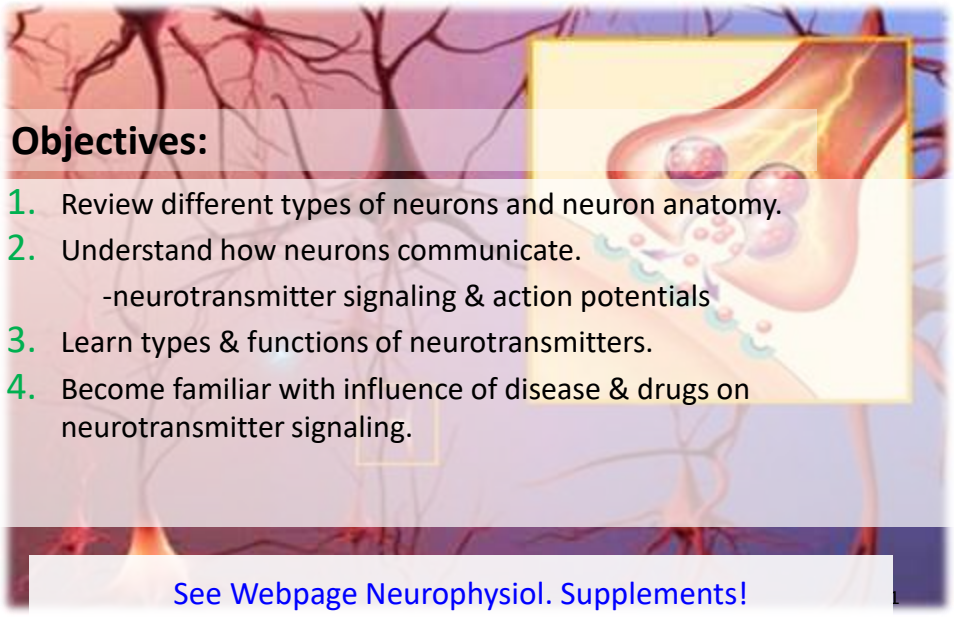
Ch 4: Neurons, Neurotransmitters, and Cell Communication.



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**

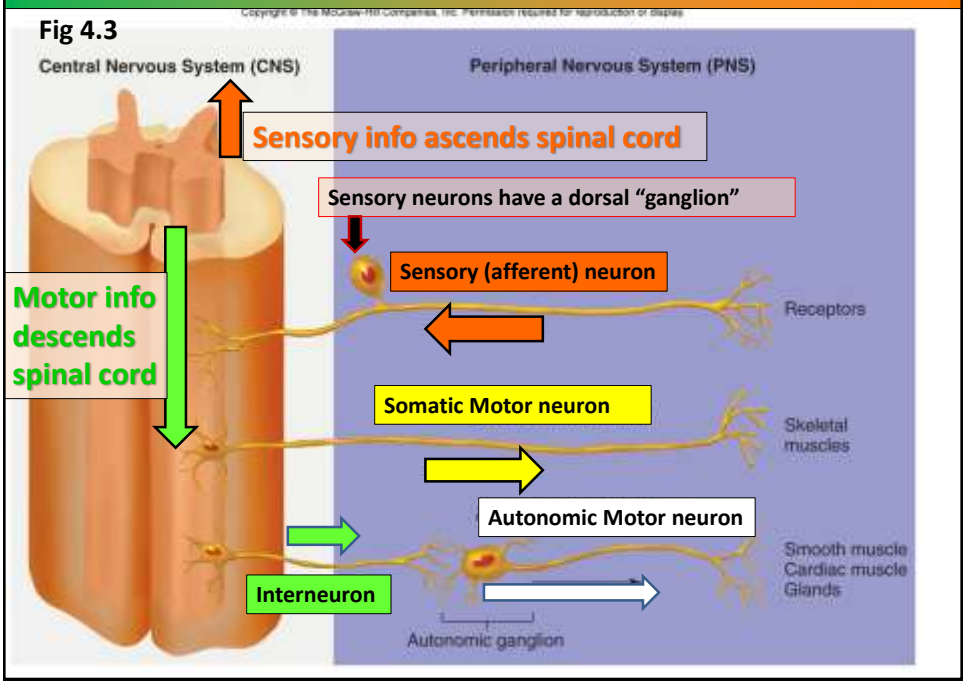
   a) **Sensory (afferent) neurons** =

   b) **Motor (efferent) neurons** =

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

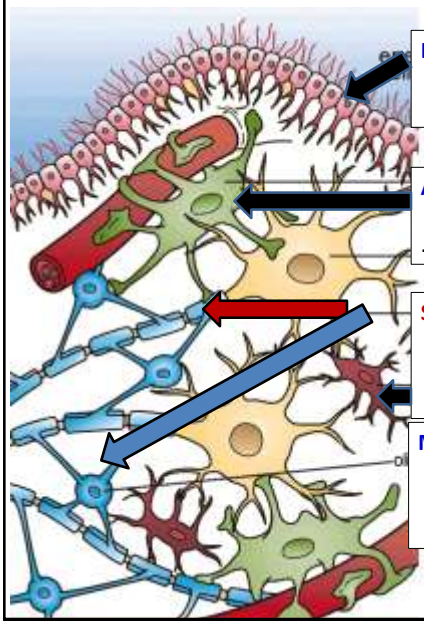
3. **Neuroglial (Glial) Cells** =

1. Different Types of Neurons and Neuron Anatomy



1. Different Types of Neurons and Neuron Anatomy

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



Ependymal cells =

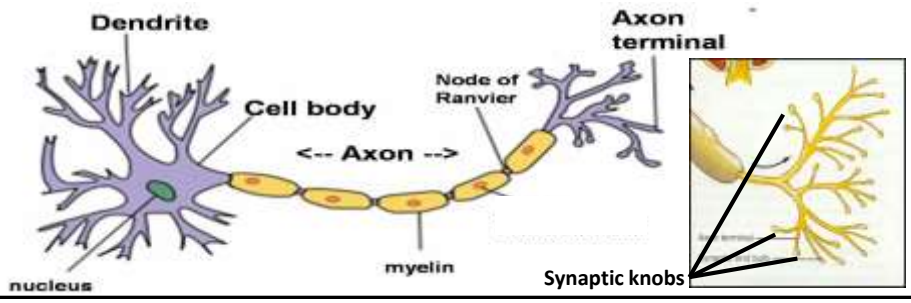
Astrocytes =

Schwan cells (PNS) & **Oligodendrocytes (CNS)** =

Microglia =

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.

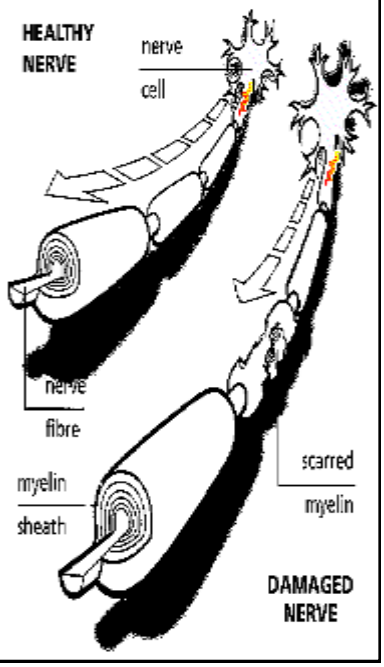


Multiple Sclerosis *– Clinical App Pg 102 and online.*

= 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

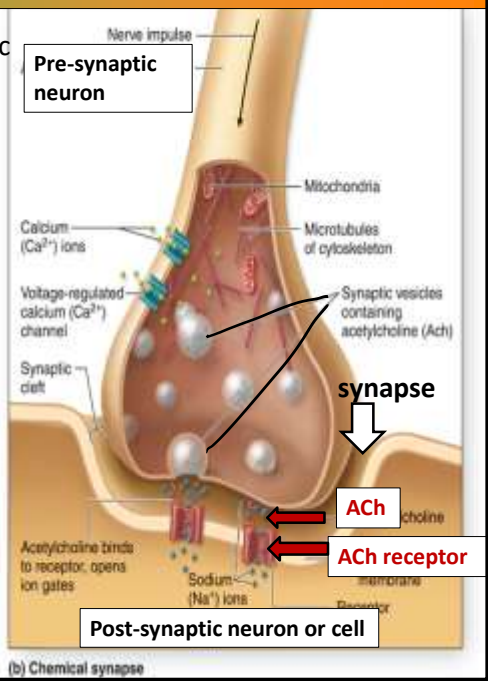
Secretory vesicles = vesicles in synaptic knobs that store neurotransmitters.

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 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 – schwan 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.**

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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.

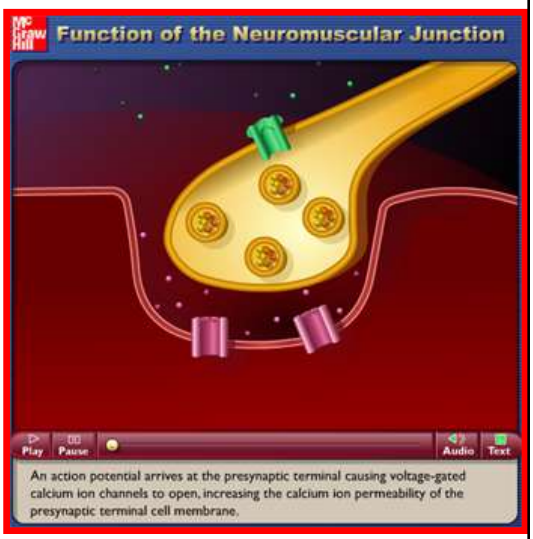
Neurotransmitter signaling:

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"** =
  _____ **=** _____

  _____ **=** _____

- **EPSP can produce "summation"** = *Repeated* (high frequency)
  _____= _____

  _____ = _____

Example: the increase in heart rate with epinephrine binding to its _____ 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 _____ 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
- Binding of receptor by ACh causes _____ channels to open.
- **Na+** channel opens causes _____ in a cell.

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

Some sensory neurons also have nicotinic cholinergic receptors

1) Receptor types:

A. Nicotinic (Ion-gated) receptor

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- **Na+** channel opens causes _____ in a cell.

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:

- Receptor binding actives and enzyme then a G-protein
- G-protein then opens ion channels.
  - IF **Na+ and Ca+2** channel opens = _____
  - IF **K+ or Cl-** channel opens = _____
- For ACh, norepinephrine & epinephrine, & other neurotransmitters
- **Thus, gland cells, and cardiac and smooth muscle cells have muscarinic receptors for involuntary movement.**

Ex. Nicotinic cholinergic (ACh) receptors

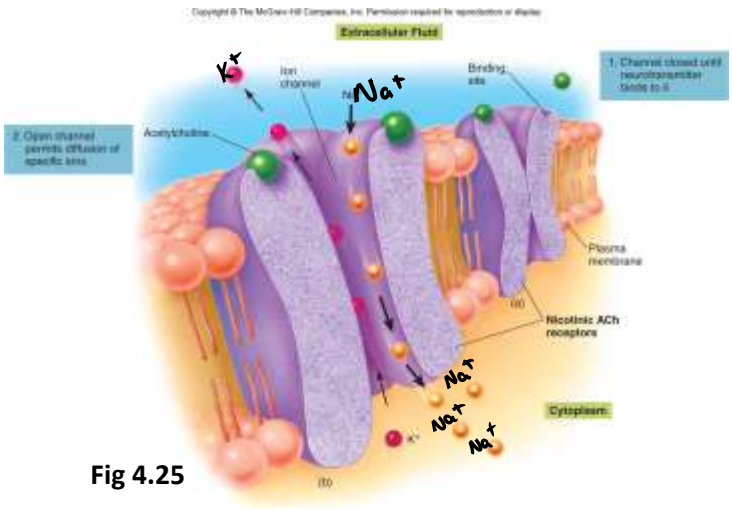


Fig 4.25

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

Ex. Muscarinic adrenergic (epinephrine, norepinephrine) receptors

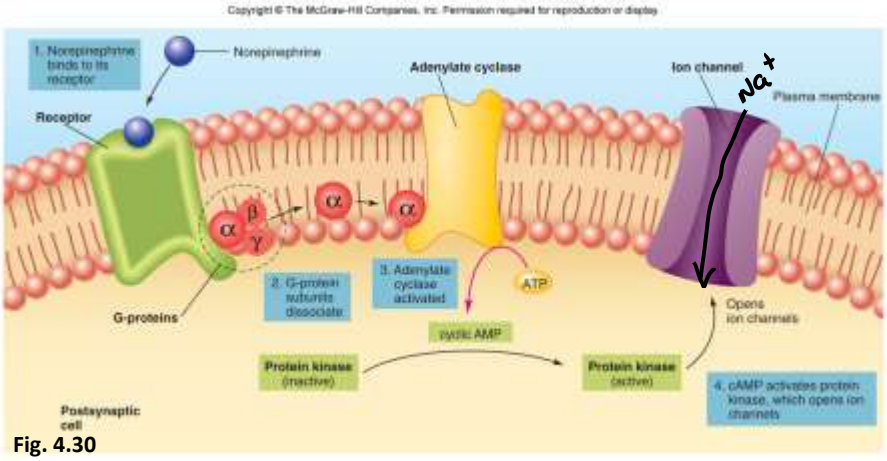


Fig. 4.30

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

Ex. Muscarinic GABA receptor

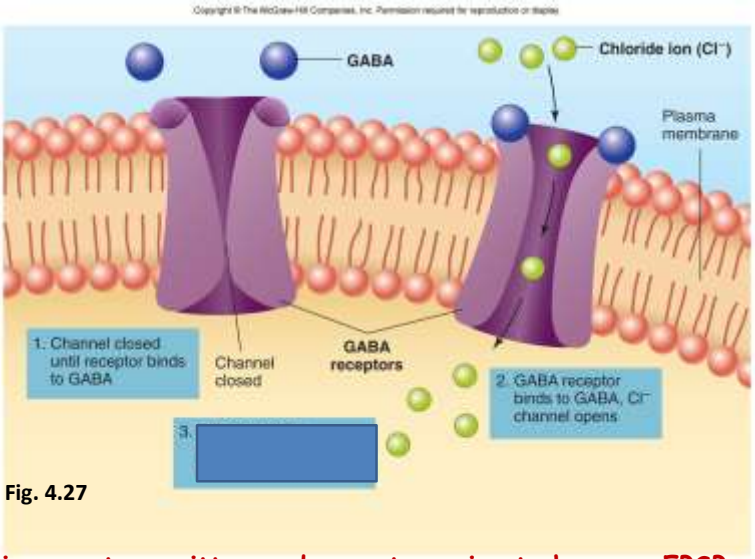


Fig. 4.27

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

For ACh and its receptors:

TABLE 6.4 Effects of Acetylcholine (ACh) in the PNS

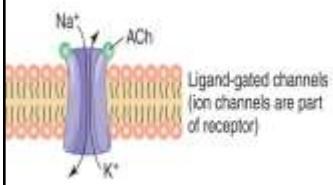
Neurons Releasing ACh	Location	Type of ACh Receptor	Response	Physiological Effect
Somatic motor	Skeletal muscles	Nicotinic	Depolarization, producing action potentials	Muscle contraction
Preganglionic neurons of ANS	Autonomic ganglia	Nicotinic	Depolarization, producing action potentials	Stimulates postganglionic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

ACh & Nicotinic Cholinergic Receptors

Postsynaptic membrane of

> All autonomic ganglia from spinal cord

> For voluntary control of skeletal muscles

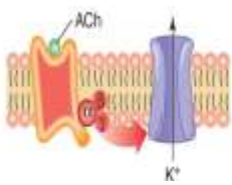


Open Na+ channels
Na+ enters cell
Cell depolarized (AP forms)

Excitation

ACh & Muscarinic Cholinergic Receptors

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

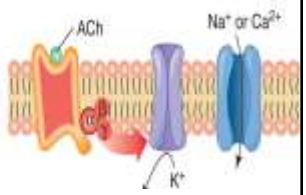


Open K+ channels
K+ leaves cell
Cell repolarized (rests)

(K+ channels opened)

Inhibition

↓ Heart rate



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

(K+ channels closed)

Excitation

↑ GI tract activity

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 it's smaller, inactive parts.**
- Ex. ACh-E =

MAO =

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)

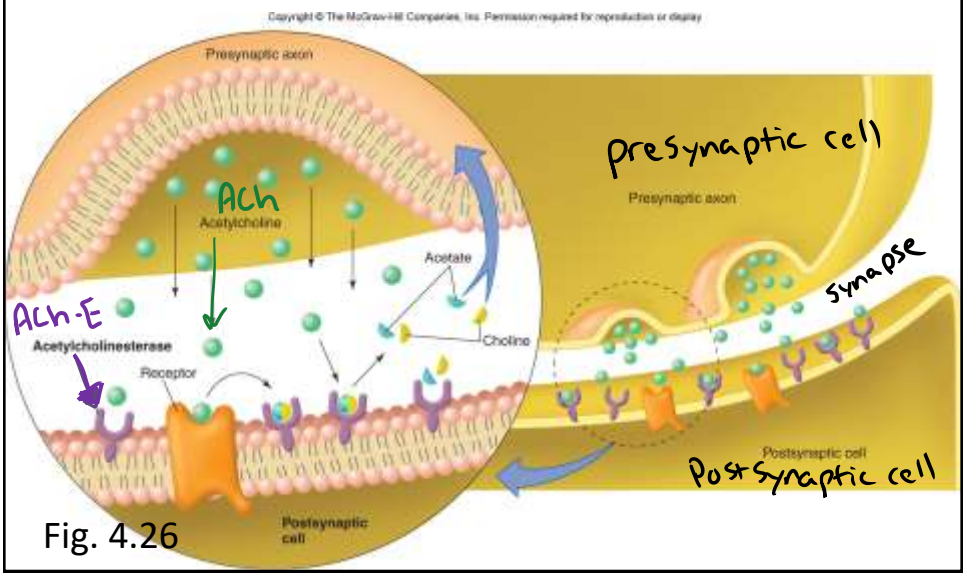
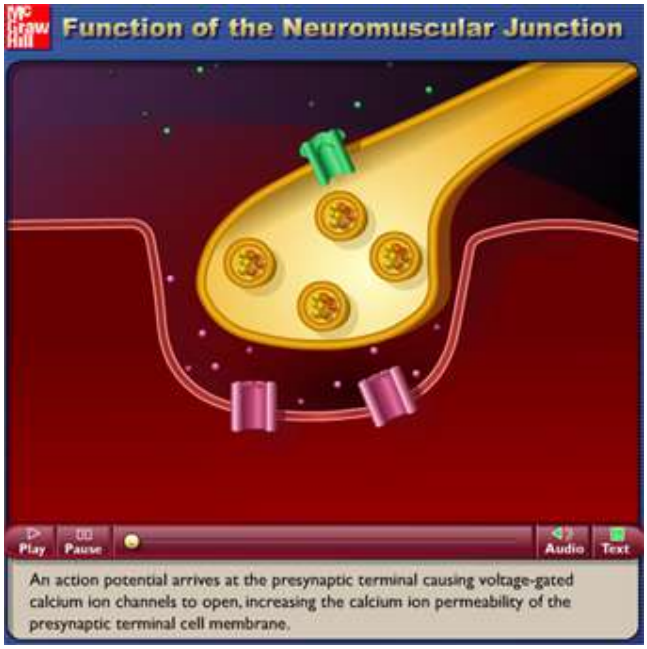


Fig. 4.26

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

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4. Types and Functions of Neurotransmitters

+ stimulatory – inhibitory	CNS neurotransmitters	PNS neurotransmitters
I. Choline-derived:	- ACh is +	- ACh - autonomic Parasympathetic regul. - is + or –
II. Mono-amine derived (catecholamines):	- norepinephrine (+) - dopamine - Serotonin (10% receptors in brain)	- epinephrine (autonomic Sympathetic regul.) - is + or – Serotonin (90% receptors in intestines)
III."Other" amino acid derived:	- Glutamate (+) - Glycine (-) - GABA (-) (gamma amino butyric acid)	
IV. Soluble gas:	- nitric oxide (NO)	

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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

I. Acetylcholine (ACh)

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2) Muscarinic cholinergic receptor

- for autonomic sympathetic or parasympathetic regulation of smooth muscles, cardiac muscle, and glands.
- inhibitory (IPSPs) on cardiac muscle if _____ or _____ 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!!!**

Malathion fogging by truck

Carbamate spraying of crops

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

To Treat symtoms:

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

Tetanus victim

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**

Toxins that are ACh Agonists : *Clinical Applications* online

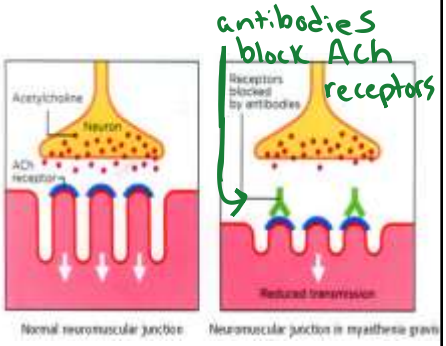
Clinical "presentation" of someone w/ACh insufficiency =

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.

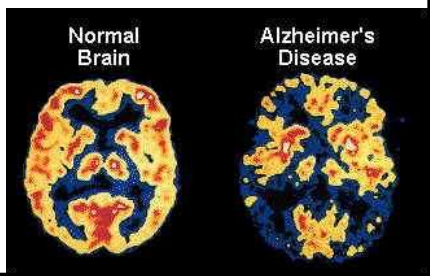
Alzheimer's disease

> loss of ACh producing neurons in brain.

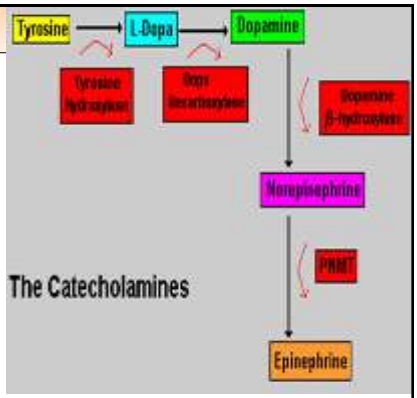
> Excess glutamate production in brain (glutamate toxicity - **online**)

> 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

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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 build up serotonin in synapses?

Read Physiology in Health & Disease Pg 119 for SSRI's

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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

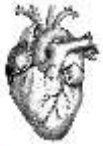
Norepinephrine/epinephrine

> 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.

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Table 6.3 | Selected Adrenergic Effects in Different Organs

Organ	Adrenergic Effects of Sympathoadrenal System	Adrenergic Receptor
Eye	Contraction of radial fibers of the iris dilates the pupils	α_1
Heart	Increase in heart rate and contraction strength	β_1 primarily
Skin and visceral vessels	Arterioles constrict due to smooth muscle contraction	α_1
Skeletal muscle vessels	Arterioles constrict due to sympathetic nerve activity	α_1
	Arterioles dilate due to hormone epinephrine	β_2
Lungs	Bronchioles (airways) dilate due to smooth muscle relaxation	β_2
Stomach and intestine	Contraction of sphincters slows passage of food	α_1
Liver	Glycogenolysis and secretion of glucose	α_1, β_2

Source: Simplified from table 6-1, pp. 143–144, of Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. Eleventh edition. J.E. Hardman et al., eds. 2006. McGraw-Hill.

Adrenergic antagonists & agonists
See Clinical Apps online

Remember??

B1 & B2 blocker =

B1-specific blocker =

B1 & B2 agonist =

B1 agonist =

B2 agonist =

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.
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

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