get from shellfish harvested during Red Tide (Red algae have **saxitoxin**)
- Blocks ACh nicotinic cholinergic Na+ channels (Na+ can't enter cells and stimulate muscle constraction)
- Causes **hypotonia**

C) Pufferfish poisoning (see online)

- Get from improperly prepared Fugu fish (pufferfish) where poison glands with **tetradotoxin** remain.
- Blocks ACh nicotinic cholinergic Na+ channels (Na+ can't enter cells and stimulate muscle constraction)
- Causes **hypotonia**

36. **Other Disorders of ACh (ACh antagonist disorders)**

Myasthenia gravis (see clinical app online) = autoimmune attack on ACh receptors

- muscle weakness, pharyngeal (swallowing) problems, respiratory weakness.

Alzheimer's = memory and cognitive problems thought to be due to loss o:

- ACh-producing neurons in brain.
- excess glutamate (glutamate toxicity) in brain
- treatment with ACh agonists (use acetylcholinesterase inhibitors) & glutamate blockers

37. **II) Monoamine Neurotransmitters** = made from single amino acid.
Catecholamines = include dopamine, norepinephrine, & epinephrine (made from tyrosine)
Serotonin – made from tryptophan.

Regulated by **1) Reuptake** – primarily with serotonin
QUES: "What are SSRI's?" ANS = selective serotonin reuptake inhibitors. They inhibit its uptake, leaves more serotonin in synapses. Are serotonin agonists. Good treatment for low serotonin disorders (anxiety, depression)
2) Enzyme breakdown by MAOs. – breaks down dopamine, norepinephrine, & epinephrine. If have disorder of low levels of these neurotran, can treat with **MAO-inhibitor (MAO-I)**

38. **If have low levels dopamine, serotonin, norepinephrine can treat with diff. MAO-I's**
Two classes MAO-I's:
i) MAO class A = agonist to norepinephrine & serotonin *(think A for anxiety and appetite)*
ii) MAO class B = agonist to dopamine *("dope beat" to memorize)*
(see online reading)

QUES: "If SSRI's work best for ↑ serotonin, why would someone use MAO-I A? ANS = not everyone responds to drugs the same way. SSRI's might work for a lot of people, but some won't respond, so there is another option.

39. Serotonin
> 10% of receptors for serotonin in brain (that's not a lot, so if serotonin levels are low it has profound effect)
> 90% of receptors in intestines - thought to regulate appetite (but we still don't know exactly)
> low serotonin associated with depression, anxiety, obesity

QUES: "What can you give to ↑serotonin levels?" ANS = SSRI's or MAO-I A.

40. **Dopamine** – produced by substantia nigra neurons in midbrain.
2 functions:
1) fine motor control (nigrostantial dopamine system of brain)
> low dopamine associated with **Parkinson's disease** (see online clinical app)
- disease marked by muscle coordination problems
> **Excess dopamine** associated with **schizophrenia**. High dopamine associated with the hallucinations, delusions, and psychosis of the disease.

2) Emotional reward system (mesolimbic dopamine system)
When we do something that feels good, get dopamine release, and it reinforces the behavior. Can be responsible for addictions.

41. **See clinical app online about cocaine (increases dopamine 2.5 times) is an agonist to these neurotransmitters (amphetamines increase dopamine in brain by 10 X baseline levels!)**
> hallucinations – too much serotonin & dopamine
> muscle tremors & addiction – too much dopamine
> high energy, fight/flight behavior – too much norepinephrine in brain & epinephrine in body.

42. **Norepinephrine / epinephrine**

> Epinephrine in PNS – for autonomic sympathetic regulation of body actions during fight/flight
↑ heart rate, resp. rate, & BP, and ↓ GI activity
> Norepinephrine in CNS for general arousal

Works by 2 types of muscarinic receptors:

1) **alpha (α) adrenergic receptors *(think α = apple, and you digest an apple)***
- inhibit GI smooth muscle (↓ peristalsis), and gland secretions
- vasoconstrict arteries to GI tract (diverts blood away to brain, heart, & muscles)

2) **Beta (β) adrenergic receptors**

i) β1 adrenergic receptor = found on heart cells to ↑ heart rate (**you have 1 heart = β1)**

ii) β2 adrenergic receptor = found on bronchiole smooth muscle (bronchodilation) ***(you have 2 lungs = β2)***
Also found on arteriole smooth muscle to skeletal muscles (vasodilation for better blood flow)

43. **Table on sympathetic effects of epinephrine and its adrenergic receptors**

*Go over only parts with asterisk!

> Heart has **β1 adrenergic receptor –** to ↑ HR during fight/flight
> GI arteriole smooth muscle has **α adrenergic receptors –** to vasoconstrict & ↓ blood flow during fight/flight
> Skeletal muscle arteriole smooth muscle has **β2 adrenergic receptor –** to vasodilate & ↑ blood flow to muscle
> Bronchiole smooth muscle has **β2 adrenergic receptor –** to bronchodilate to ↑ air flow into lungs

Drugs that are agonists or antagonists (blockers) to these receptors:

> **General B1 & B2 Blocker = Propranolol**. Blocks receptors on heart & bronchioles. Keeps heart rate down (& BP down), but also causes some bronchoconstriction. Good treatment for patient with hypertension and NO respiratory problems (could drive asthma patient into respiratory collapse)

> **B1 specific Blocker = Atenolol. *(It has been altered or attenuated to be specific for B1)*** Blocks only receptor on heart. Good for patient with hypertension (will bring BP down) who also has respiratory problem (Ex. Asthma, COPD) because it won't block B2 receptor and cause bronchoconstriction.

> B1 & B2 Agonist – Isoproteronol. will stimulate both receptors. Will ↑ heart rate & cause bronchodilation. Good for patient with low BP or heart problem and opens up airways (bronchodilation)

> **B1 Agonist = Dobutamine *(makes da heart beat faster).*** Good for patient with low BP and heart problems.

> B2 Agonist = Albuterol. Targets only B2 receptor on bronchioles. Good for patient needs airways opened (asthma)

44. **III) Other Amino-Acid derived Neurotransmitters**

1) Glutamate (glutamic acid)
> always stimulatory in brain (80-90% of brain synapses)
> regulated by astrocyte removal from synapse
> Excess glutamate (glutamate toxicity) is bad – associated with Parkinsons, Alzheimers

2) Glycine = inhibitory in spinal cord ***(is serene in spinal cord)***

3) GABA = inhibitory in brain ***(laid Back in Brain like GABA!)***

45. **Glycine (*remember it is serene in the spinal cord!)***

> **inhibitory** (IPSPs) by opening Cl- channels

> works in spinal cord to inhibit antagonist muscle groups. (When coordinating muscle movement, the primary action muscle is stimulated to contract while antagonist muscle is inhibited by glycine, so that when biceps brachii flexes elbow the triceps brachii doesn't counteract that action by trying to extend elbow>)

Strychnine poisoning – is glycine blocker. It inhibits glycine relaxation of diaphragm. Diaphragm stays contracted and you can't ventilate (die of asphyxiation).

46. **GABA *(Be cool in Brain like GABA)***

> inhibitory in brain (90% synapses) by opening Cl- channels

> Coordinates muscle movement in cerebellum (fine motor control & stored muscle memory patterns)

> Low GABA associated with Huntington's disease (and remember that problems with caudate nucleus of cerebrum also involved.)

QUES: "Why in Valium a treatment for Huntington's disease (also treatment for cholinergic syndrome)?"
ANS = it's a GABA agonist and stimulates muscle relaxation (good for someone with spastic muscle movement)

47. **Nitric Oxide (NO) – a gaseous neurotransmitter**

(see online writing assignment)

> Important for erection

- sexual arousal causes NO release in penile corpus cavernosa
- NO causes production of 2nd messenger **cGMP**
- **cGMP** causes smooth muscle of arteries in corpus cavernosa to relax (**vasodilation**)
- vasodilation of penile arteries causes erection
- after arousal wanes, enzyme breakdown of cGMP by **phosphodiesterase**. Arteries vasoconstrict. Erection ends.

> **Erectile dysfunction (ED) drugs** work as **phosphodiesterase inhibitors**

- they prevent phosphodiesterase from breaking down cGMP. Penile arteries stay vasodilated.
- **phosphodiesterase inhibitor is a cGMP agonist.**