physiology

premed 2018 - JU

◉ Sheet ○ Slides

Number

13

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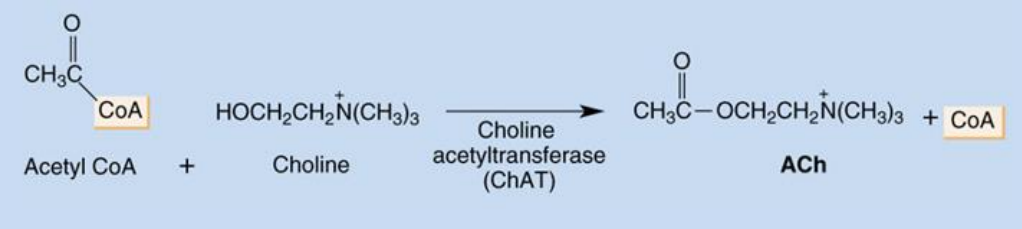
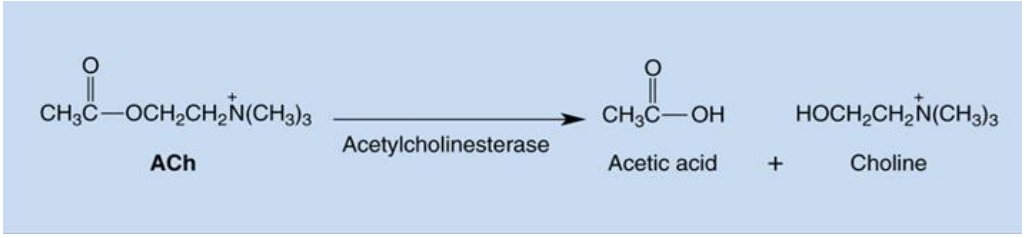
- Recall that **Acetyl Choline** is *synthesized* from the reaction between *Acetyl Coenzyme A (Acetyl CoA)* with *Choline* under the presence of ***Choline acetyltransferase (ChAT)***.



- Recall that **Acetyl Choline** can be *inactivated* by ***Acetylcholinesterase (AChE)*** to form *Acetic acid* and *Choline.*



The life cycle of Acetylcholine (ACh):

1) **Acetylcholine** is *released* from a *vesicle* in the *presynaptic terminal* into the synaptic cleft.

> **NOTE:** In order for a molecule to be considered a ***neurotransmitter***, it must be **released** from the presynaptic terminal.

2) **Acetylcholine (ACh)** binds to its receptors and causes either an *excitatory postsynaptic potential (EPSP)* or *inhibitory postsynaptic potential (ISPS).*
3) **Acetylcholine (ACh)** is inactivated in the *synaptic cleft* by ***acetylcholinesterase*** in the reaction above.
4) Choline can undergo reuptake by the presynaptic terminal via ***secondary active cotransport (symport).***

> Remember that active transport is either **primary** or **secondary**.
> **Primary active transport** *is done by a pump.*
> **Secondary active transport** *is either cotransport or counter-transport*

Distribution of Acetylcholine (ACh):

a) In ***neuro-muscular junction***: Acetylcholine is found in the **junction** between a **skeletal muscle** and its **neuron**, it ***excites*** somatic skeletal muscles.

b) In the ***autonomous nervous system (ANS):*** The **ganglia** of both the ***sympathetic*** and the ***parasympathetic nervous systems.*** ***Postganglionic neuron*** of the ***parasympathetic nervous system*** secretes **acetylcholine** as well. So do a **few neurons** of the ***sympathetic nervous system*** (such as sweat glands and adrenal medulla).

Remember that: the ***sympathetic N.S.*** originates from the **Thoracolumbar vertebrae** while the ***parasympathetic N.S.*** originates from the **Craniosacral vertebrae.**

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c) In the ***central nervous system (CNS):*** it is **widespread** in areas of the CNS such as the **hypothalamus** and **hippocampus**.

- **Acetylcholine (ACh)** can function as either an ***excitatory*** OR an ***inhibitory neurotransmitter***, depending on the organ involved, and according to the **type of receptor.**

  they cause the opening or closing of chemical (ligand) gated channels.

1) **Nicotinic ACh receptors:**
   - They are ***ionotropic membrane receptors*** (coupled to ligand-gated channels, either K^+ or Na^+).
   - Cause either ***depolarization*** or ***hyperpolarization.***
   - Stimulated by **nicotine** (nicotine is the **agonist**)
   - Inhibited by **curare** (curare is the **antagonist**)

     Two types of Nicotinic receptors:
     1) Found in **autonomic ganglia** and hormone-producing cells of adrenal medulla. (N_1)
     2) Found in **motor endplate** between the neuron and skeletal muscles. (N_2)

2) **Muscarinic ACh receptors (has two types):**

   a) Muscarinic subtype receptor (M_1):

   - Metabotropic receptor
   - Uses signal transduction (second messengers)

     e.g. IP_3 , DAG, cytosolic Ca^{2+} which are produced by ***Phospholipase C***
   - It is cell specific. It decreases heartrate and increase effectivity of smooth muscle in intestines (heartrate ↓, smooth intestinal muscles ↑)

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*If someone is suffering from abdominal cramps (مغص). We give him something that **blocks** acetylcholine. e.g. acetylcholinesterase*

- Stimulated by **Muscarine** (Muscarine is the **agonist**)
- Inhibited by ***Atropine.*** (Atropine is the **antagonist**)
- It is found in:
  i. All **parasympathetic target organs**.
  ii. Some **sympathetic targets** (endocrine sweat glands → increasing sweating, skeletal muscle blood vessels → vasodilation).

Mechanism:

1) Acetylcholine (ACh) binds to the metabotropic M_1 receptor stimulating an enzyme called ***phospholipase C (which breaks down phospholipids).***
2) Phospholipase C produces ***diacylglycerol (DAG)*** and ***inositol triphosphate (IP_3)***
3) Inositol triphosphate (IP_3) binds to the ER causing calcium release.

DAG=Glycerol (3 carbon chain) + 2 fatty acids

   - *We now have a high concentration of **DAG** and **cytosolic calcium**.*
   - Calmodulin will not excite its protein kinase unless calcium is bound to it.
4) Calmodulin + Calcium = activation of Protein Kinase B, which phosphorylates a channel (either K^+ or Na^+) causing its opening.

b) Muscarinic subtype (M_2) :

- Found in ***central nervous system (CNS)***
- Uses a *signal transduction system* via **G-Proteins**. By either **opening** K^+ channels or **decreasing** cAMP levels (Inhibitory effect).
- Stimulated by **Muscarine** (Muscarine is the **agonist**)
- Inhibited by ***Atropine.*** (Atropine is the **antagonist**)

We have two types of acetylcholine agonists (***Cholinergic Agonists***): Increase the response of the effector cells that are innervated by cholinergic neurons.

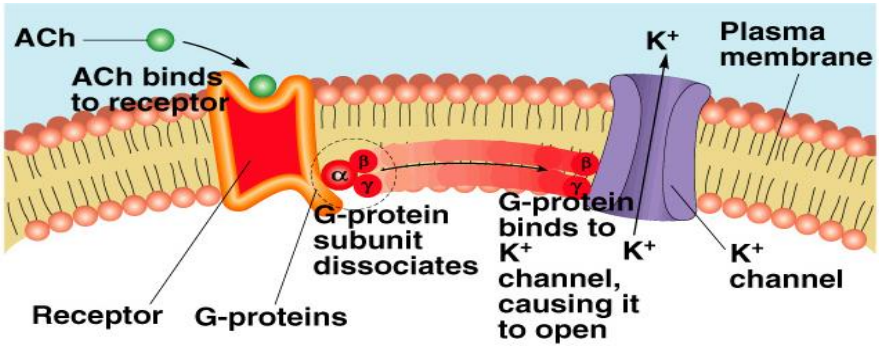
a) Direct agonists
   i. *Muscarine* for muscarinic receptors
   ii. *Nicotine* for nicotinic receptors
b) Indirect agonists (prolong the action of acetylcholine)
   i. Acetylcholinesterase (AChE) inhibitors

Individuals who suffer from depression have low concentration of serotonin. And they are treated by Prozac which prevents serotonin reuptake.

In contrast, we have one type of acetylcholine antagonists (**Cholinergic Antagonists**):

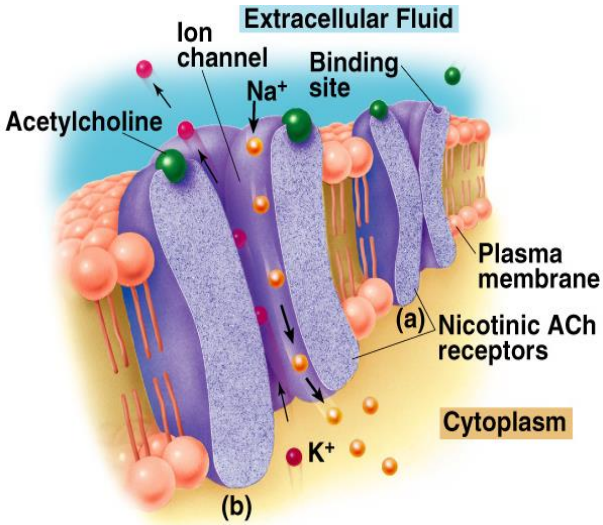
a) <u>Direct antagonists</u>
   i. *Atropine* for muscarinic receptors
   ii. *Curare* for nicotinic receptors

One of Pesticides components is organic phosphate, which is an *agonist* for acetylcholine. Therefore, they lead to abdominal cramps and constriction of the pupil (miosis).



Muscarinic Receptor

Nicotinic receptor



Monoamines

- They are derived from amino acids. They act as neurotransmitters and can be classified as follows:
  a) <u>*Catecholamines:*</u> (derived from **tyrosine**)
     i. **Dopamine (DA)**
     ii. **Norepinephrine (NE)**
     iii. **Epinephrine (E)**

b) *Idonlamines:*

i. **Serotonin** (derived from **tryptophan**)

ii. **Histamine** (derived from **histidine**)

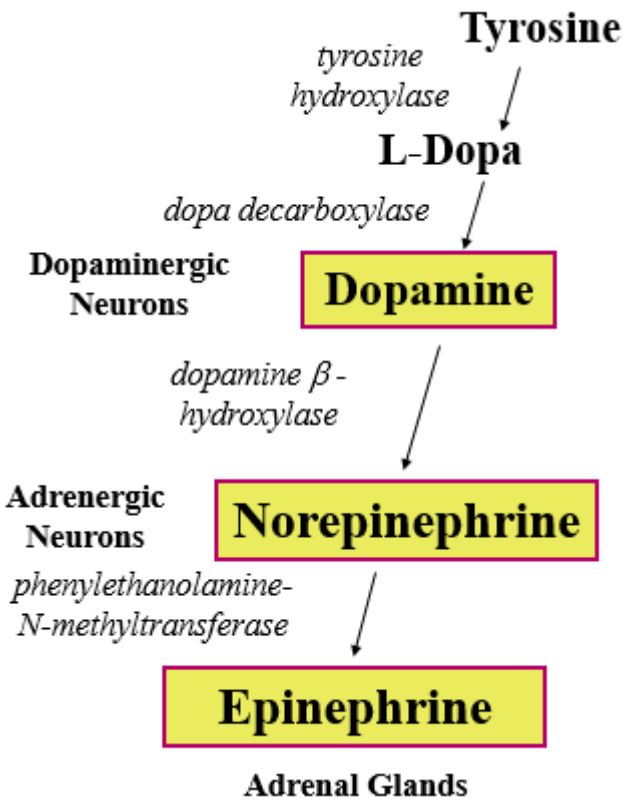
Notes:

Hydroxylation is addition of OH^-

Decarboxylation is the removal of COO^-

Norepinephrine (Nor): doesn't contain a methyl group.

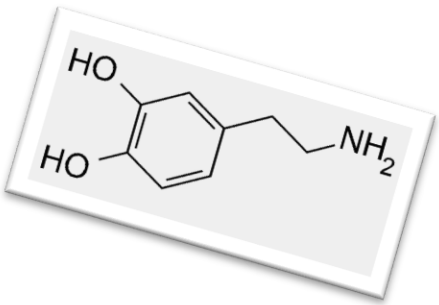
So, addition of a methyl group to norepinephrine gives epinephrine.



(1) Dopamine as a neurotransmitter {EXTRA INFO}:

It is used in some brain neurons that are active during the following:

- Emotional responses
- Addictive behaviours
- Pleasurable experiences



Dopamine-releasing neurons help regulate:

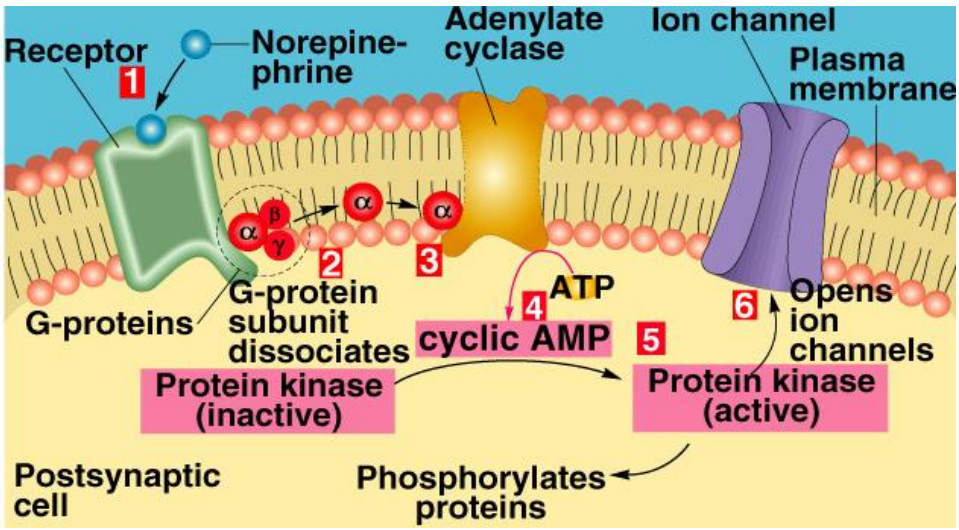
- Skeletal muscles tone
- Some aspects of movement due to contraction of skeletal muscles

Parkinson's disease:

Occurs due to the deficiency and degeneration of neurons that release dopamine causing muscular stiffness and muscles may alternately contract and relax (Pill rolling). We treat it by giving the patient L-Dopa since dopamine cannot enter the brain.

(2) Norepinephrine (NE) as a neurotransmitter:

- Found in 2 locations which are:
  a) In the PNS:
     I. Smooth muscles of blood vessels, causes **vasoconstriction** and therefore **increases** blood pressure
     II. Smooth muscles of gastrointestinal tract (GI) → **Relaxation** (inhibition)
     III. Cardiac muscles → **increases** the heartrate and the force of contraction
     IV. Glands → **increases** sweating and **inhibition** of digestive enzyme secretion.



Note:

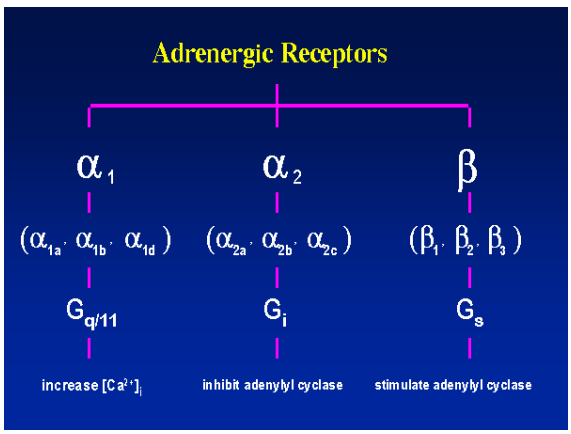
Phosphorylation does not always mean activation; it can cause activation or inhibition of the protein.

Adrenergic receptors:

{EXTRA INFO}: ''Integral proteins are activated by norepinephrine (as a NT or hormone) and epinephrine (as a hormone).'' They are 3 types and these 3 are divided into 3 "subtypes" as the chart illustrates.

The difference between epinephrine (E) and norepinephrine (NE) is the methyl group on the epinephrine.

- Norepinephrine is found more on α adrenergic receptors whereas epinephrine is found more on β receptors



"All our dreams can come true, if we have the courage to pursue them".

-Walt Disney

α_1 receptor:

- It is stimulated by ***norepinephrine (NE)*** and ***epinephrine (E).***
- It is causes **constriction** in the following locations:
    i. Blood vessels of the skin → ***vasoconstriction***
    ii. Mucosa
    iii. Abdominal viscera
    iv. Kidneys
    v. Salivary glands → ***decrease*** *in salivation*
    vi. Sphincter muscles of the stomach and urinary bladder
- It also causes **pupil dilation** due to the **contraction** of the radial muscle of the eye iris.

REMEMBER!
The parasympathetic and the sympathetic nervous systems do opposite actions to one another.
The sympathetic is responsible for the "Fight or flight" actions. (e.g. dilation of the pupil)
Whereas the parasympathetic is responsible for the "Rest and Digest" actions. (e.g. constriction of pupil)

α_2 receptor:

- It is stimulated by ***norepinephrine (NE)*** and ***epinephrine (E).***
- Membrane of adrenergic axon terminals (**pre-synaptic receptors**)
- **Inhibition** of norepinephrine (NE) release (autoreceptor)
- It is found in the following:
    i. In blood platelets → **promotes (increase)** blood clotting
    ii. In pancreas → causes **decreased** insulin secretion

β receptors:

- They are only stimulated by **epinephrine** and they are dispersed along different organs and serve different functions from one another according to its organ.

β_1 receptor:

a) Found mainly in **heart muscle cells**.
b) **Increases** heartrate and strength

β_2 receptor:

a) In **lungs** and most other **sympathetic organs** → Causes **bronchodilation** in order to **get more oxygen**.

b) **{EXTRA INFO}:**In blood vessels serving the heart (coronary vessels) → causes **dilation** to **transport more oxygen**.

c) In **smooth muscles of the gastrointestinal tract** and **pregnant uterus**. → causes **relaxation (inhibition)**

<u>β_3 receptor:</u>

a) Found in **adipose tissue**

b) Stimulates **lipolysis**

(3) <u>Amino acids as neurotransmitters:</u>

a) **Excitatory** amino acids (**EAA**)

- produces **excitatory postsynaptic potential (EPSP)** by opening Na^+ channels.
- e.g. **glutamate (glutamic acid)** and **aspartate (aspartic acid).**

b) **Inhibitory** amino acids (**IAA)**

- produces **inhibitory postsynaptic potential (IPSP)** by opening K^+ or Cl^- channels.
- e.g. **Gamma-amino-butyric acid (GABA)** → most **common NT** in **CNS.**

Glycine → used in spinal nerves.

(4) <u>Polypeptides as neurotransmitters:</u>

i. **Cholecystokinin (CCK)** → promotes **satiety** (الشَّبَع)

ii. **Substance P** → major neurotransmitter in **sensations of pain**

(5) <u>Monoxide gases:</u>

i. **Nitric oxide (NO)**

- Exerts its effects by stimulating **cGMP**
- Involved in **vasodilation** and **relaxation of smooth muscles.**
- Involved in **memory** and **learning.**

ii. **Carbon monoxide (CO)**

- Stimulate **production** of **cGMP** within **neurons.**
- Increases odor adaptation (adaptation of smell) in olfactory neurons.
- May be involved in **neuroendocrine regulation** in **Hypothalamus**

Sensory receptors:

The doctor goes briefly through sensory receptors. So the detailed version of sensory receptors will be found in the next sheet إن شاء الله

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- Sensory receptors are organs that are responsible for the **sensation** of **touch**, **sensation** of **pressure**, **sensation** of **pain**, and **sensation** of **temperature**.
- Sensory receptors are **NOT proteins**
- Sensory receptors **convert** any type of stimulus (energy) to **electrical energy** in the form of **action potentials**. A process called **transduction.**
- The receptor determines whether the stimulus is a stimulus of pain, pressure, touch etc... (They are specific for their own stimuli)
- They are classified according to *modality* (stimulus they induce)
    - Mechanoreceptors → Receptors for detecting ***touch*** and ***pressure.***
    - Thermoreceptors → Receptors for detecting ***change in temperature.***
    - Nociceptor → Receptors for detecting ***pain.***
    - Electromagnetic (Photoreceptors) → detect ***light*** (Rods and Cones)
    - Chemoreceptors → detect ***taste, smell.***
- They are also classified according to *location.*
    - Exteroceptors → located at or near body surface
    - Interoceptors
    - Proprioceptors → sense of ***position***

SHORT QUIZ

1- α1, α2, and β receptors are all associated with:

a-Skeletal muscles movement.

b-Sympathetic effects.

c-Parasympathetic effects.

d-All of the above.

2- Tachycardia is a case where the heart rate **exceeds** the normal state, which of the following could be given to treat this case?

a-L-dopa.

b-Acetylcholine esterase.

c-Atropine.

d-none of the above.

3- Ahmed eats all the time and he's never full, he went to a doctor and was given pills that unfortunately **worsened** his case. What do these pills contain?

a-Peptidase.

b-Cholecystokinin.

c-Carbon monoxide.

d-Acetylcholine esterase.

4- Having more β3 receptors could potentially lead to:

a-Higher consumption of Acetylcholine.

b-Less insulin secretion.

c-Higher capability for Acetylcholine synthesis.

d-None of the above.

Answers

1-B. α1, α2, and β are all adrenergic receptors associated with Epinephrine and Norepinephrine, which are responsible for most sympathetic effects.

2-D. To have a slower heartrate we need acetylcholine, so none of the choices work.

3-A. Cholecystokinin (CCK) is a neuro**peptide** responsible for satiety, giving this case a peptidase can lead to the degeneration of CCK and thus worsening the symptoms.

4-C. β3 receptors are located in adipocytes and stimulate lipolysis. Lipolysis is the main source of Acetyl CoA which is required in the synthesis of Acetylcholine.

Remember!!

Physiology is NOT a memorizing science. It depends mainly on the understanding and comprehending the topics carefully and using logic.

The examples included in this sheet are NOT for memorizing. They merely serve the purpose of getting the idea across to the reader.

NOTE THAT: {EXTRA INFO} means that the following statement was not said by the professor during lecture, and It was added from other sources such as 'Sheets of Medical year 2017' so please have a look at them as they are helpful in getting the idea or the bigger picture, or just having a nice piece of information for your life هَلُمَّ جَرًّا.

GOOD LUCK !!