Biochemical Neuron
BCH 575

Dr. Nat. Med Arwa Khayyat

Biochemistry department

Building 5 Room 226

Email: aalkhyyat@ksu.edu.sa

Cours outline……..

1. Neurotransmitters
2. Neuronal Signal transduction
3. Blood brain barrier(BBB)
4. Brain Metabolism
5. Neurodevelopment disorder
6. Open discussion topics

Neurotransmitters
Chapter 6

Neurotransmitters (NTs)

- Neurotransmitters are endogenous chemicals that allow neurons to communicate with each other throughout the body.
- They enable the brain to provide a variety of functions, through the process of chemical synaptic transmission.
- These endogenous chemicals are integral in shaping everyday life and functions
- Different types of cells secrete different neurotransmitters.
- Each brain chemical works in widely spread but fairly specific brain locations.

Dale’s principle

- **Dale's principle** is a rule attributed to the neuroscientist Henry Hallett Dale(1935)
- The convention established by Dale classifies neurons into mutually exclusive groups by neurotransmitter (cholinergic, glutamatergic and GABAergic). The idea that a neuron has only one neurotransmitter is often called Dale’s principle .

- Many peptide-containing neurons violate Dale's principle because these cells usually release more than one neurotransmitter: an amino acid or amine and a peptide.

- When two or more transmitters are released from one nerve terminal, they are called. **co-transmitters.**

- Many examples of neurons with co-transmitters have been identified in recent years, including some that release two small transmitters (e.g., GABA and glycine). Nonetheless, most neurons seem to release only a single amino acid or amine neurotransmitter, which can be used to assign them to distinct.

Classes of transmitters

- **Most of the known neurotransmitter molecules are either**

(1) Amino acids

(2) Amines

(3) Peptides

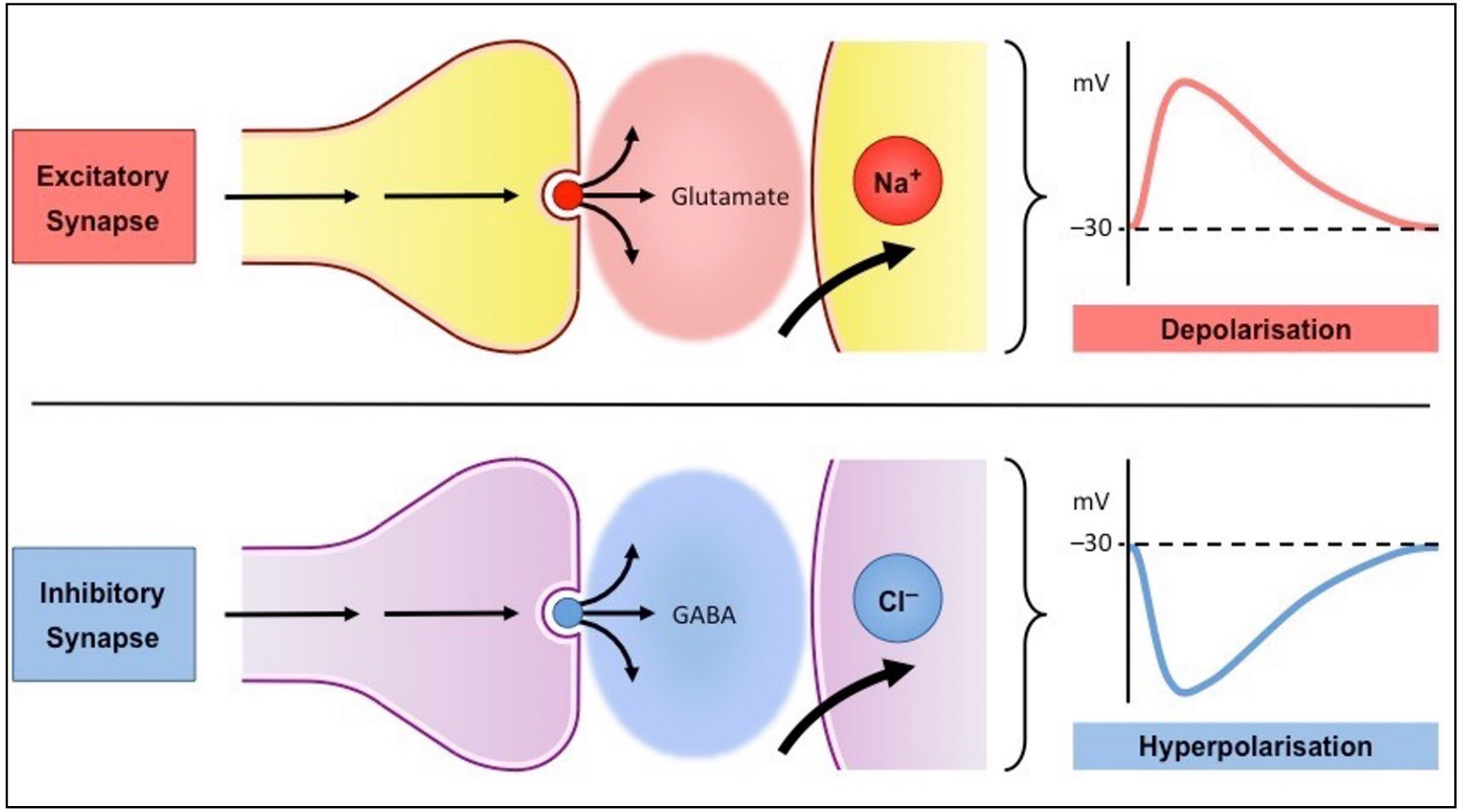
- ACh is one exception, but it is derived from acetyl CoA, a ubiquitous product of cellular respiration in mitochondria, and choline, which is important for fat metabolism throughout the body.
- Amino acid and amine transmitters are generally each stored in and released by different sets of neurons.

Types of Neurotransmitters:

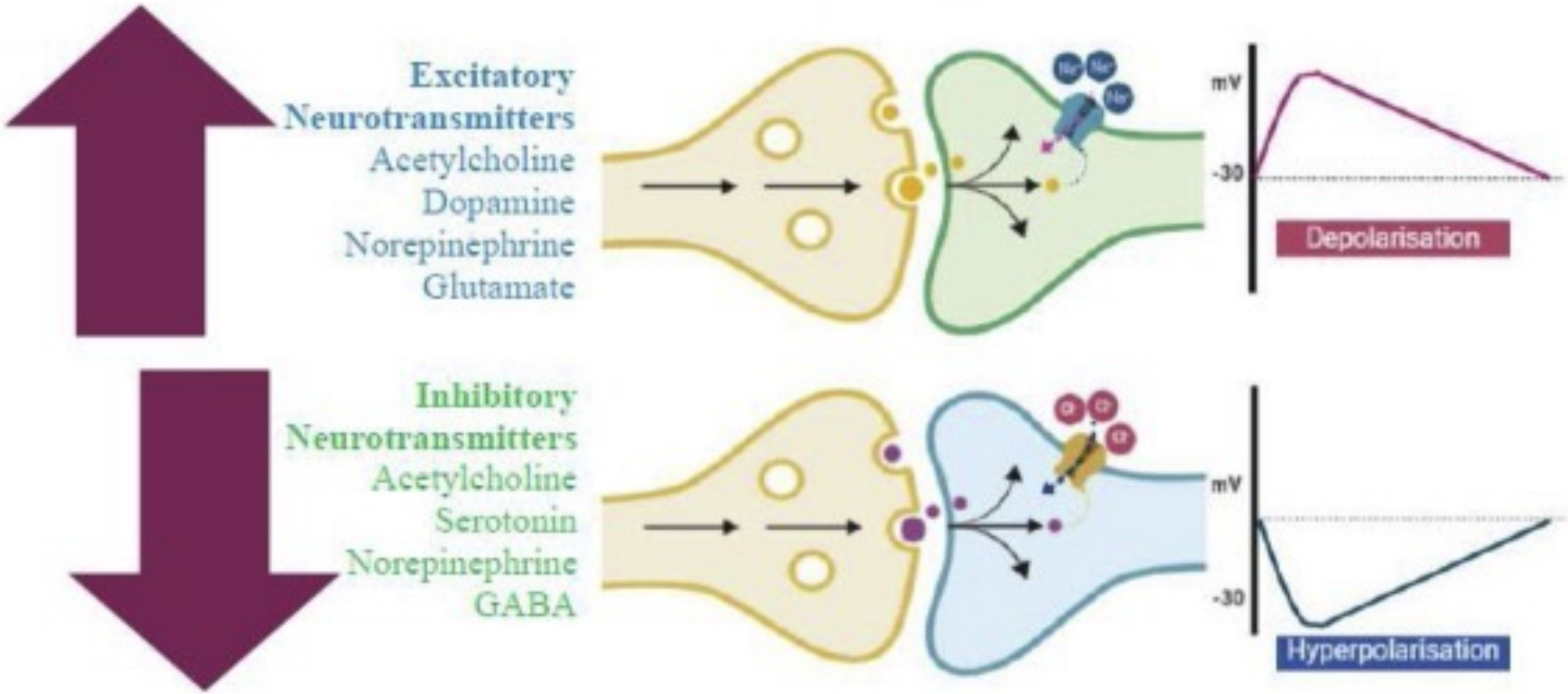
- There are two kinds of neurotransmitters – INHIBITORY and EXCITATORY.
- **Excitatory** neurotransmitters increase the likelihood of postsynaptic neurons depolarization and generation of an action potential (they are what stimulate the brain).
- **Inhibitory** neurotransmitters reduce the likelihood of postsynaptic neurons depolarization and generation of an action potential.

. Those that calm the brain and help create balance are called inhibitory.

- Inhibitory neurotransmitters balance mood and are easily depleted when the excitatory neurotransmitters are overactive.



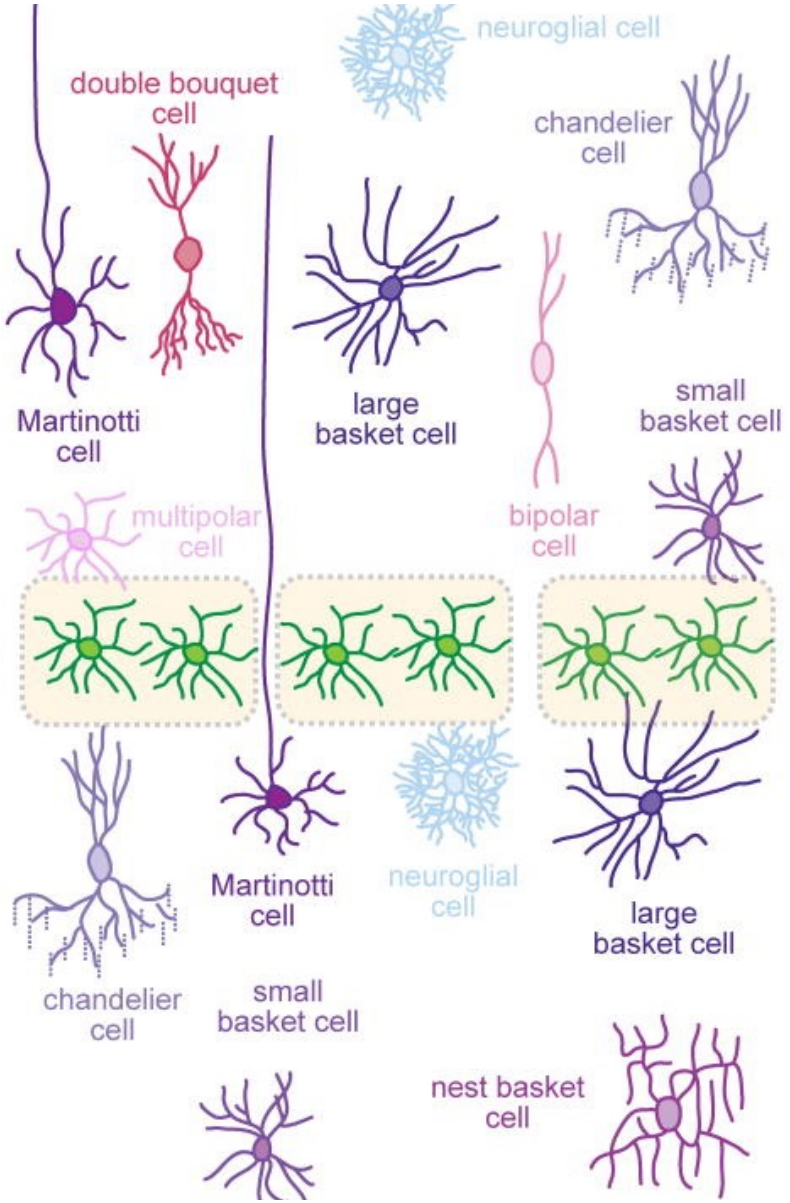
Example of an excitatory neurotransmitter is glutamate, whereas GABA is an inhibitory neurotransmitter.



Recent advancement in nanosensors for neurotransmitters detection: Present and future perspective - ScienceDirect

EXCITATORY	INHIBITORY
Neurons that relase nurotransmitters to make the post synaptic neuron generate an action potential	Neurons that relase nurotransmitters to make the post synaptic neuron less likely to generate an action potential
In cerebral cortex are Pyramidal neurons	3 types in cerebral cortex : stellate neurons, chandelier neurons and basket neurons
Project either locally or long range projections between different cortical areas	Project within localized region that are small
Make the post synaptic neuron depolarize	Make the post synaptic neuron hyperpolarize
Information flow can be either unidirectional or bidirectional	Responsible for the the control of bidirectional excitation
Responsible for the transmission of nerve signals stimulsting the brain	Responsible for the counterbalance the action of excitatory neurons
Causes open sodium channels	Causes open chloride channels

Cerebral Cortex Neurons : Pyramidal neurons, Stellate neurons, Chandelier neurons and Basket neurons



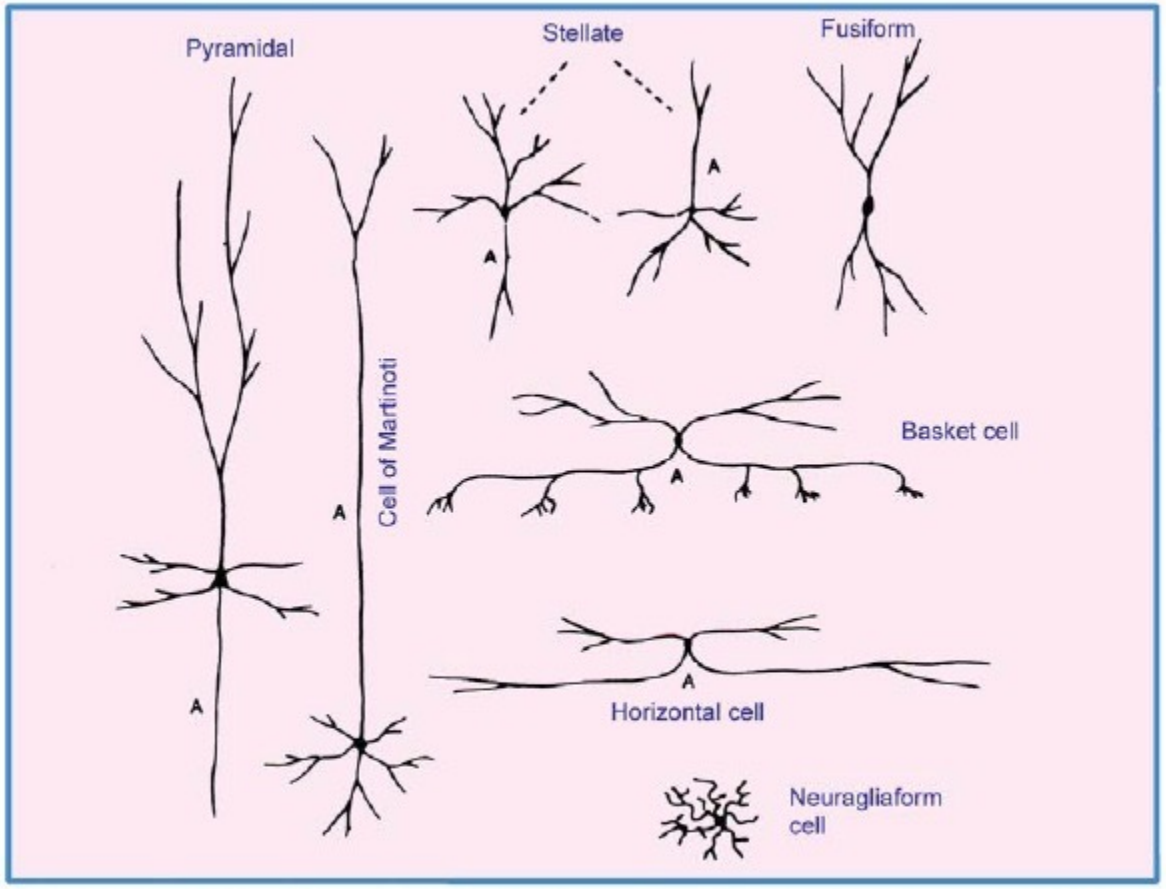


Fig. 15.1. Some of the cell types to be seen in the cerebral cortex. A=axon. Other varieties not shown include bipolar cells, chandelier cells and double bouquet cells.

- In molecular level, when an excitatory or an inhibitory neurotransmitter binds to its postsynaptic receptor **called Postsynaptic Potential**
- Ionotropic receptors are one class of postsynaptic receptors that incorporate an ion channel within their molecular structure.
- When a neurotransmitter binds to its postsynaptic receptor it causes ion channels to open, or close.
- This movement of ions across the neuronal membrane generates an electrical current, the postsynaptic current (PSC), which in turn changes the postsynaptic membrane potential to produce a postsynaptic potential (PSP).

•Postsynaptic potential (PSP) types:

1. Excitatory postsynaptic potentials (EPSPs)
2. Inhibitory postsynaptic potentials (IPSPs)

Excitatory postsynaptic potentials (EPSPs) increase the likelihood of a postsynaptic action potential occurring and are induced by excitatory neurotransmitters.

Excitatory Synaptic Signaling(Example: Glutamate)

Glutamate exerts its effects via ionotropic receptors such as AMPA or NMDA receptors as well as metabotropic receptors – mGlu1-mGlu8.

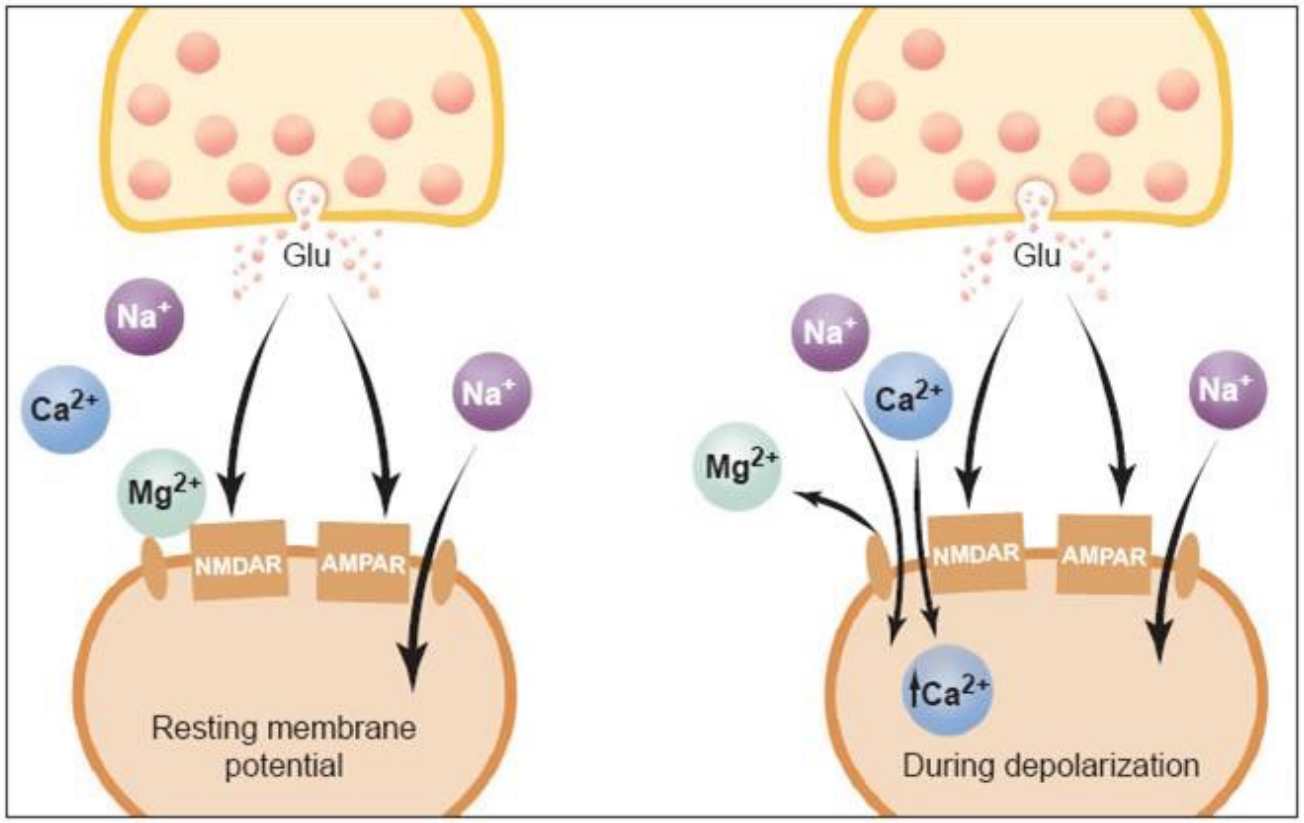
When glutamate molecules binding to an AMPA receptor, its integral ion channel opens and ions flow across the postsynaptic neuronal membrane.

AMPA receptor is a **non-selective cation channel**, which is mostly permeable to sodium and potassium ions. The direction and magnitude of ionic flow across the membrane depends on the postsynaptic membrane potential and concentrations of sodium and potassium across the membrane.

After the opening of an AMPA ion channel, **sodium ions** will flow into the postsynaptic cell according to their concentration gradient. They will be also 'attracted' into the neurons by the negative charge of the postsynaptic neurone.

as the postsynaptic membrane potential is close to the potassium **equilibrium potential** the driving force for the **potassium ions** will not be very significant – the potassium ions will be leaving the cell according to their concentration gradient

the electrochemical gradient driving sodium ions into the cell is stronger than the gradient driving potassium ions out of the cell. Consequently, the resultant sodium current leads to changes in the membrane potential, an excitatory postsynaptic potential (EPSP), which makes the membrane potential more positive. Hence, EPSP brings membrane potential closer to the threshold needed for an action potential generation.



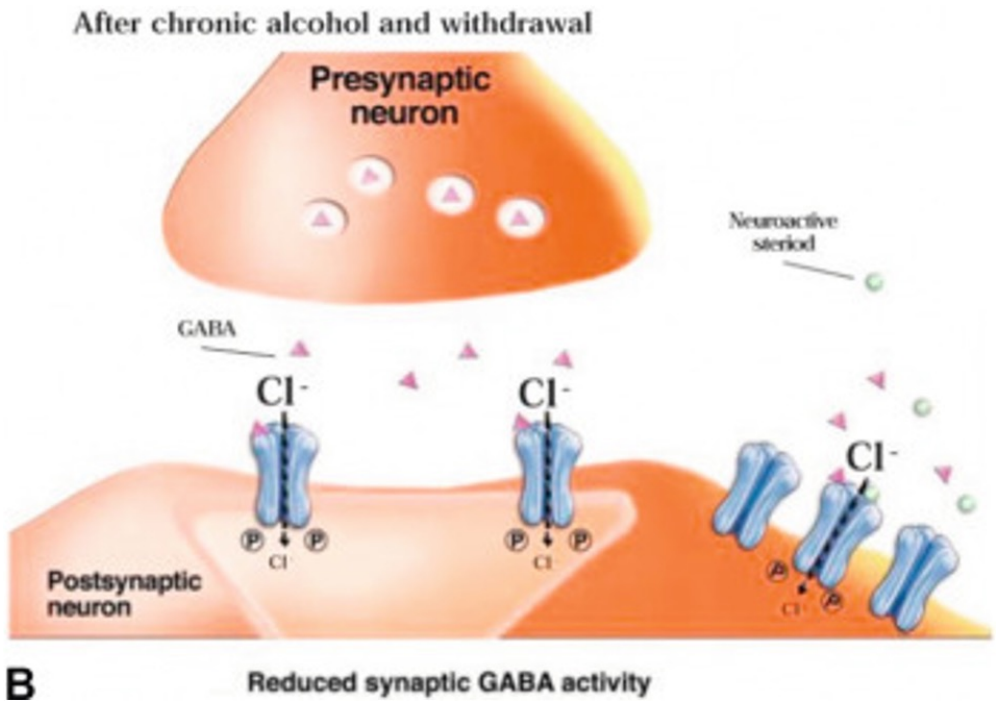
Inhibitory postsynaptic potentials (IPSPs) decrease the likelihood of a postsynaptic action potential occurring and are induced by inhibitory neurotransmitters.

Excitatory Synaptic Signaling(Example: GABA)

- GABA is the major inhibitory neurotransmitter acts via ionotropic receptors ,GABAA receptors as well as metabotropic receptors

- The binding of GABA to GABAA receptors induces the opening of ion channels that are selectively permeable to chloride ions. Consequently, GABA causes chloride ions to flow across the postsynaptic membrane.

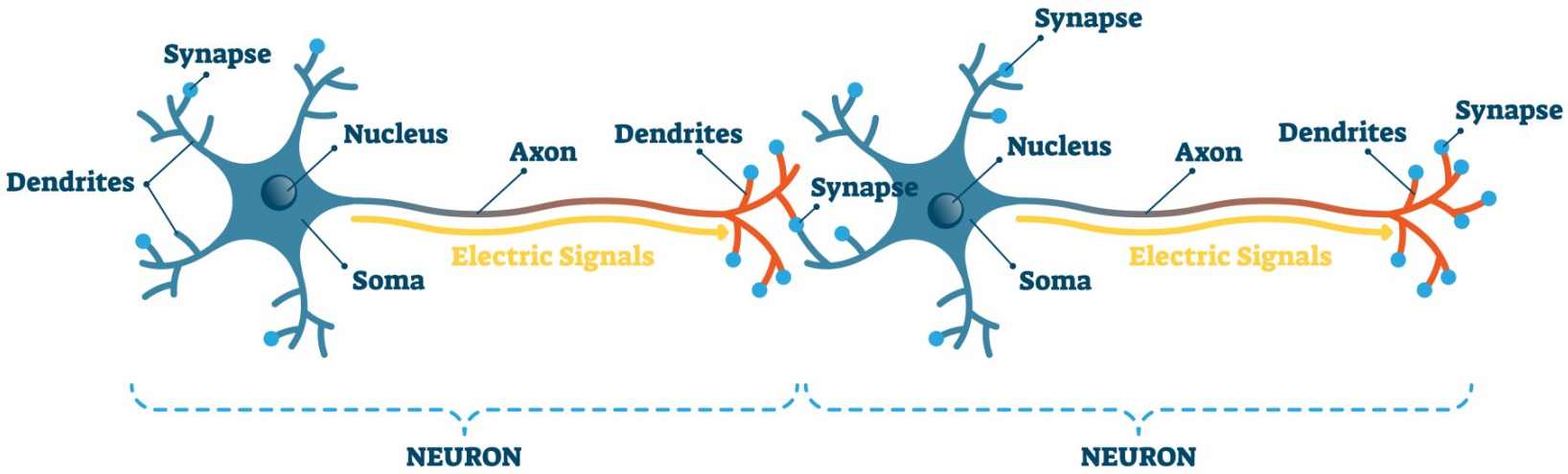
- As chloride ions are more abundant extracellularly, they will flow down their concentration gradient into the cell, producing a hyperpolarizing current and hence generating a hyperpolarising inhibitory postsynaptic potential.



Synapses

Specialized Sites where neurons communicate with other cells

- Neurons
- Muscle cells
- Endocrine cells



Types of synapses

Chemical (vast majority)

The neurotransmitter (NT) interacts with postsynaptic cell within 0.5 ms

Electrical

At electric synapses, ions pass directly from the pre to the postsynaptic cell through gap junctions.

Studying Neurotransmitter Systems

- Neurotransmitter - three criteria
  - Synthesis and storage in presynaptic neuron
  - Released by presynaptic axon terminal
  - Produces response in postsynaptic cell
- Enzymes concerned with the synthesis of neurotransmitters are present both in the cell body and in the nerve ending.
- A portion of neurotransmitter is produced in the cell body and transported to the nerve ending.

Neurotransmitters (NTs)

Impulses are transmitted by the release of NTs from the axon terminal of the presynaptic cell into the synaptic cleft. NTs bind to specific receptors on the postsynaptic cell causing a change in the ion permeability and the potential of the postsynaptic plasma membrane

Neurotransmitters receptors

- **Ligand-activated ion channels**

1. also known as ionotropic receptors.
2. These receptors are membrane-spanning ion channel proteins that open directly in response to ligand binding.
3. have either an excitatory or an inhibitory effect, depending on the ions that can pass through the channel and their concentrations inside and outside the cell.
4. typically produce very quick physiological responses.

- **Metabotropic receptors**:

1. These receptors are not themselves ion channels.
2. Neurotransmitter binding triggers a signaling pathway, which may indirectly open or close channels.
3. Signaling through these **metabotropic receptors** depends on the activation of several molecules inside the cell and often involves a second messenger pathway.
4. Snice it involves many signaling steps, it is much slower than signaling through ligand-activated ion channels.
5. Some metabotropic receptors have excitatory effects when they're activated, while others have inhibitory effects

Neurotransmitters (NTs)

- Neurotransmitters can be broadly split into two groups – the 'classical' small molecule neurotransmitters and the relatively larger neuropeptide neurotransmitters.
- Within the category of small molecule neurotransmitters, the biogenic amines (dopamine, noradrenaline, serotonin and histamine) are often referred to as a 'discrete group' because of their similarity in terms of their chemical properties

Neurotransmitters (NTs)

The number and kind of neurotransmitter molecules received by the receptor cell, as well as the kind of receptor, determines whether the effect will be to stimulate or to inhibit.

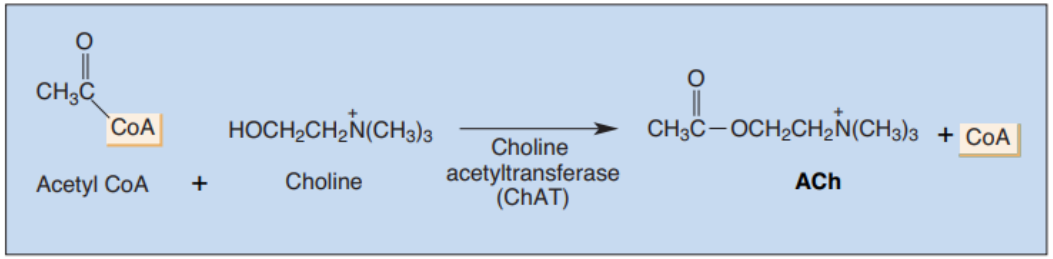
- Neurotransmitters function by changing the permeability of the cell **membrane** to various ions such as **sodium** and **potassium**.
- If an excess of sodium ions flow into the nerve cell, an impulse is generated. If an excess of potassium ions flow out, the impulse is inhibited.

1. Cholinergic Neurons

- Cetylcholine (ACh) is the neurotransmitter at the neuromuscular junction and is therefore synthesized by all the motor neurons in the spinal cord and brain stem.
- ACh synthesis requires a specific enzyme, choline acetyltransferase (ChAT) .
- Like nearly all presynaptic proteins, ChAT is manufactured in the soma and transported to the axon terminal.
- Only cholinergic neurons contain ChAT, so this enzyme is a good marker for cells that use ACh as a neurotransmitter.
- ChAT synthesizes ACh in the cytosol of the axon terminal, and the neurotransmitter is concentrated in synaptic vesicles by the actions of a vesicular ACh transporter
- ChAT transfers an acetyl group from acetyl CoA to choline
- The source of choline is the extracellular fluid, where it exists in low micromolar concentrations.

Cetylcholine (ACh) synthesis

- Choline is taken up by the cholinergic axon terminals via a specific transporter that requires the cotransport of Na to power the movement of choline. Because the availability of choline limits how much ACh can be synthesized in the axon terminal, the transport of choline into the neuron is said to be the rate-limiting step in ACh synthesis.
- For certain diseases in which a deficit in cholinergic synaptic transmission has been noted, dietary supplements of choline are sometimes prescribed to boost ACh levels in the brain.



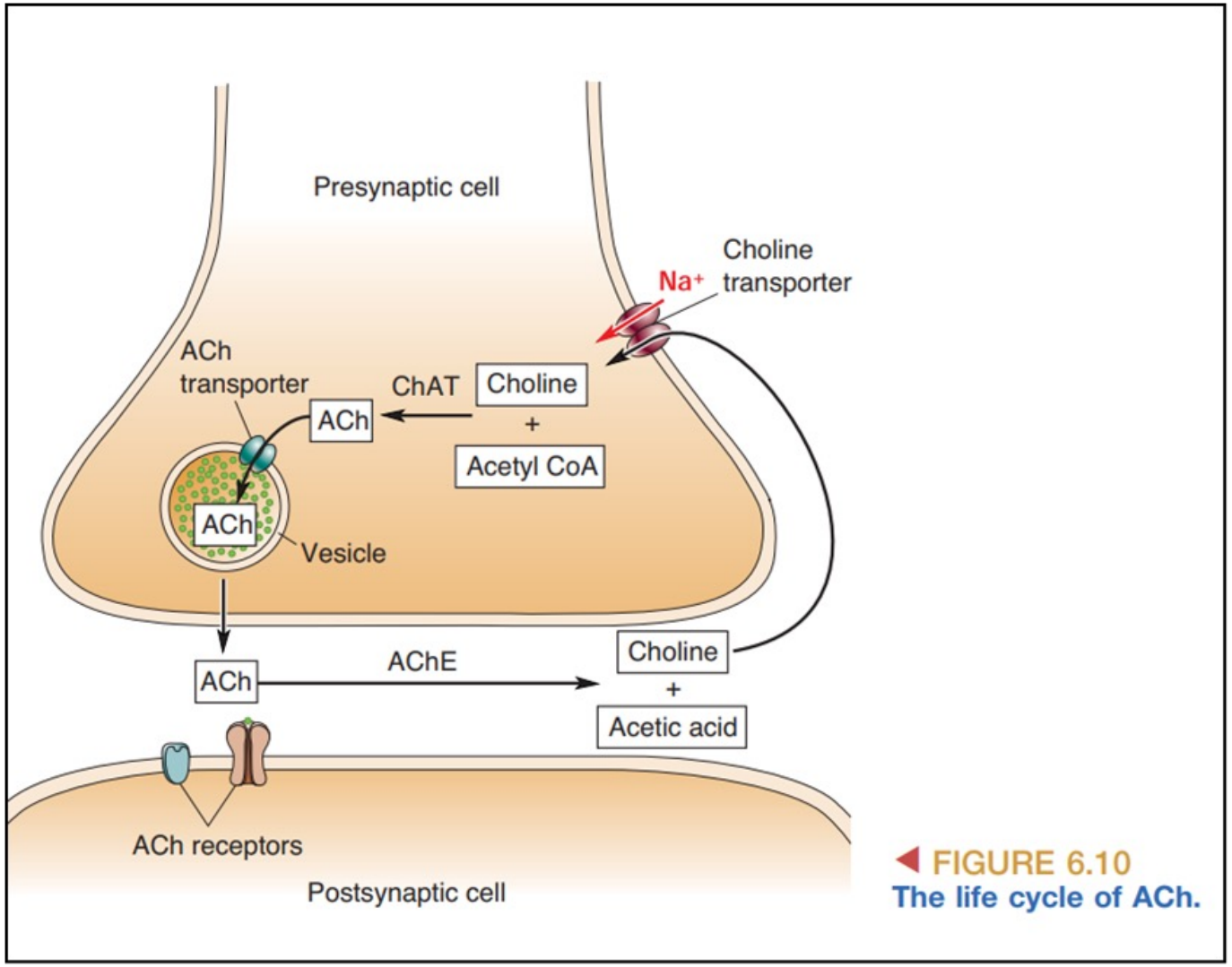
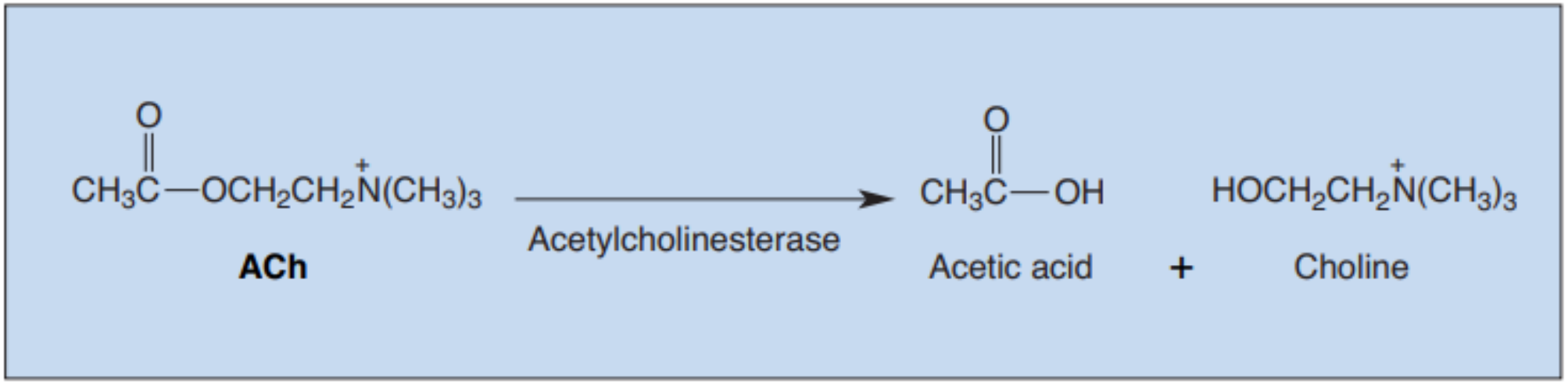


FIGURE 6.10
The life cycle of ACh.

Cetylcholine (ACh) degradation

- Cholinergic neurons also manufacture the ACh degradative enzyme acetylcholinesterase (AChE).
- AChE is secreted into the synaptic cleft and is associated with cholinergic axon terminal membranes. However, AChE is also manufactured by some noncholinergic neurons, so this enzyme is not as useful a marker for cholinergic synapses as ChAT.
- AChE degrades ACh into choline and acetic acid as the following figure shows .



- Degradation of ACh happens very quickly because AChE has one of the fastest catalytic rates among all known enzymes.
- Much of the resulting choline is taken up by the cholinergic axon terminal via a choline transporter and reused for ACh synthesis (Figure 6.10).

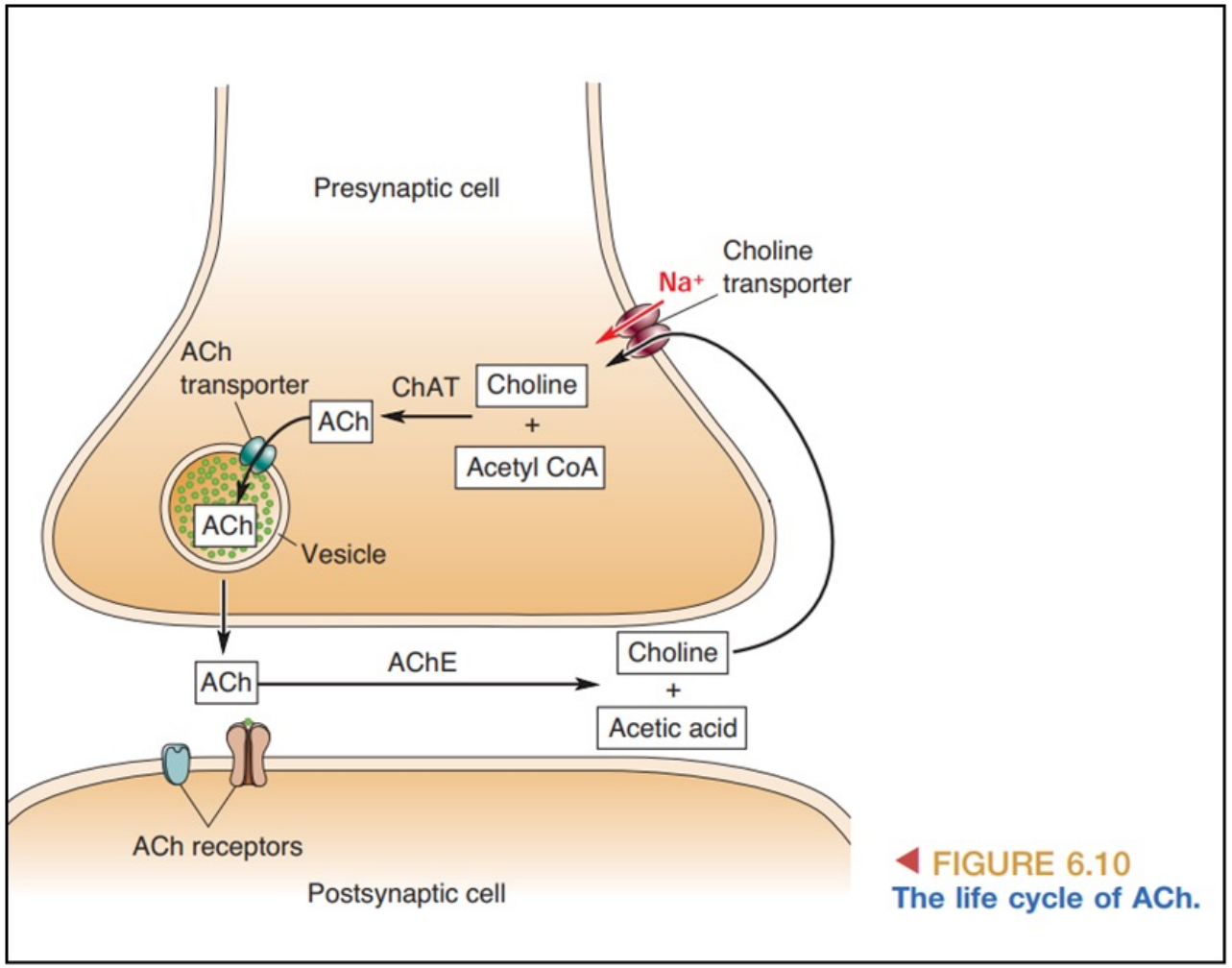


FIGURE 6.10
The life cycle of ACh.

- we mentioned that AChE is the target of many nerve gases and insecticides.
- Inhibition of AChE prevents the breakdown of ACh, disrupting transmission at cholinergic synapses on skeletal muscle and heart muscle.
- Acute effects include marked decreases in heart rate and blood pressure; however, death from the irreversible inhibition of AChE typically results from respiratory paralysis.

Synthesis, storage and release of Acetylcholine

- The biosynthesis and storage of ACh can be divided into three processes that allow for recovery of hydrolyzed transmitter by choline transport back into the nerve ending, conversion by acetylation to active transmitter and then storage in a vesicle for subsequent release

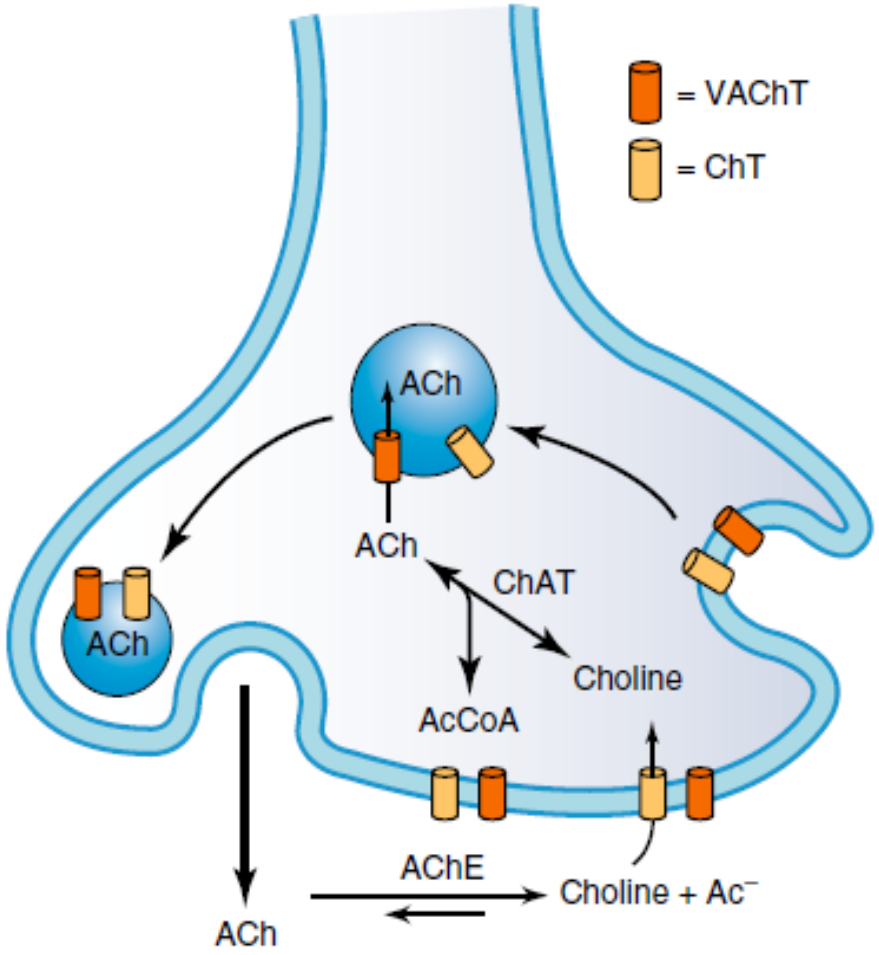
-The synthesis reaction is a single step catalyzed by the enzyme choline acetyl transferase (ChAT):

Choline + Acetyl coenzyme A ----------Acetylcholine + Coenzyme A.

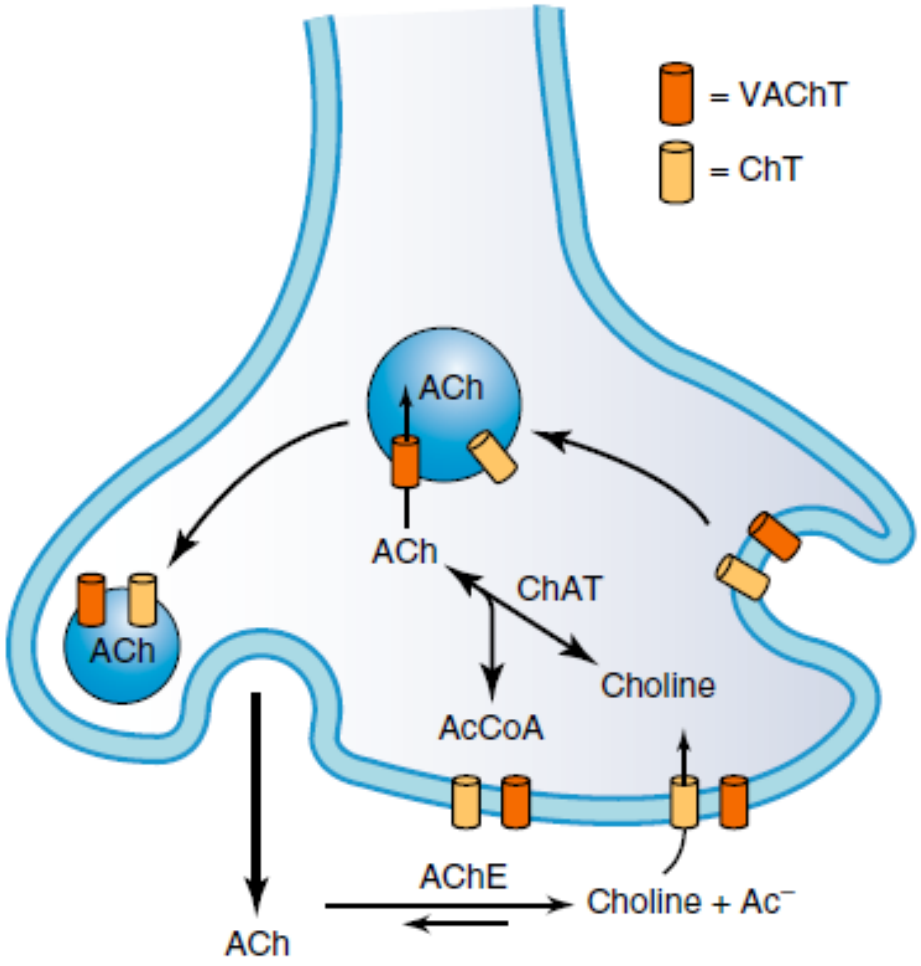
Transport, synthesis and degradative processes in a cholinergic presynaptic nerve terminal and synapse.

The choline transport protein (ChT) functions at the nerve ending membrane to transport choline into the cytoplasm, where its acetylation by acetyl CoA is catalyzed by choline acetyltransferase (ChAT) to generate acetylcholine (ACh) in the vicinity of the synaptic vesicle.

The vesicular acetylcholine transporter (VAChT) concentrates acetylcholine in the vesicle. ChT is also found on the vesicle but as functionally inactive state.

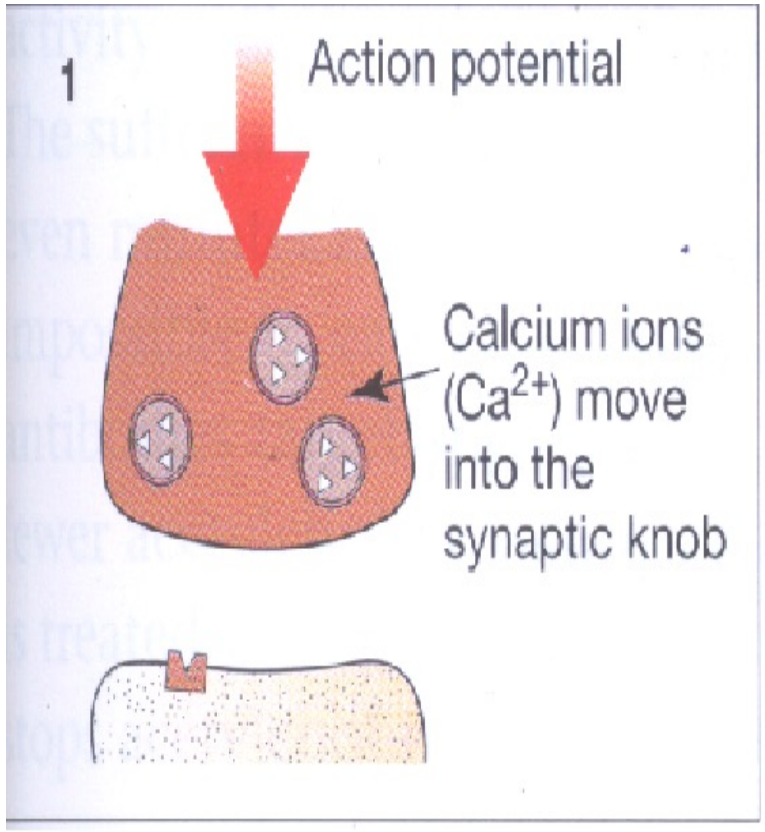


- Upon nerve stimulation, depolarization and Ca2+ entry, ACh-containing vesicles fuse with the membrane and release their contents.
- The fusion of the membrane results in more ChT being exposed to the synaptic gap, where it becomes active.
- ACh is hydrolyzed to acetate and choline catalyzed by acetylcholinesterase (AChE), allowing for recapture of much of the choline by ChT.



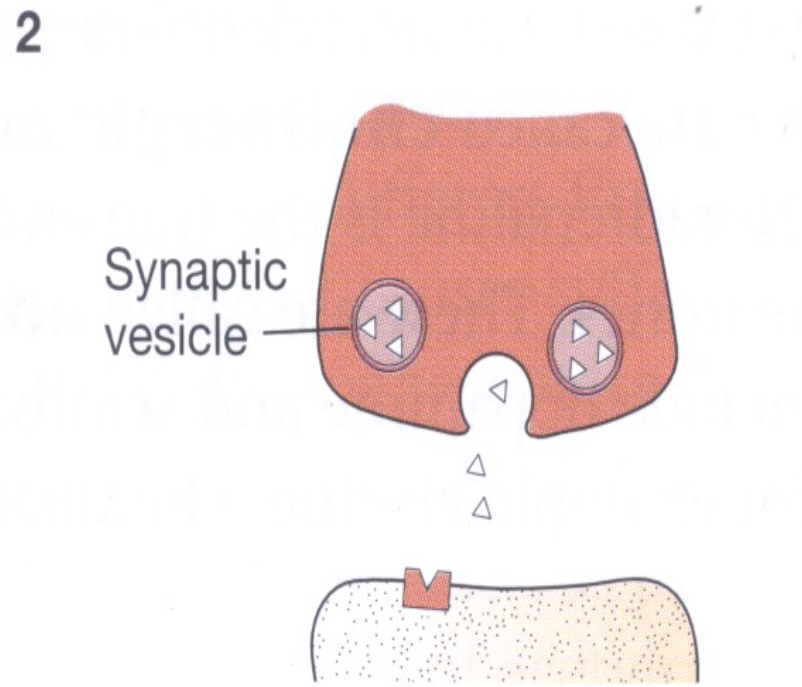
cholinergic synapse: Stage 1

An action potential arrives at presynaptic membrane. Voltage gated calcium channels in the presynaptic membrane open, calcium ions enter the presynaptic neurone.



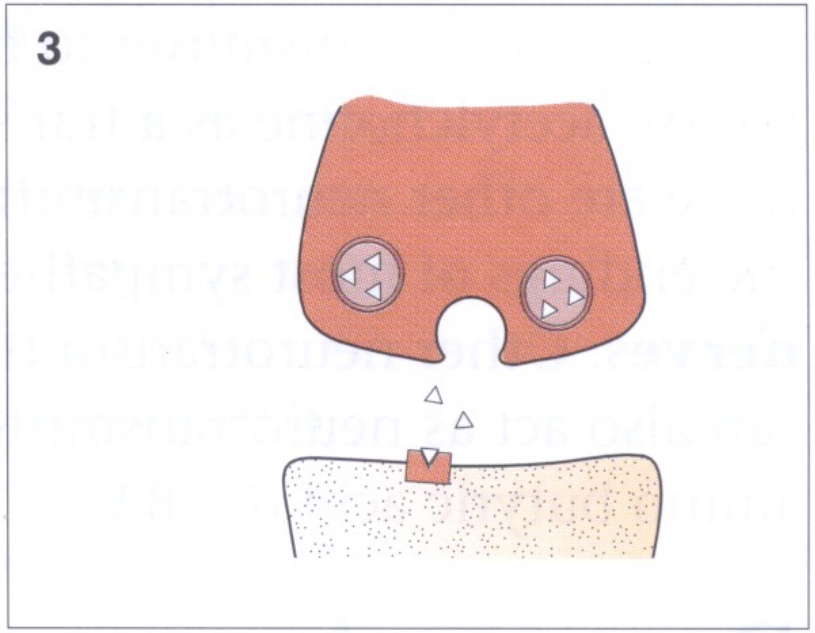
cholinergic synapse? Stage 2

- Calcium ions cause synaptic vesicles to fuse with the presynaptic membrane, releasing acetylcholine into the synaptic cleft.



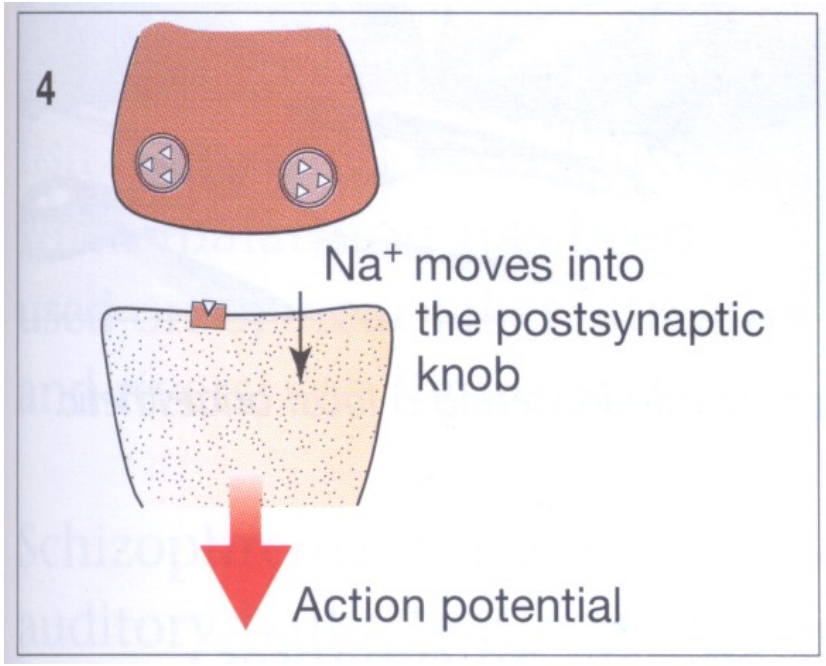
What happens at a cholinergic synapse? Stage 3

- Acetylcholine diffuses cross the synaptic cleft and binds to specific neuroreceptor sites in the post synaptic membrane.



cholinergic synapse? Stage 4

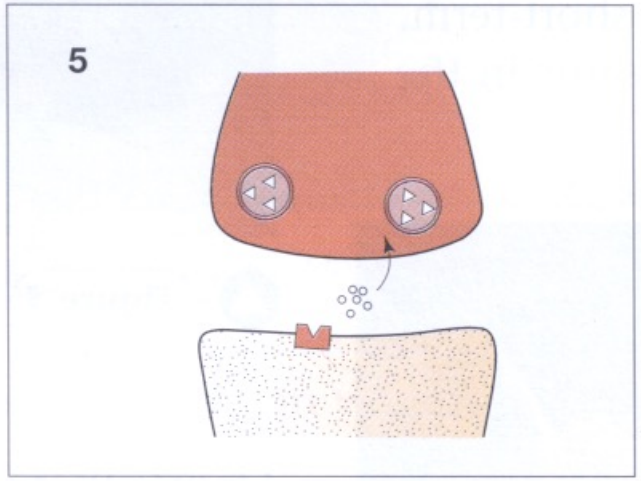
- Sodium channels open. Sodium ions diffuse into the postsynaptic membrane causing depolarisation, which may initiate an action potential.

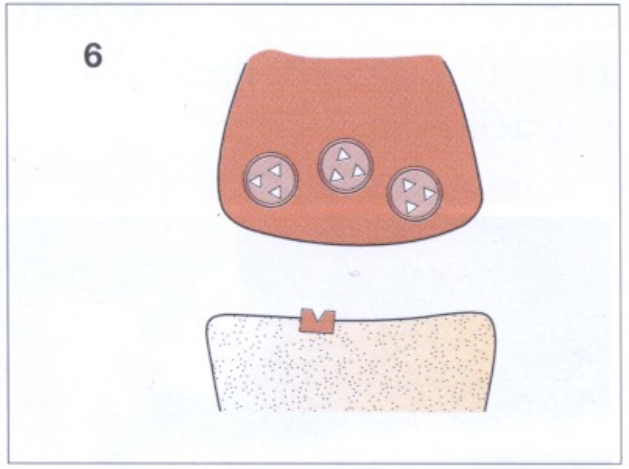


cholinergic synapse? Stage 5

- Acetylcholinesterase breaks down acetylcholine.

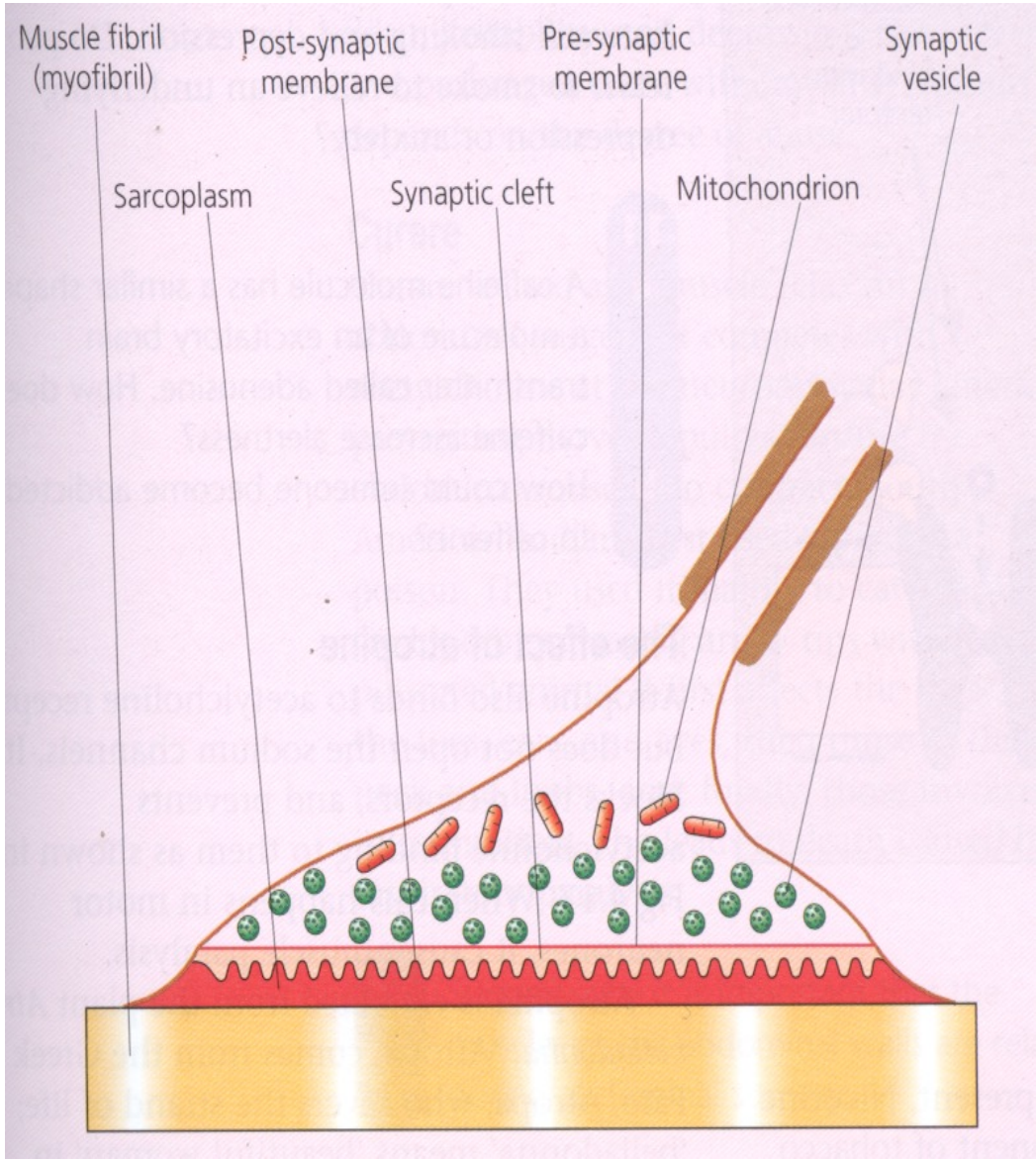
  The products diffuse back into the presynaptic neurone where acetycholine is resynthesised using ATP from the mitochondria.





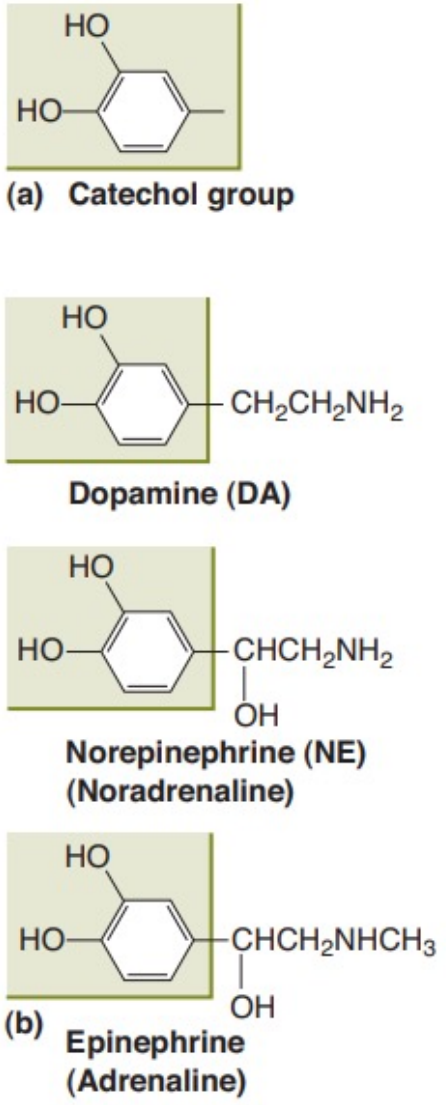
Neuromuscular Junctions

- Same stages as cholinergic synapses, but in this case the postsynaptic membrane is the muscle fibre membrane, (Sarcolemma). Depolarisation of the sarcolemma leads to contraction of muscle fibre.



2. Catecholaminergic Neurons

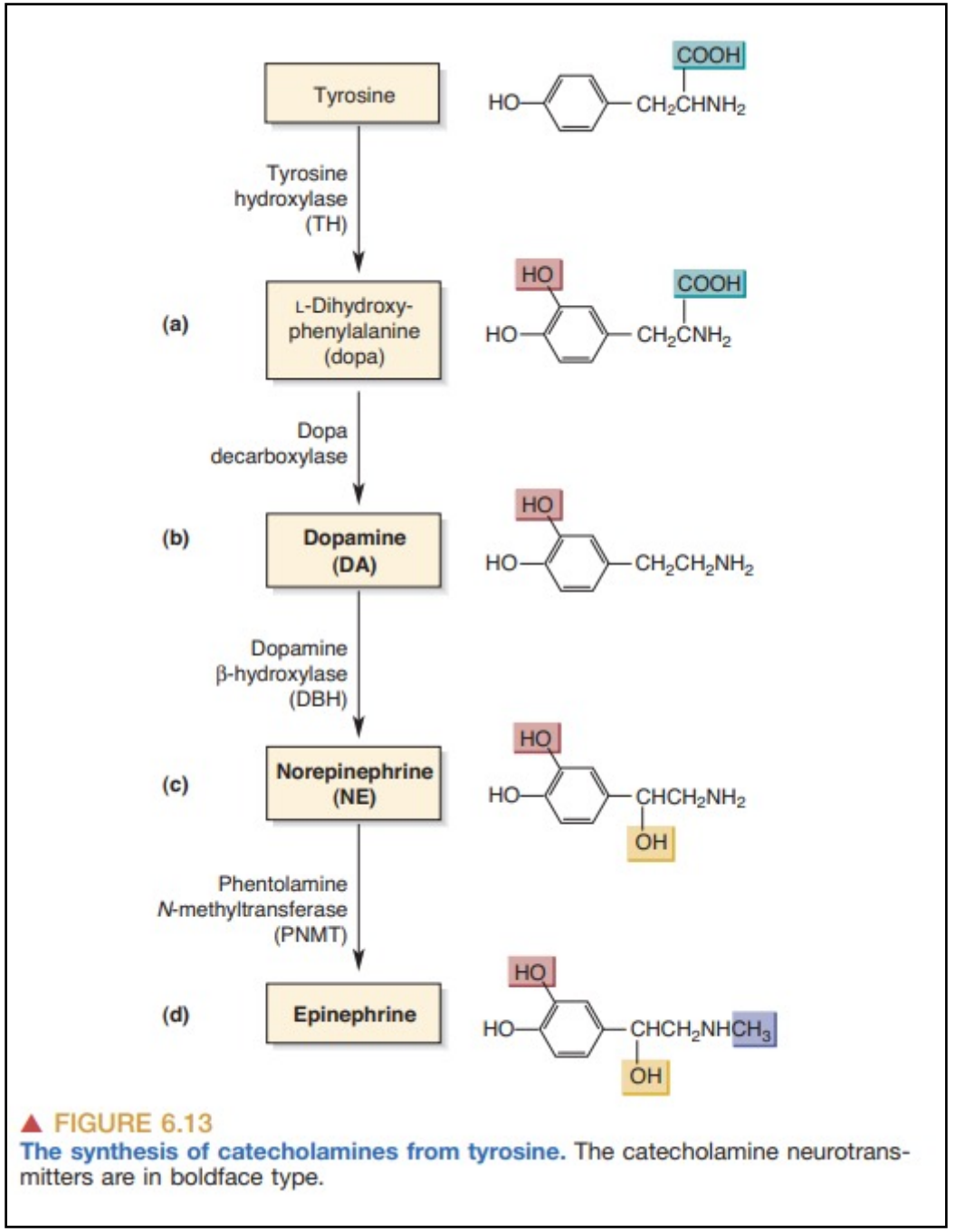
- The amino acid tyrosine is the precursor for three different amine neurotransmitters that contain a chemical structure called a catechol **called catecholamines.**
- The catecholamine neurotransmitters involved dopamine (DA), norepinephrine (NE), and epinephrine, also called adrenaline
- Catecholaminergic neurons are found in regions of the nervous system involved in the regulation of movement, mood, attention, and visceral function



▲ FIGURE 6.12
The catecholamines. **(a)** A catechol group. **(b)** The catecholamine neurotransmitters.

Catecholaminergic synthesis

- All catecholaminergic neurons contain the enzyme tyrosine hydroxylase (TH), which catalyzes the first step in catecholamine synthesis,
- the conversion of tyrosine to a compound called dopa (L -dihydroxyphenylalanine)
- The activity of TH is rate limiting for catecholamine synthesis.
- Dopa is converted into the neurotransmitter DA by the enzyme dopa decarboxylase. Dopa decarboxylase is abundant in catecholaminergic neurons.



▲ FIGURE 6.13
The synthesis of catecholamines from tyrosine. The catecholamine neurotransmitters are in boldface type.

End-product inhibition of tyrosine hydroxylase

- The tyrosine hydroxylase activity is regulated by various signals in the cytosol of the axon terminal.

In the case of decreased catecholamine release by the axon terminal causes  increase the concentration of catecholamine in the cytosol, thereby inhibiting TH. This type of regulation is called end-product inhibition.

On the other hand, during periods when catecholamines are released at a high rate, the elevation in [Ca 2] that accompanies neurotransmitter release triggers an increase in the activity of TH, so transmitter supply keeps up with demand.

- In addition, prolonged periods of stimulation actually cause the synthesis of more mRNA that codes for the enzyme