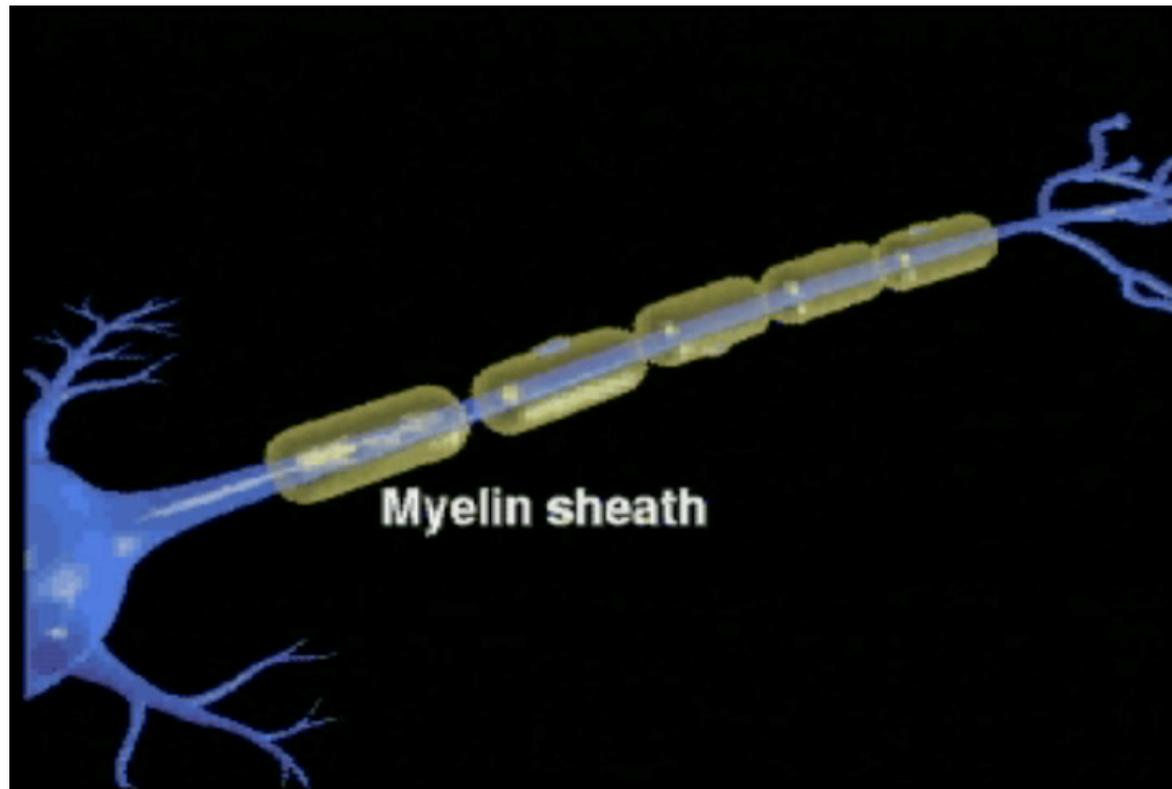
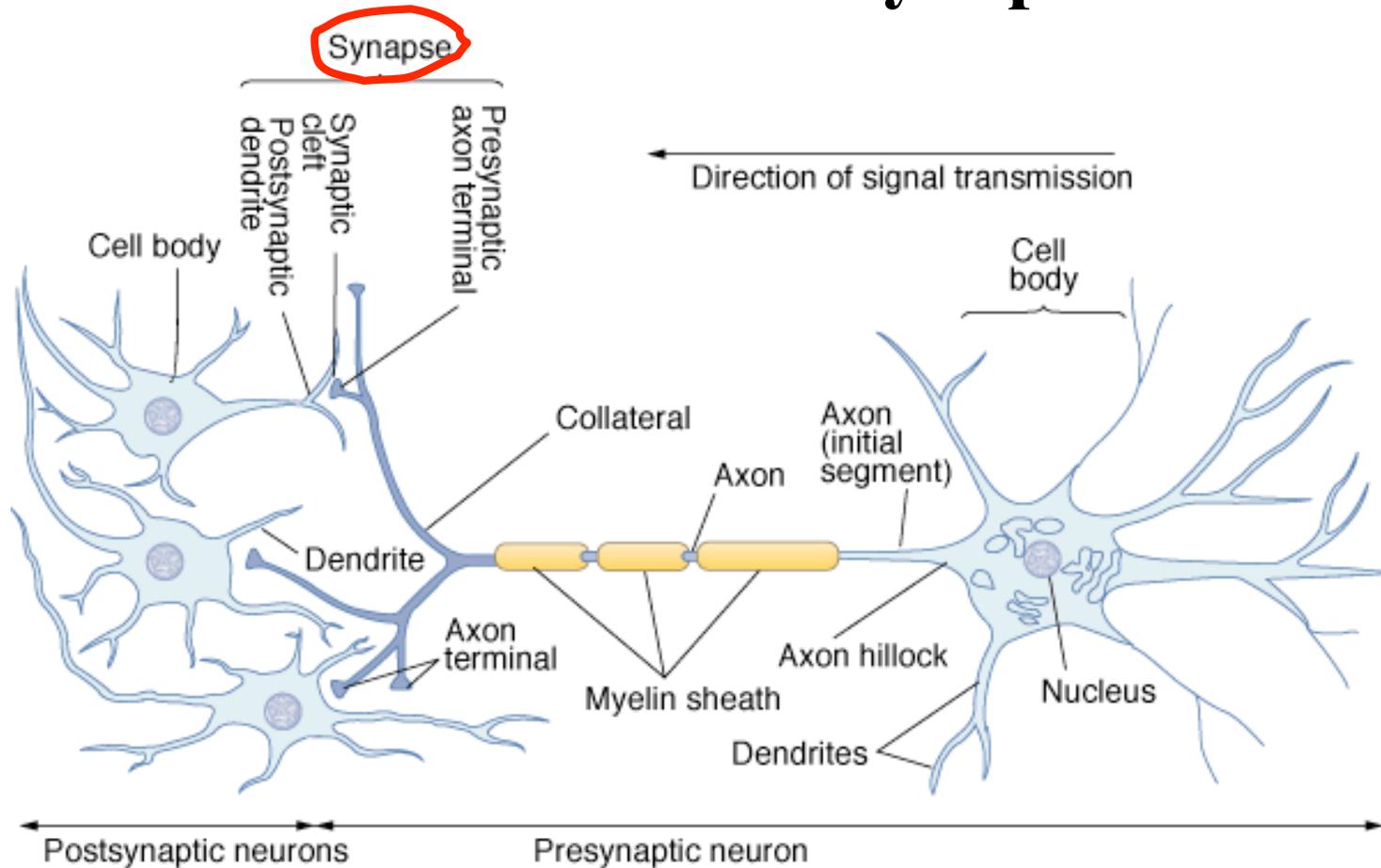


Synaptic Transmission

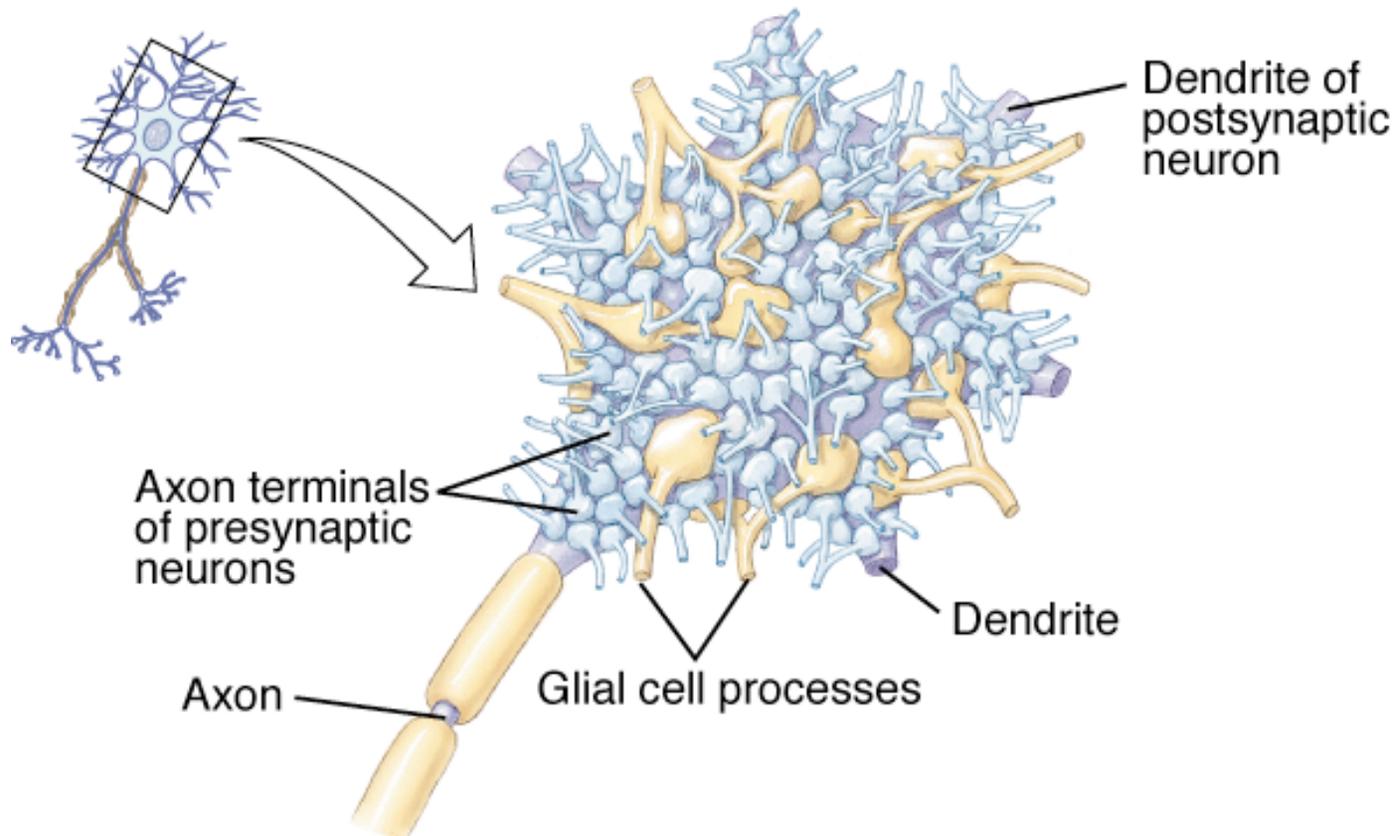


Cell-to-Cell Communication Between Neurons Takes Place At Synapses



F8-2

- A synapse is a region at which a neuron communicates with its target cell. The synapse is composed of 3 parts: (a) the axon terminal; (b) the synaptic cleft, the space between the cells and (c) the membrane of the postsynaptic cell.



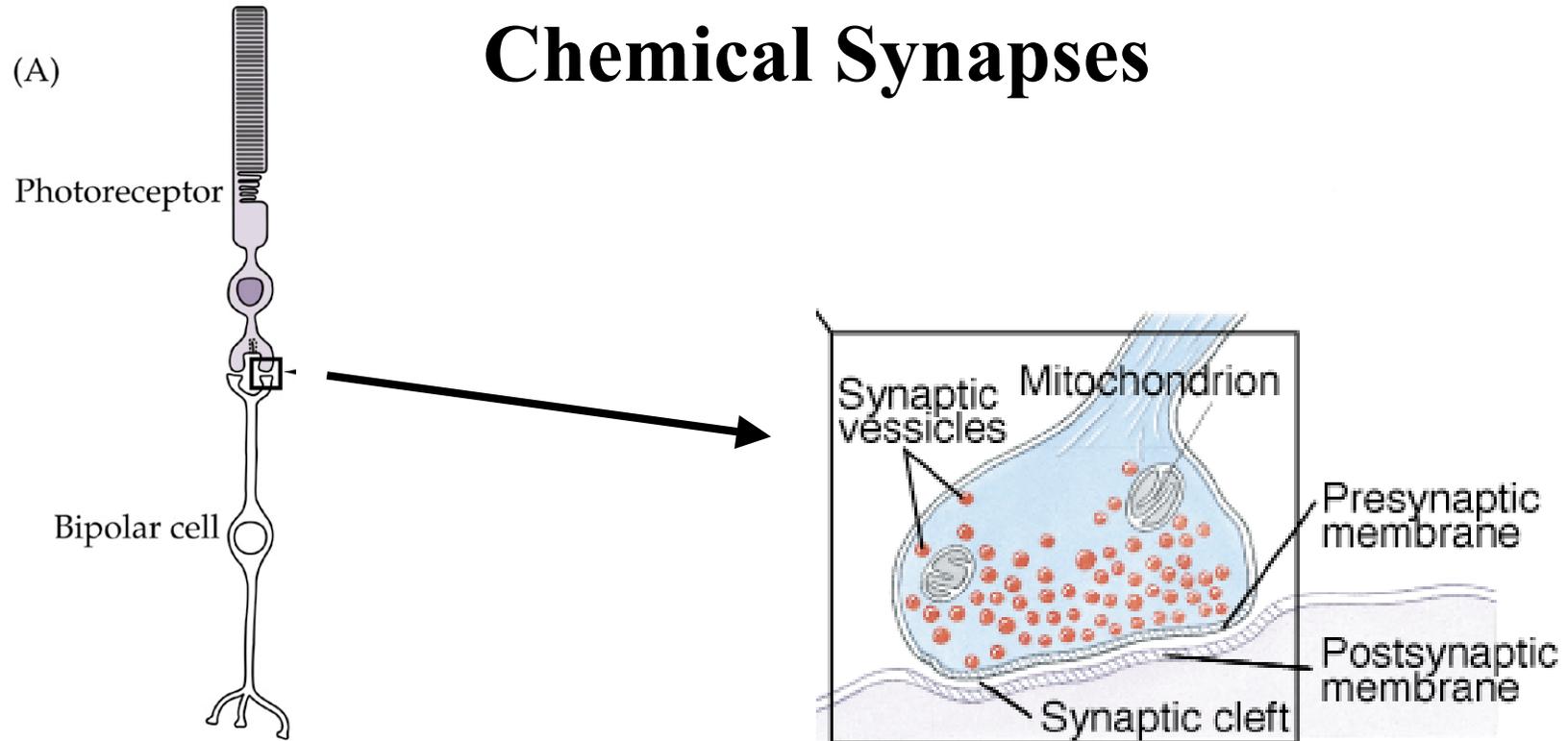
F8-11

- A nerve cell in the brain may have about 10, 000 to 150, 000 synapses.
- Synapses can be either electrical or chemical

Disorders of Synaptic Transmission

- Synaptic transmission is the most vulnerable step in neuronal signaling. It is a point where things could go wrong, disrupting normal function.
- Nervous disorders such as Parkinson's disease, schizophrenia and depression are due to problems with synaptic transmission.
- Caffeine, nicotine, alcohol and common drugs affect synaptic transmission.
- Myasthenia gravis is an autoimmune disease where the body fails to recognise the nAChR as part of the 'self' and produces molecules to attack its receptors. This causes the membrane to withdraw the receptors from the surface and destroy them inside. The destruction of receptors produces a diminished excitatory response to ACh released from the nerve terminal and the inability of the muscle fibres to contract.

Chemical Synapses



- The vast majority of synapses in the nervous system are chemical. F8-24
- They use chemical substances called neurotransmitters, to carry information from one cell to the next. Synaptic vesicles contain neurotransmitters which are released on demand.
- Some vesicles are docked at the membrane waiting to release their content upon the arrival of a trigger signal. Others are stored in the reserve pool, just above the docked vesicles.

Neurotransmitters In the Nervous System

T8-5 Neurotransmitter	Chemical Structure	Comments
Peripheral Nervous System		
Acetylcholine (ACh)	Unique structure	Autonomic and somatic motor neurons
Norepinephrine (NE)	Amine	Autonomic neurons
Central Nervous System		
Dopamine	Amine	Brain (Substantia Nigra)
Norepinephrine, Epinephrine (E)	Amine	Brain (Locus Coeruleus, spinal cord; also act as hormones)
Serotonin (5-HT)	Amine; related to preceding 3 transmitters	Brain (Raphe Nuclei)
Histamine	Amine	Parts of brain (Tuberomammillary Nucleus); more common as paracrine
Glutamate, aspartate	Amino acids	Excitatory
Glycine, GABA (gamma-aminobutyric acid)	Amino acids	Inhibitory
Adenosine, ATP	Purines	Often co-secreted with other neurotransmitters
Endorphins, enkephlins, dynorphins	Opioid peptides	Analgesics
Substance P	Polypeptide	Transmitter in pain pathway
Neuropeptide Y	Peptide	Autonomic neurons

- Amino acid, amine and purine neurotransmitters:

- synthesized in the axon terminals

- enzymes needed for their synthesis is delivered by slow axonal transport.

- Polypeptide neurotransmitters:

- synthesized in the cell bodies and delivered to the terminal by fast axonal transport.

- Gaseous transmitters, Nitric Oxide (NO):

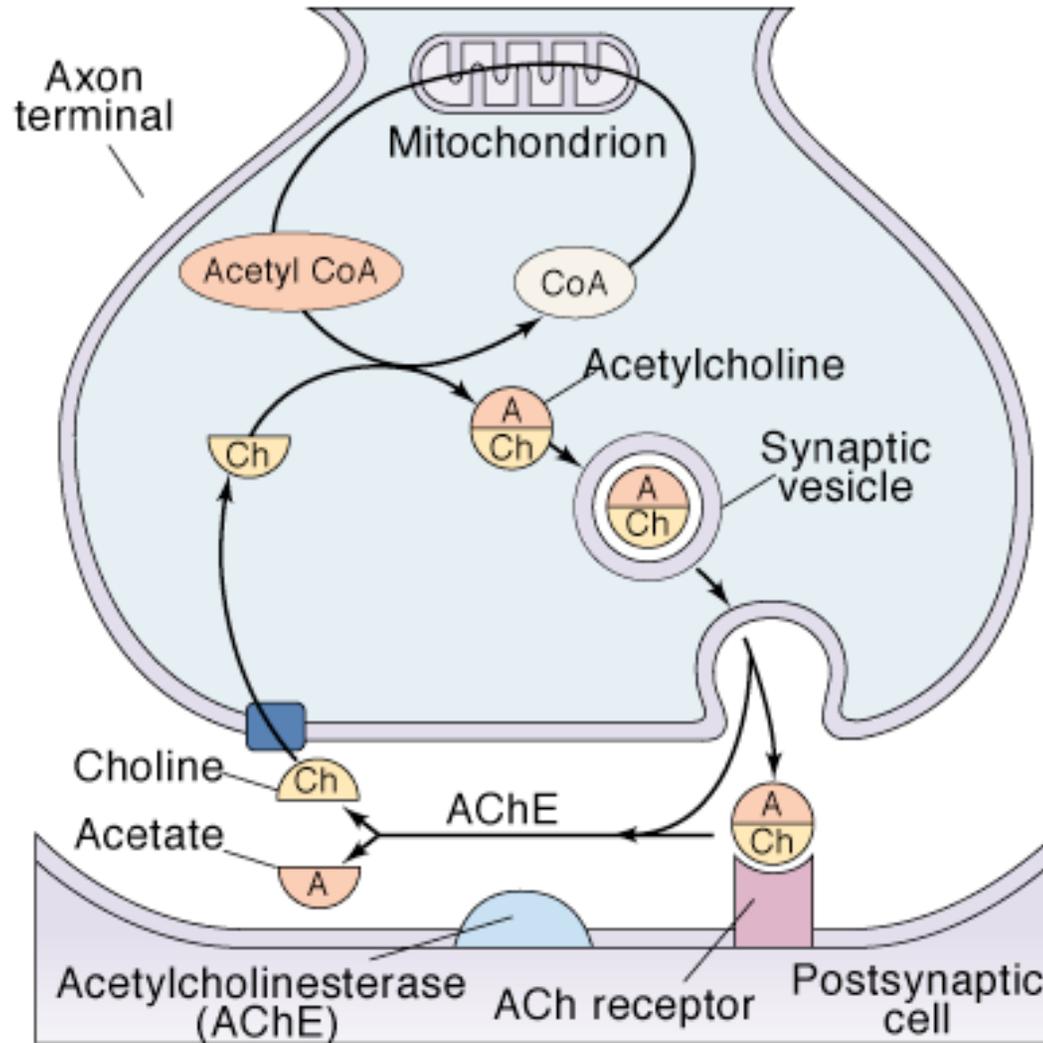
- synthesized from oxygen and the amino acid arginine. Not stored in vesicles.

- diffuses into its target cell rather than a membrane bound receptor and binds to proteins and nucleic acids.

- it has a half-life of about 2-30s.

- - For example, NO is synthesized in the endothelial lining of blood vessels and relaxes smooth muscle cells in the body walls of the vessels upon release.

Acetylcholine (ACh): Synthesis and Breakdown



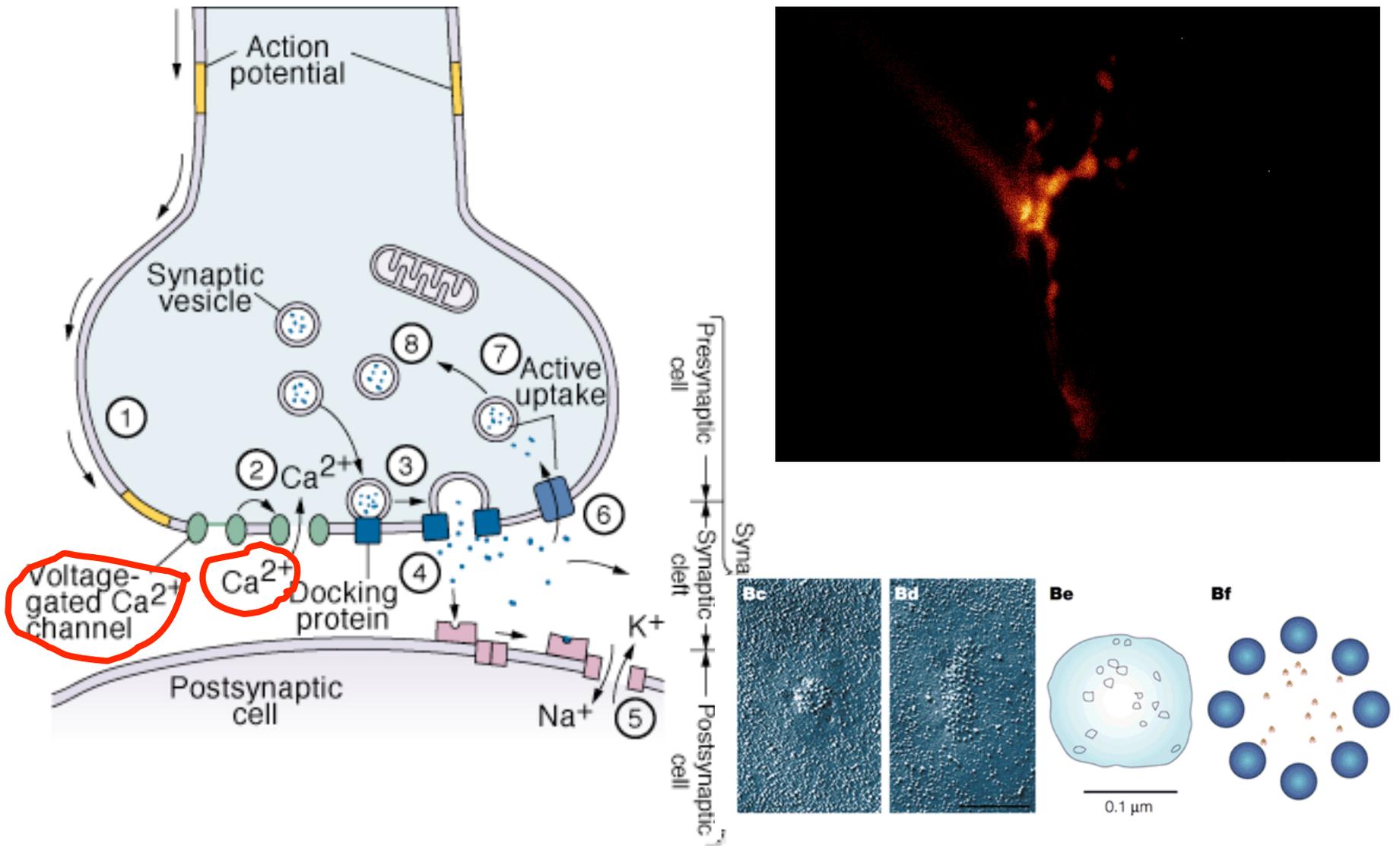
- Made from choline (Ch) and acetyl coenzyme (Acetyl CoA) in the axon terminal then filled into synaptic vesicles. This reaction is catalyzed by choline acetyltransferase (ChAT).

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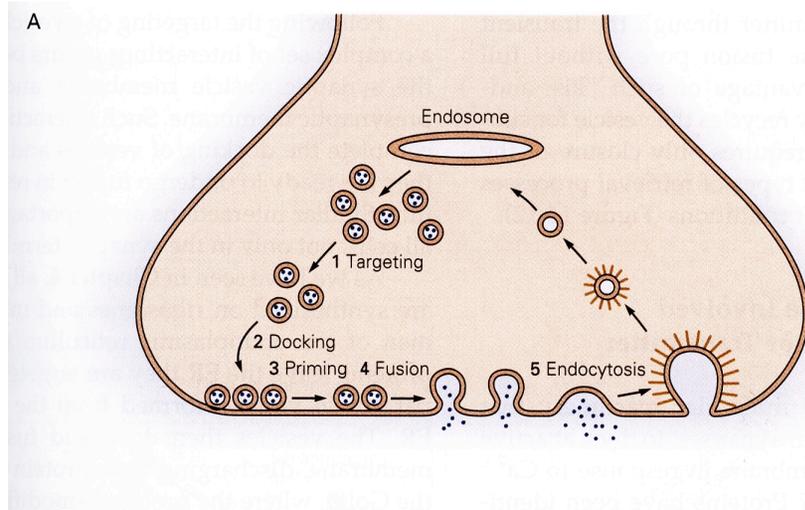
- Once released into the cleft, its rapidly broken down by the enzyme acetylcholinesterase (AChE).
- Ch is transported back into the axon terminal and reused to make ACh.

- Ch is found in the membrane phospholipids.
- Acetyl CoA is a metabolic intermediate which links glycolysis to the citric acid cycle.
- AChE is bound to the extracellular matrix and postsynaptic cell.
- E.g. ACh is the major neurotransmitter at synapses formed between a somatic motor neuron and skeletal muscle fibres, or better known as the neuromuscular junction. Binds to acetylcholine receptors (AChR) on the postsynaptic cell.

Ca²⁺ Triggers Neurotransmitter Release



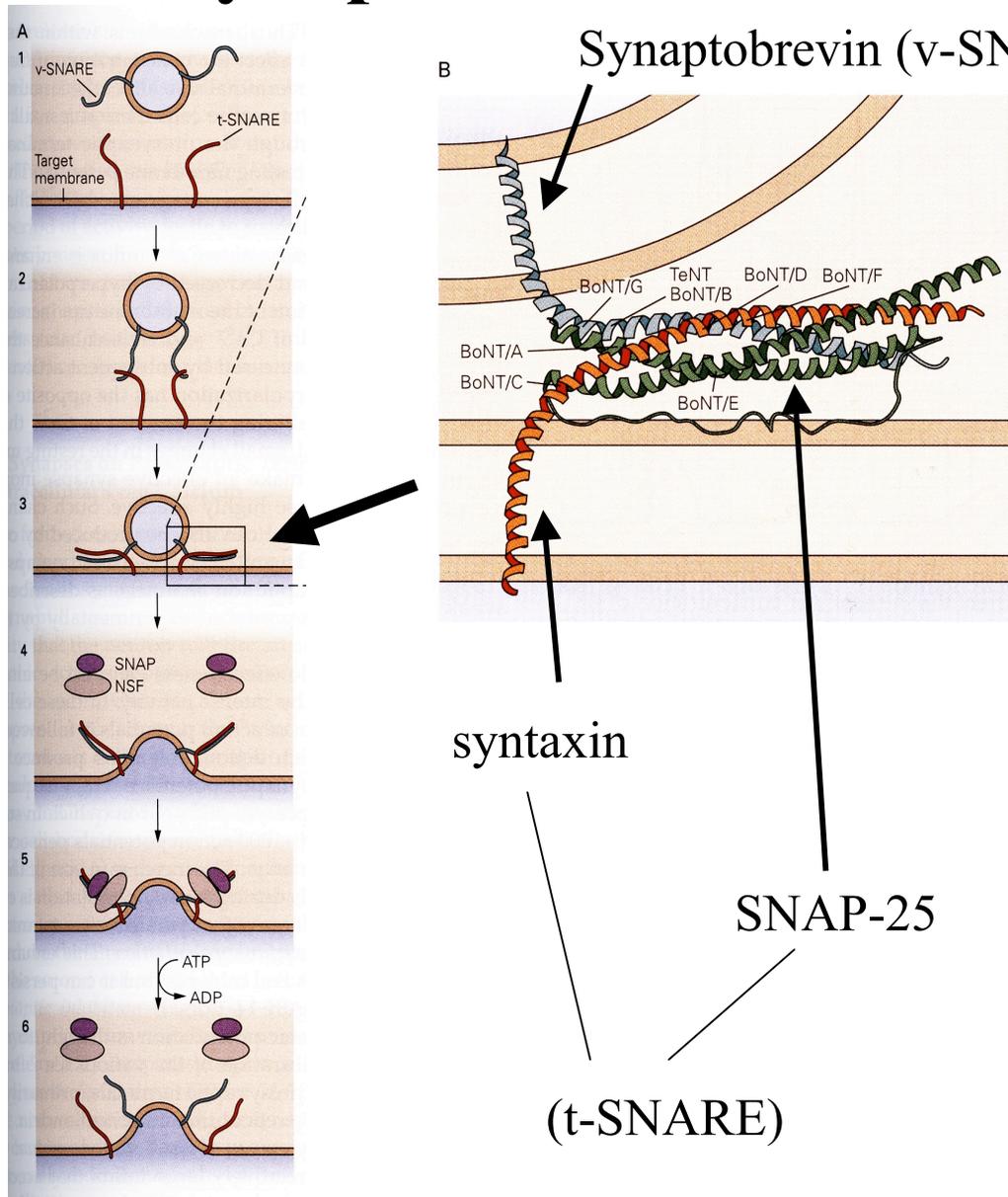
Synaptic Vesicle Cycle: Endocytosis and Exocytosis



FM1-43 destaining revealing exocytosis at the frog neuromuscular junction.

- Exocytosis (step 4): A means by which cells secrete large impermeable molecules. Vesicles fuse with the membrane and expose their content to the extracellular fluid.
- Endocytosis (step 5): A means by which molecules or particles move into cells. The membrane indents and forms vesicles.
- Both processes need energy input in the form of ATP.

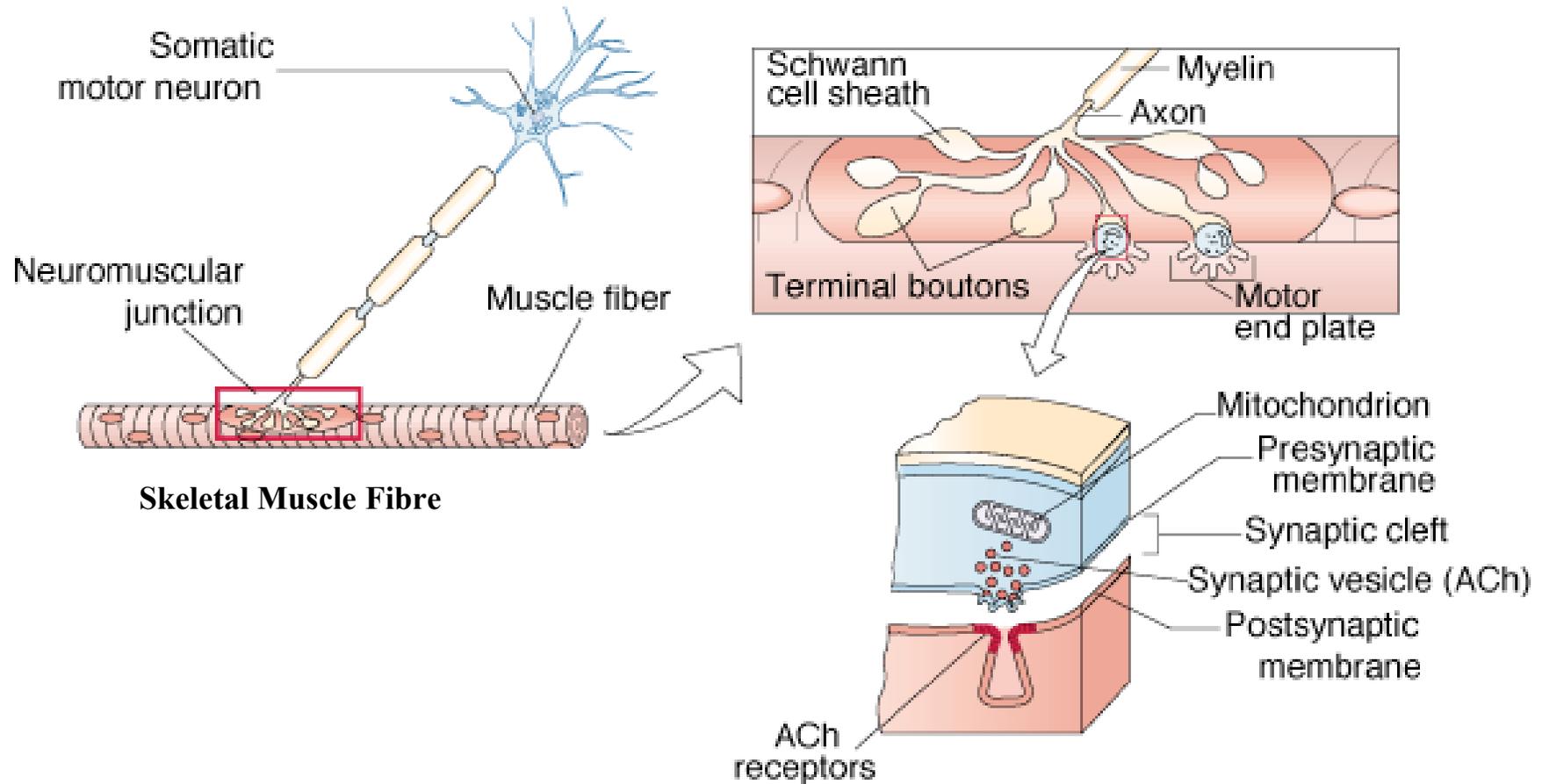
Synaptic Vesicle Fusion and Exocytosis



• Blockade of Exocytosis

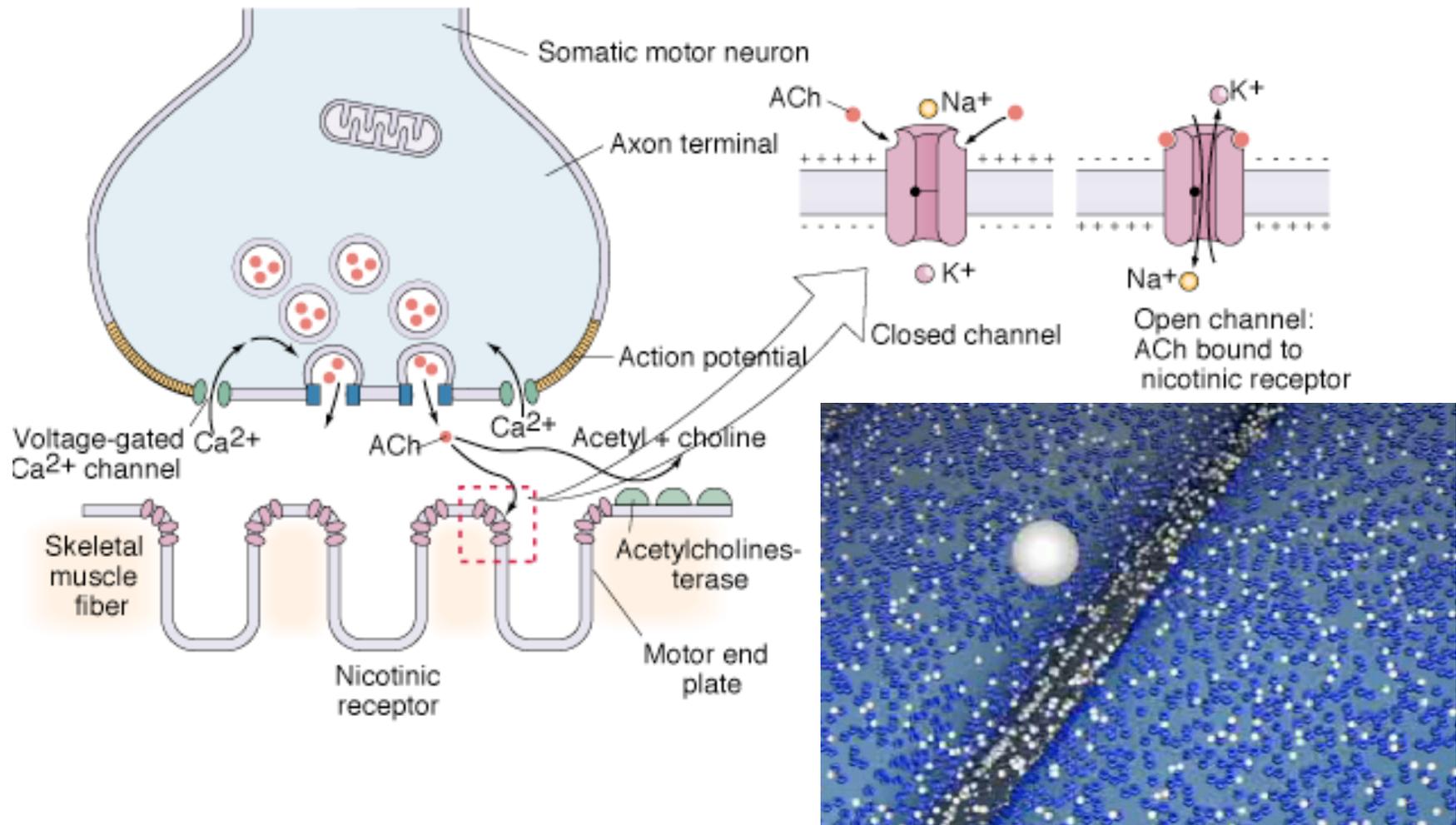
- Botulinum and Tetanus toxins prevent vesicles from releasing their content of neurotransmitter.
- Injection of botulinum toxins have been used to prevent writer's cramp, a disabling cramp that apparently arises as a result of hyperexcitability in the distal portion of the somatic motor neuron.

Neuromuscular Junction



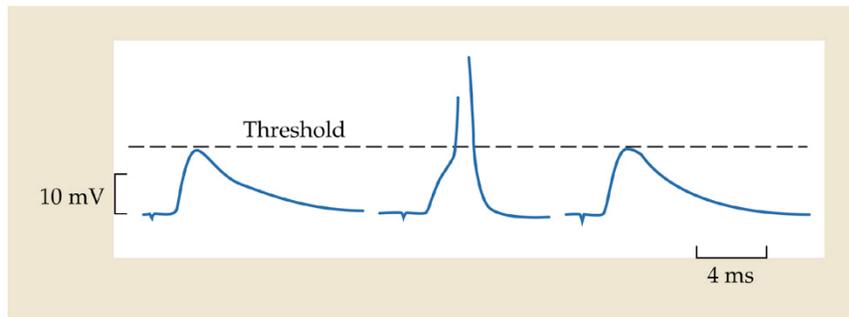
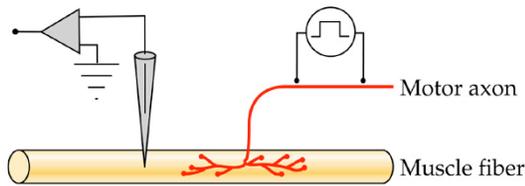
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- The excitatory response is called an end-plate potential (epp).



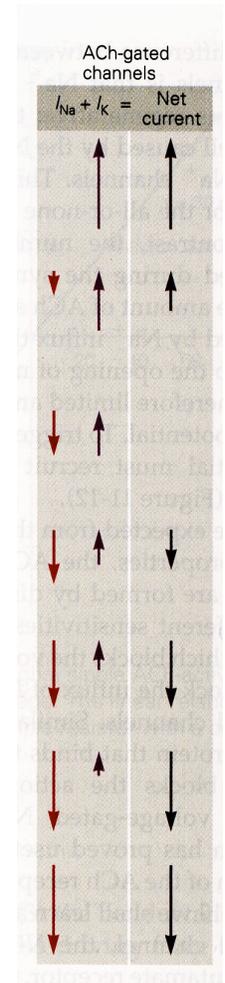
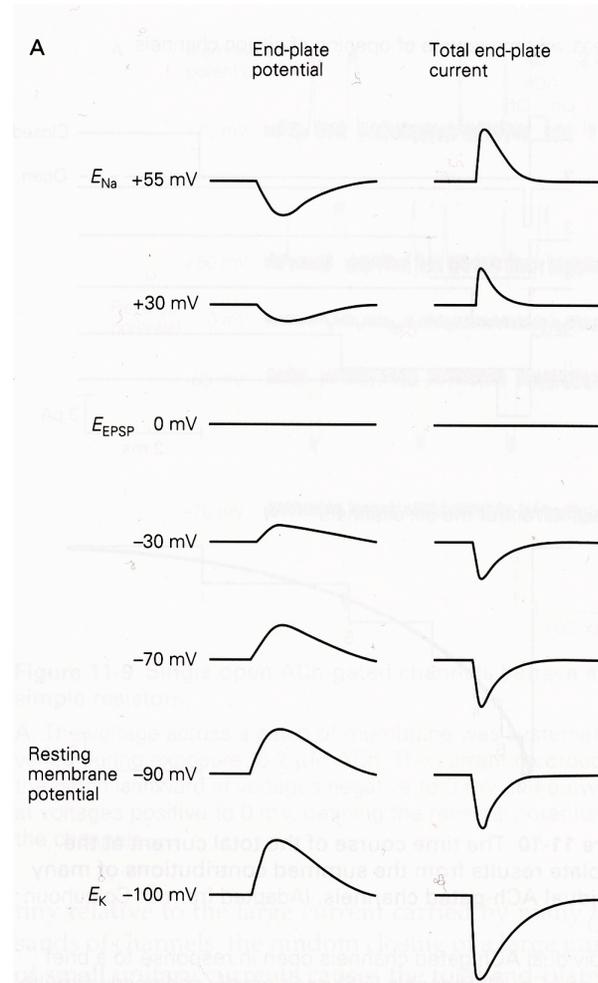
- Through the channel, more Na^{+} flows down its electrochemical gradient than K^{+} , causing a net +ve ion movement into the muscle. This net flow of +ve ions depolarizes the muscle membrane, causing APs to be fired and triggers contraction.

Excitatory Synaptic Potentials (EPSPs) And Their Reversal Potential



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- The reversal potential allows determination of the ions which are permeable through the cell membrane.
- The reversal potential for excitatory synapses is above the threshold for action potential generation (approx. -55 mV).



Disruption of Neuromuscular Transmission using Toxins

• Blockade on nAChR

- Curare, the famous poison used by Sth. American Indians on darts to hunt monkeys blocks nAChRs.
- Blocks channel opening and propagation of APs.
- Used as a muscle relaxant.

• Inhibit ACh Breakdown: Anticholinesterases

- They slow the breakdown of ACh in the synaptic cleft and allows ACh to remain active at the motor end plate for long durations.
- This is how nerve gases and pesticides (organophosphates) work.
- They are used to treat patients with myasthenia gravis who have a deficiency of nAChRs at the motor end plate. ACh needs to hang around the cleft for long periods to elicit a response.

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