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.

*Powerpoint updated 9/6/18*

1. Different Types of Neurons and Neuron Anatomy

Anatomy REVIEW!

1. Neurons

   a) Sensory (afferent) neurons = carry sensory info to CNS.
   b) Motor (efferent) neurons = carry motor commands from brain

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

3. Neuroglial (Glial) Cells = helper cells w/specific function.
1. Different Types of Neurons and Neuron Anatomy

**Fig 4.3**

Central Nervous System (CNS)  

Peripheral Nervous System (PNS)

- **Sensory info ascends spinal cord**
- **Motor info descends spinal cord**
- **Sensory (afferent) neuron**
- **Somatic Motor neuron**
- **Autonomic Motor neuron**
- **Interneuron**

**Announcements:**

> Office hrs this Wed (Sep 12) – Lab reports, questions on lecture material?

> Whatever happens with hurricane Florence, we’ll figure it out!

> Exam 1 is next Wed (Sep 19th) **PRINT out exam outline NOW** (in case of power outages and internet disruption)

> I will be posting my own Notes that go with each PowerPoint for Ch 4, 8, 9, & 10.
5 Types of Glial Cells (4 in CNS & 1 in PNS)

- **Ependymal cells** = cells that produce cerebral spinal fluid that bathes & cushions brain.
- **Astrocytes** = form blood brain barrier, take up and release neurotransmitters.
- **Schwan cells (PNS) & Oligodendrocytes (CNS)** = cells that produce the myelin sheath around neuron axons
- **Microglia** = cells that are macrophages of brain & spinal cord. Seek out & destroy invaders

### 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 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 or gland cell.

Pre-synaptic neuron = neuron before synapse.

Post-synaptic neuron = neuron or cell after synapse. Has a receptor for neurotransmitter.
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”, which stimulates a cell.

2. **K+ channels open**, K+ exits cell, causes “repolarization”, which inhibits cells.
Neurotransmitter signaling:

1. Pre-synaptic neuron releases neurotransmitter (like ACh) into synapse.
2. Neurotrans. binds to receptor on post-synaptic cell, opens ion (usually Na+) channels on cell membrane.
3. Na+ floods into cell, causes action potential (AP) to form.
4. AP travels through cell.

Neurotransmitter binding to receptor opens ion channel:

CAN EITHER:

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

- EPSP can produce “graded potential” = amount of neurotransmitter
  small amt = small response
  great amt = great response

- EPSP can produce “summation” = Repeated (high frequency)
  low frequency = small response
  high frequency = great response

Example: the increase in heart rate with epinephrine binding to its β-adrenergic receptor on heart muscle cells is due to opening of Na+ and Ca+2 channels!
Neurotransmitter binding to receptor opens ion channel:
CAN EITHER:
A) Cause an Action Potential (Excitatory post-synaptic potential or EPSP) = IF neurotransmitter binds to receptor that opens Na+ or Ca+2 channels, & causes an AP to form.
   - EPSP can produce “graded potential”
   - EPSP can produce “summation”

B) Inhibits an Action Potential (Inhibitory post-synaptic potential or IPSP) = IF neurotransmitter binds to a receptor & opens K+ or Cl- channels, prevents an AP from forming.
Example: the decrease in heart rate with ACh binding to its 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 – for voluntary control of skeletal muscle
     B. Muscarinic (G-protein coupled) receptor – for autonomic control of glands, smooth muscle, & cardiac muscle.

2) Removal systems for neurotransmitters (4 removal systems)
1) Receptor types:

A. Nicotinic (Ion-gated) receptor

- For neurotransmitter stimulation of skeletal muscles
- Binding of receptor by ACh causes Na+ channels to open.
- Na+ channel opens causes stimulation in a cell (muscle contracts).

Thus, skeletal muscle cells have nicotinic cholinergic receptors for ACh for voluntary movement.

Some sensory neurons also have nicotinic cholinergic receptors

B. Muscarinic (G-protein coupled) receptor: for autonomic regulation of cardiac & smooth muscle, and glands.

- Receptor binding actives and enzyme then a G-protein
- G-protein then opens ion channels.
  - If Na+ and Ca2+ channel opens = \( \text{stim} / E_{\text{PSP}} \)
  - If K+ or Cl- channel opens = \( \text{inhibit} / E_{\text{PSP}} \)
- For ACh, norepinephrine & epinephrine, & other neurotransmitters
  - If ACh – receptor called muscarinic cholinergic
  - If epinephrine (adrenaline) – receptor called adrenergic receptor
Ex. Nicotinic cholinergic (ACh) receptors

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

Ex. Muscarinic adrenergic (epinephrine, norepinephrine) receptors

Is this neurotransmitter and receptor going to have an EPSP or IPSP response? _____________________________
Ex. Muscarinic GABA receptor

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

For ACh and its receptors:

<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>Na⁺ channel opens</td>
<td>Depolarization, producing action potentials</td>
</tr>
<tr>
<td>Autonomic control</td>
<td></td>
<td>Cholinergic</td>
<td>Muscle contraction</td>
<td>Depolarization, producing action potentials</td>
</tr>
<tr>
<td>Sympathetic parasympathetic</td>
<td>Smooth muscles, glands</td>
<td>Mucoparasympathetic</td>
<td>Response depends ...</td>
<td>Hyperpolarization, slowing the rate of automatic production of action potentials</td>
</tr>
</tbody>
</table>

Branchiole smooth muscle relaxes
GI smooth muscle contracts
ACh & Nicotinic Cholinergic Receptors

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

Open Na⁺ channels
Na⁺ enters cell
Cell depolarized (AP forms)

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

Producible autonomic parasympathetic (rest and digest) functions in cardiac muscle, smooth muscle, & glands.

Ach & Muscarinic Cholinergic Receptors

Open Na⁺ channels
Na⁺ enters cell
Cell depolarized (AP forms)

1) Receptor Types:
2) Neurotransmitter Removal Systems:
4 Systems:
   i) Diffusion = neurotransmitter dissipates out of synapse
   
   Enzyme Breakdown = an enzyme breaks down neurotransmitter into its smaller, inactive parts.
   - Ex. ACh-E = acetylcholinesterase – enzyme that breaks down ACh

   MAO = monoamine oxidase – enzyme that breaks down monoamine neurotransmitters (Ex. Epinephrine, dopamine, serotonin)

   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 =
**Ex. Enzyme breakdown of neurotransmitter:**

Acetylcholinesterase (ACh-E) = enzyme that breaks down ACh in synapses. (Ex. Between somatic motor neurons & skeletal muscles)

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**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>- inhibitory</th>
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<tbody>
<tr>
<td>I. Choline-derived:</td>
<td></td>
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<tr>
<td>- ACh</td>
<td></td>
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<tr>
<td>- is +</td>
<td></td>
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<tr>
<td>II. Mono-amine derived (catecholamines):</td>
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<tr>
<td>- norepinephrine (+)</td>
<td></td>
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<tr>
<td>- dopamine</td>
<td></td>
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<tr>
<td>- Serotonin (10% receptors in brain)</td>
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<td>III. “Other” amino acid derived:</td>
<td></td>
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<tr>
<td>- Glutamate (+)</td>
<td></td>
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<tr>
<td>- Glycine (-)</td>
<td></td>
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<tr>
<td>- GABA (-) (gamma amino butyric acid)</td>
<td></td>
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<tr>
<td>IV. Soluble gas:</td>
<td></td>
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<tr>
<td>- nitric oxide (NO)</td>
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</table>

CNS neurotransmitters

- ACh
- is +

PNS neurotransmitters

- ACh
- autonomic Parasympathetic regul.
- is + or –
- epinephrine (autonomic Sympathetic regul.)
- is + or –
- Serotonin (90% receptors in intestines)
I. Acetylcholine (ACh)

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

- Involves 2 types cholinergic receptors:
  1) Nicotinic cholinergic receptor
     - ACh released @ neuromuscular junction (between somatic motor neuron & skeletal muscle cells)
     - excitatory only (EPSPs), opens ___________ channels
     - causes skeletal muscles to ____________________.

  2) Muscarinic cholinergic receptor

- for autonomic sympathetic or parasympathetic regulation of smooth muscles, cardiac muscle, and glands.
  - inhibitory (IPSPs) on cardiac muscle if ______ channels open.
    (Ex. ↓ heart rate & contractile strength)
  - stimulatory (EPSPs) in GI smooth muscle & glands if ______ or ______ channels open. (↑ GI activity)
Drugs/agents that influence activity of a neurotransmitter:

**Agonist** = substance that can increase the levels or activity of a neurotransmitter, or even its receptor.

**Antagonist** = substance that can decrease the levels or activity of a neurotransmitter, or its receptor.

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. 1: Organophosphate pesticides are ACh-EI’s**
- Malathion – mosquito control
- Carbamate – general insecticide
- Chlorpyrifos (dursban) – used in flea & tick meds
  (banned in USA, 2001)  **DO NOT USE!!!**
Ex. 2: Non-organophosphate pesticide = Pyrethrins
(from Chrysanthemum plant)

- Likely an ACh-EI in cats (DO NOT USE!!!), but not dogs

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

Ex. 3: Sarin gas (biological weapon - 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:

DUMBBELSS - stands for
Diarrhea
Urination
Miosis (constricted pupils)
Bradycardia
Bronchoconstriction
Excitation (muscle twitches)
Lacrimation
Salivation
Sweating

Treatment for cholinergic syndrome from ACh-EI exposure:

To reverse cholinergic syndrome:
Protopam or 2 PAM (brand name) (Pralidoxime active ingredient)
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 & smooth muscles.

Question: is Atropine an ACh agonist or antagonist?

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?
Toxins that are ACh Agonists:
Clinical App Pg 110
AND online

**A. Tetanus** = toxin produced by ______________________
(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

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Toxins that are ACh Antagonists: Clinical Applications online

Clinical “presentation” of someone w/ACh insufficiency =

**A. Botulism** = toxin produced by ______________________
> Prevents ACh from leaving presynaptic vesicles
  (no ACh no skeletal muscle contractions!)
> 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 “**tetrodotoxin**”.
> Blocks ACh nicotinic cholinergic channels (prevent Na+ entry)
> Prevents skeletal muscle contraction
> **flaccid paralysis or hypotonia** (is an ACh antagonist)
“Other Disorders” of ACh insufficiency a.k.a. ACh antagonists:

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 build up 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

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**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

**QUEST:**

What can you give to build up serotonin in synapses?

Read *Physiology in Health & Disease* Pg 119 for SSRI’s
II. Monoamine Neurotransmitters

**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”

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**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 =
       brochodilate 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>Contraction of radial fibers of the iris dilates the pupils</td>
<td>α₁</td>
</tr>
<tr>
<td>Heart</td>
<td>Increase in heart rate and contraction strength</td>
<td>β₁ primarily</td>
</tr>
<tr>
<td>Skin and visceral vessels</td>
<td>Arterioles constrict due to smooth muscle contraction</td>
<td>α₁</td>
</tr>
<tr>
<td>Skeletal muscle vessels</td>
<td>Arterioles constrict due to sympathetic nervous</td>
<td>α₁, β₁</td>
</tr>
<tr>
<td>Lungs</td>
<td>Bronchioles (airways) dilate due to smooth muscle relaxation</td>
<td>β₂</td>
</tr>
<tr>
<td>Stomach and intestine</td>
<td>Contraction of sphincters slows passage of food</td>
<td>α₁</td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogenolysis and secretion of glucose</td>
<td>α₁, β₂</td>
</tr>
</tbody>
</table>

# 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 with Alzheimer’s (also influenced by ACh) & Parkinson’s (also influenced by dopamine)


## 3. GABA – inhibitory in brain

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

**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 or cholinergic syndrome?*

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)
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