Ch 4: Neurons, Neurotransmitters, and Cell Communication.

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.

See Webpage Neurophysiol. Supplements!

1. Different Types of Neurons and Neuron Anatomy

Anatomy REVIEW!

1. Neurons

   a) Sensory (afferent) neurons = neurons that pick up sensory info and transmit it upwards (afferent path) through spinal cord to brain for analysis.

   b) Motor (efferent) neurons = neurons that transmit a motor command from brain down spinal cord (efferent path) to effectors (muscle cells or glands)

2. Interneurons (in CNS) = strictly in CNS. Relays info. in spinal cord.

3. Neuroglial (Glial) Cells = helper cells of neurons. Different glial cells have different jobs.
1. Different Types of Neurons and Neuron Anatomy

**Fig 4.3**

Central Nervous System (CNS)

- Sensory (afferent) neuron
- Somatic Motor neuron
- Interneuron
- Autonomic Motor neuron

**1. Different Types of Neurons and Neuron Anatomy**

**5 Types of Glial Cells (4 in CNS & 1 in PNS)**

- **Ependymal cells** = CNS cells lining brain ventricles that produce cerebral spinal fluid (CSF)
- **Astrocytes** = CNS cells the function in blood-brain barrier in pia mater.
- **Schwan cells (PNS) & Oligodendrocytes (CNS)** = produce myelin sheaths around axons.
- **Microglia** = CNS Clean-up crew. Phagocytic immune cells the seek out & destroy invaders and remove wastes in CNS.
1. Different Types of Neurons and Neuron Anatomy

- **Dendrites** = picks up sensory info from other neurons.
- **Cell body** = where cell nucleus of neuron found.
- **Axon** = elongated tube that transmits impulse from cell body to synaptic knobs (end of neuron)
- **Myelin sheath** = insulated wrappings around axon that keeps signal from dissipating from axon. [unmylenated axon = 0.5 m/sec VS mylenated axon = 100 m/sec]
- **Nodes of Ranvier** = gaps between myelin sheaths where signal jumps to next node (faster conduction)
- **Synaptic knobs** = neuron end where electrical impulse turned into a neurotransmitter.

- **Multiple Sclerosis – Clinical App Pg 102 and online.**

  - = autoimmune destruction of myelin sheaths of white matter CNS (oligodendrocytes), which creates scar tissue or “scleroses” on the axons.

  It slows transmission of electrical impulses, especially in motor neurons involved in movement.

  Patients have motor (movement) and many other problems.
1. Different Types of Neurons and Neuron Anatomy

**Secretory vesicles** = vesicles in synaptic knobs that store neurotransmitters.

**Neurotransmitter** = message that crosses the synapse to start an action potential in next cell. (Ex. ACh)

**Synapse** = gap between 2 neurons or between a neuron and a muscle cell or gland.

**Pre-synaptic neuron** = neuron before synapse.

**Post-synaptic neuron** = neuron or cell after synapse. Has a receptor for neurotransmitter.

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**Review**

- Types of neural tissue
  - Neurons (sensory/afferent, motor/efferent, and interneurons)
  - Neuroglial (Glial) cells
    - CNS – astrocytes, microglia, ependymal cells, oligodendrocytes
    - PNS – schwann cells, satellite cells
- Anatomy of a neuron
  - Cell body, dendrites, axon, myelin sheath, Nodes, synaptic knobs, synapse, secretory vesicles, neurotransmitters, pre-synaptic neurons, post-synaptic neurons.
2. How Neurons Communicate with Cells

**Neurotransmitter signaling** = a chemical signal binds to receptor on cell membrane (ex. When acetylcholine binds to a receptor), which:

1. **Opens Na+ channel** in membrane, Na+ floods into cell causing action potential (AP) or “depolarization”

2. K+ channels open, K+ exits cell, causes “repolarization”.

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The videos shown in this PowerPoint can be found on the Fox Physiology companion website - see Chemical Synapse video!

http://highered.mheducation.com/sites/0073403628/student_view0/index.html

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**Neurotransmitter signaling:**

1. Pre-synaptic neuron releases neurotransmitter (like ACh) into synapse.

2. Neurotrans. binds to receptor on post-synaptic cell, which opens ion (usually Na+) channels on cell membrane.

3. Na+ flooding into cell causes action potential (AP) to form.

4. AP travels through cell.
Neurotransmitter binding to receptor opens ion channel in cell:

**Binding of neurotransmitter to receptor causes either:**

**A) An Action Potential (Excitatory post-synaptic potential or EPSP)** = neurotransmitter binds to receptor that opens Na+ or Ca+2 channels, & causes an AP to form.

- EPSP can produce **“graded potential”** = *more neurotransmitter* binding to more receptors causes stronger cell response. Also, the less neurotransmitter binding = weaker the cell response.

- EPSP can produce **“summation”** = *Repeated* stimulation by neurotransmitter over time causes cumulative increase in cell response.

**Example:** the increase in heart rate with epinephrine binding to its \( \beta_{1} \) adrenergic receptor on heart muscle cells is due to opening of Na+ and Ca+2 channels!

**B) Inhibits an Action Potential (Inhibitory post-synaptic potential or IPSP)** = neurotransmitter binds to a receptor & opens K+ or Cl- channels, prevents an AP from forming. **Cell stays rested or repolarized.**

**Example:** the decrease in heart rate with ACh binding to its \( \text{muscarinic cholinergic} \) receptors on heart muscle is due to opening of K+ channels!
Regulation of Neurotransmitter Action:

The 2 R's:

1) Receptor types
- neurotransmitter effect depends on what kind of receptor it binds to.
  
  **Either:**
  
  A. Nicotinic (ion-gated) receptor
  B. Muscarinic (G-protein coupled receptor)

2) Removal systems for neurotransmitters (4 removal systems)

1) Receptor types:

A. **Nicotinic (Ion-gated) receptor**

  - Receptor is part of the ion channel (one unit)
  - Binding of receptor directly opens ion channel.
    - Na⁺ channel opens = depolarization (an AP)
  - For acetylcholine (ACh) neurotransmitter
  - Nicotinic cholinergic receptors on skeletal muscle fibers (voluntary movement of skeletal muscles) and some sensory neurons.
1) Receptor types:

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**B. Muscarinic (G-protein coupled) receptor:**
- Receptor separate from ion channel (not one unit)
- Receptor binding actives and enzyme then a G-protein
- G-protein then opens ion (Na+, Ca+2, & K+) channels.
  - Na+ and Ca+2 channel opens = depolarization
  - K+ or Cl- channel opens = repolarization
- For ACh, norepinephrine & epinephrine, & other neurotransmitters
- Found in autonomic motor neurons (involuntary movement of cardiac and smooth muscle, and glands)

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**Ex. Nicotinic cholinergic (ACh) receptors**

Is this neurotransmitter and receptor going to have an EPSP or IPSP response? **EPSP**
Ex. Muscarinic adrenergic (epinephrine, norepinephrine) receptors

Is this neurotransmitter and receptor going to have an EPSP or IPSP response? **EPSP**

Ex. Muscarinic GABA receptor

Is this neurotransmitter and receptor going to have an EPSP or IPSP response? **IPSP**
For ACh and its receptors:

**TABLE 6.4  Effects of Acetylcholine (ACh) in the PNS**

<table>
<thead>
<tr>
<th>Neurons Releasing ACh</th>
<th>Location</th>
<th>Type of ACh Receptor</th>
<th>Response</th>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic motor</td>
<td>Skeletal muscles</td>
<td>Nicotinic</td>
<td>Depolarization, producing action potentials</td>
<td>Muscle contraction</td>
</tr>
<tr>
<td>Preganglionic neurons of ANS</td>
<td>Autonomic ganglia</td>
<td>Nicotinic</td>
<td>Depolarization, producing action potentials</td>
<td>Stimulates postganglionic neurons of the ANS</td>
</tr>
<tr>
<td>Postganglionic parasympathetic neurons</td>
<td>Smooth muscles, glands</td>
<td>Muscarinic</td>
<td>Depolarization, producing action potentials</td>
<td>Contraction of smooth muscles; secretion of glands</td>
</tr>
<tr>
<td>Postganglionic parasympathetic neurons</td>
<td>Heart</td>
<td>Muscarinic</td>
<td>Hyperpolarization, slowing the rate of automatic production of action potentials</td>
<td>Slowing of heart rate</td>
</tr>
</tbody>
</table>

**ACh & Nicotinic Cholinergic Receptors**

- All autonomic ganglia from spinal cord
- For voluntary control of skeletal muscles

**ACh & Muscarinic Cholinergic Receptors**

- Produces autonomic parasympathetic (rest and digest) functions in heart, smooth muscle, & glands.

- Open Na+ channels
  - Na+ enters cell
  - Cell depolarized (AP forms)
  - Excitation
  - Skeletal muscle contracts

- Open K+ channels
  - K+ leaves cell
  - Cell repolarized (rests)
  - Inhibition

- Open Na+ channels
  - Na+ enters cell
  - Cell depolarized (AP forms)
  - Excitation
  - GI tract activity
  - Heart rate
1) Receptor Types:
2) Neurotransmitter Removal Systems:

4 Systems:

i) **Diffusion** = neurotransmitter dissipates out of synapse

ii) **Enzyme Breakdown** = an enzyme breaks down neurotransmitter into its smaller, inactive parts.
   - Ex. **ACh-E** = acetylcholinesterase = enzyme breaks down Ach.
   - **MAO** = monoamine oxidase = enzyme breaks down monoamine neurotransmitters (epinephrine, serotonin, dopamine)

iii) **Glial removal** = removal by astrocytes in CNS.

iv) **Reuptake** = presynaptic neuron takes back neurotransmitter from synapse (back to vesicles).
   - Ex. Prozac, Lexapro, Citalopram are SSRI’s.
   - **SSRI** = selective serotonin reuptake inhibitor. Serotonin builds up in synapse. Serotonin agonist

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**Ex. Enzyme breakdown of neurotransmitter:**

**Acetylcholinesterase (ACh-E)** = enzyme that breaks down ACh in synapses. (Ex. Between somatic motor neurons & skeletal muscles)
Ex. Of ACh release into synapse, binding to receptor on a cell & opening Na+ channel, then breakdown of ACh by ACh-E

**Review**

- Neurotransmitters @ synapse
  - EPSPs & IPSPs are different from APs
  - Graded potential (can undergo summation)
  - No thresh-holds or refractory period

- 2 Ways neurotransmitters regulated:
  - Receptor types (nicotinic & muscarinic)
  - Enzyme removal systems
### 4. Types and Functions of Neurotransmitters

<table>
<thead>
<tr>
<th>+ stimulatory</th>
<th>CNS neurotransmitters</th>
<th>PNS neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>- inhibitory</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**I. Choline-derived:**
- ACh
  - is + or –

**II. Mono-amine derived (catecholamines):**
- norepinephrine/epinephrine (+)
- dopamine
- Serotonin (10% receptors in brain)

**III. “Other” amino acid derived:**
- Glutamate (+)
- Glycine (-)
- GABA (-) (gamma amino butyric acid)

**IV. Soluble gas:**
- nitric oxide (NO)

**I. Acetylcholine (ACh)**

- In both CNS & PNS
- Both excitatory (EPSPs) and inhibitory (IPSPs) – depending …
- Enzyme breakdown by acetylcholinesterase (ACh-E)

**- Involves 2 types cholinergic receptors:**

1) **Nicotinic cholinergic receptor** *(voluntary motor control)*
   - released @ neuromuscular junction (between somatic motor neuron & skeletal muscle cells)
   - excitatory only (EPSPs), opens Na+ channels
   - causes skeletal muscles to **contract!**

2) **Muscarinic cholinergic receptor** *(autonomic Function)*
   - for autonomic sympathetic or parasympathetic regulation of smooth muscles, cardiac muscle, and glands.
   - inhibitory (IPSPs) on cardiac muscle (↓ heart rate & contractile strength)
   - stimulatory (EPSPs) in GI smooth muscle and glands (↑ GI activity)
Neuromuscular junction = found between a motor neuron and a muscle cell.
This example is between a somatic motor neuron & skeletal muscle cell.
Neurotransmitter = ACh
Receptor = nicotinic cholinergic.

I. Acetylcholine (ACh) & neuromuscular junction

Drugs/agents that influence activity of a neurotransmitter:

*Agonist* = substance that can increase the levels or activity of a neurotransmitter.

*Antagonist* = substance that can decrease the levels or activity of a neurotransmitter.
I. Inhibition of enzyme ACh breakdown.

A) Acetylcholinesterase inhibitor (ACh-EI)
- inhibits enzymatic ACh breakdown,
- ACh builds up in synapse with muscles
- causes “cholinergic syndrome”

Question: Is an ACh-EI an ACh AGONIST? OR ANTAGONIST?

Ex. Organophosphate pesticides are ACh-EI's
- Malathion – mosquito control
- Carbamate – general insecticide
- Chlorpyrifos – used in flea & tick meds (banned in USA, 2001)

I. Acetylcholine (ACh) - inhibition of enzyme breakdown.

Ex. Sarin gas (nerve gas) are ACh-EI’s
- Clinical App Pg 113 AND online

Sarin attack in subways:
 Tokyo, Japan 1995

2012 – Syria threatening use of sarin chemical warfare against rebels.
“Clinical Presentation” of someone cholinergic syndrome =

Mnemonic for cholinergic syndrome:

<table>
<thead>
<tr>
<th>DUMBBELSS</th>
<th>Stands for</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Motility of colon smooth muscle.</td>
<td></td>
</tr>
<tr>
<td>Urination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miosis</td>
<td>Constricted pupils</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>HR</td>
<td></td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>Skeletal</td>
<td></td>
</tr>
<tr>
<td>Excitation</td>
<td>Muscle twitches</td>
<td></td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Excess tears</td>
<td></td>
</tr>
<tr>
<td>Salivation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment for cholinergic syndrome from ACh-EI exposure:

To reverse cholinergic syndrome:

**Pralidoxime (2-PAM)** is the cure for cholinergic syndrome – it stops phosphorylation of ACh-E.

To Treat symptoms:

**Atropine** *(Physiology in Health & Disease Pg 119 and online)*
- ACh antagonist
- Blocks ACh muscarinic cholinergic receptors on heart & GI smooth muscles. Slows down GI tract motility.

**Valium (benzodiazepine)** *Clinical App Pg 114 and online*
Works by stimulating GABA inhibition of muscle activity (keeps muscles relaxed).

**Ques:** is Valium a GABA agonist or antagonist?
ACh agonists: Clinical App Pg 110 AND online

**A. Tetanus** = toxin produced by *Clostridium tetani* (found on rusty metal – puncture wound)
- is an ACh agonist
- promotes muscle tetany (“spastic paralysis” OR “hypertonia”)
- **trismus**, or lockjaw
- also a Glycine and GABA antagonist (prevents muscle relaxation).

- prevent w/booster of **tetanus vaccine** every 10 yrs
- suspect exposure, give shot of **tetanus antitoxin**

ACh antagonists: Clinical Applications Pg 110 AND online

Clinical “presentation” of someone w/ACh insufficiency = **hypotonia** = inhibited skeletal muscle activity

**A. Botulism** = toxin produced by *Clostridium botulinum*
> Prevents ACh from leaving presynaptic vesicles
> Causes **flaccid paralysis or hypotonia** (is an ACh antagonist)

**B. Paralytic shellfish poisoning (online)**
> Shellfish harvested during red tide have “saxitoxin”
> Blocks ACh nicotinic cholinergic channels (prevent Na+ entry)
> Prevents skeletal muscle contraction
> **flaccid paralysis or hypotonia** (is an ACh antagonist)

**C. Pufferfish poisoning (online)**
> Fugu fish have “tetradotoxin”.
> Blocks ACh nicotinic cholinergic channels (prevent Na+ entry)
> Prevents skeletal muscle contraction
> **flaccid paralysis or hypotonia** (is an ACh antagonist)
Toxidromes video
(focus on Anticholinergic and cholinergics)

BP = blood pressure
HR = heart rate
R = respiratory rate
T = temperature

**Anticholinergics** = atropine, 2 PAM, benadryl, botulism toxin, saxitoxin, tetrodotoxin.

**Cholinergics** = organophosphate pesticides, sarin gas,

“Disorders” of ACh insufficiency
(ACh antagonist):

**Myasthenia gravis** (Clinical App Pg 113)
AND online
> Autoimmune destruction of ACh receptors.
> Reduced muscle function, weakness, pharyngeal swallowing problems.

**Alzheimer’s disease**
> Loss of ACh producing neurons in brain.
> Excess glutamate production in brain (glutamate toxicity - online)
> Memory problems.
> Treatment involves ACh agonists and glutamate antagonists.
II. Monoamine Neurotransmitters

**Catecholamines**
> dopamine, norepinephrine & epinephrine (all made from tyrosine)

**Serotonin** - made from tryptophan

**Regulated by:**
1) **Reuptake** – primarily with serotonin

**QUES:** What are SSRI’s?

2) **Enzyme breakdown by monoamine oxidase (MAO)** – breaks down dopamine, norepinephrine & epinephrine

II. Monoamine Neurotransmitters – inhibiting enzyme breakdown.

If have low levels of dopamine, serotonin, or norepinephrine can treat with MAO-I’s to buildup monoamines in synapse.

**MAO-I** = monoamine oxidase inhibitor (or a monoamine agonist)

2 types MAO-I’s:
- MAO-I A - agonist to norepinephrine & serotonin
- MAO-I B – agonist to dopamine

*Read Physiology in Health & Disease Pg 119 and online for MAO-I’s*
**II. Monoamine Neurotransmitters**

### Serotonin

- 10% of serotonin receptors in brain
  - regulates memory, moods, emotions, behavior, & hallucinations

- 90% of serotonin receptors in intestines (regulates appetite)

- Insufficient serotonin – associated with depression & obesity

**QUES:**
What can you give to buildup serotonin in synapses?

*Read Physiology in Health & Disease Pg 119 for SSRI’s*

### Dopamine

> Produced by substantia nigra neurons in midbrain (of brainstem)

2 functions:
1) **fine motor control (nigrostantial dopamine system)**
   - Insufficient dopamine – *Parkinson’s – Clinical App Pg 134* and online
     *Neuromuscular disorder*
   - Excess dopamine – “Schizophrenia”

2) **emotional reward system (mesolimbic dopamine system)**
   “addiction”
Cocaine, Dopamine, & Addiction (Clinical App Pg 118 & 159)

AND online

Cocaine is an agonist to dopamine, serotonin, and norepinephrine (excess amount of these)

Presentation reflects this:
- Hallucinations (too much serotonin)
- Muscle tremors and addiction (too much dopamine)
- High energy, fight or flight. (too much epinephrine)

II. Monoamine Neurotransmitters

Norepinephrine/epinephrine

> In PNS for autonomic sympathetic regulation (fight/flight)
   - ↑ heart and respiratory rates, ↓ activity GI tract smooth muscles

> In CNS for general arousal (stimulatory)

Works by 2 types G-protein-coupled receptors (Table 6.3)

1) alpha adrenergic receptors (α-adrenergic)
   - inhibit smooth muscles & glands of GI tract (slow GI activity).
   - vasoconstrict skin and GI tract vessels.

2) beta adrenergic receptors (β-adrenergic)
   i. β1-adrenergic receptor = to increase heart rate.
   ii. β2-adrenergic receptor =
      - bronchodilate airways
      - vasodilate arteries to skeletal muscles.
Table 6.3

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adrenergic Effects of Sympathoadrenal System</th>
<th>Adrenergic Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Constriction of radial fibers of ciliary dilates the pupils</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>Heart</td>
<td>Increase in heart rate and contraction strength</td>
<td>(\beta_1) primarily</td>
</tr>
<tr>
<td>Skin and visceral vessels</td>
<td>Arterioles constrict due to smooth muscle contraction</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>Skeletal muscle vessels</td>
<td>Arterioles dilate due to hormone epinephrine</td>
<td>(\beta_1)</td>
</tr>
<tr>
<td>Lungs</td>
<td>Bronchioles (airways) dilate due to smooth muscle relaxation</td>
<td>(\beta_1)</td>
</tr>
<tr>
<td>Stomach and intestine</td>
<td>Contraction of sphincters slows passage of food</td>
<td>(\alpha_2)</td>
</tr>
<tr>
<td>Intestine</td>
<td>Glucagonisol and secretion of glucose</td>
<td>(\alpha_2)</td>
</tr>
</tbody>
</table>


Adrenergic antagonists & agonists

See Clinical Apps online

Remember??

- **B1 & B2 blocker** = **propranolol**
- **B1-specific blocker** = **atenolol**
- **B1 & B2 agonist** = **isoproterenol**
- **B1 agonist** = **dobutamine**
- **B2 agonist** = **albuterol**

III. “Other” Amino Acid (NOT monoamine) Neurotransmitters:

1. **Glutamate** (a.k.a glutamic acid)
   - Excitatory (stimulant)
   - found in MSG (monosodium glutamate)
   - Stimulatory (EPSPs in 80 – 90% CNS synapses
   - regulated by glial cell removal (astrocytes)
   - excess glutamate (glutamate “toxicity”) associated w/Alzheimer’s (also influenced by ACh)
   & Parkinson’s (also influence by dopamine)

2. **Glycine** – inhibitory in spinal cord. Serene in spinal cord
3. **GABA** – inhibitory in brain
   \[ \text{inhibits skeletal muscles} \]
   \[ \text{brain & other functions} \]
III. “Other” Amino Acid (NOT monoamine) Neurotransmitters:

Glycine

“Serene like glycine in the spinal cord.”

- Inhibitory (IPSPs) by opening Cl- channels
- Primarily in spinal cord
- Coordinates muscle movement by regulating antagonistic muscle contraction & relaxation (Ex. biceps brachii & triceps brachii)

Strychnine poisoning - inhibits glycine relaxation of diaphragm. Diaphragm stays tense, can’t exhale. Die from asphyxiation.

GABA

- Inhibitory (IPSPs) by opening Cl- channels
- Found primarily in brain synapses (90%)
- Coordinates muscle movement in cerebellum (fine motor control and "muscle memory" patterns)
- Insufficient GABA associated w/Huntington’s disease (autosomal dominant genetic disorder).

QUESTION:
Why is benzodiazepam (Valium) a treatment for Huntington’s disease??
IV. Gaseous Neurotransmitters:

**Nitric Oxide (NO)**

*see my writing assignment example online:*

Sexual arousal stimulates parasympathetic response
> causes NO production
> NO activates G protein, guanylate cyclase, & cGMP 2nd messenger
> cGMP causes vasodilation in penile arterioles
> Corpus cavernosa fills w/blood = erection.

Stimulation wanes: enzyme breakdown.
> **Phosphodiesterase** = enzyme that breaks down cGMP and stop vasodilation

**Erectile dysfunction drugs (Viagra, Cialis, Levitra) work by:**
- Increasing NO production
- Phosphodiesterase inhibitor (= cGMP agonist)

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**Review**

- **Types of Neurotransmitters**
  - ACh
  - Monoamines (Dopamine, serotonin, norepinephrine)
  - Amino acid-based (glutamate, glycine, GABA)
  - Nitric Oxide
- Poisons that affect ACh
- Disorders of ACh system
- Disorders of other neurotransmitter systems