Nervous System

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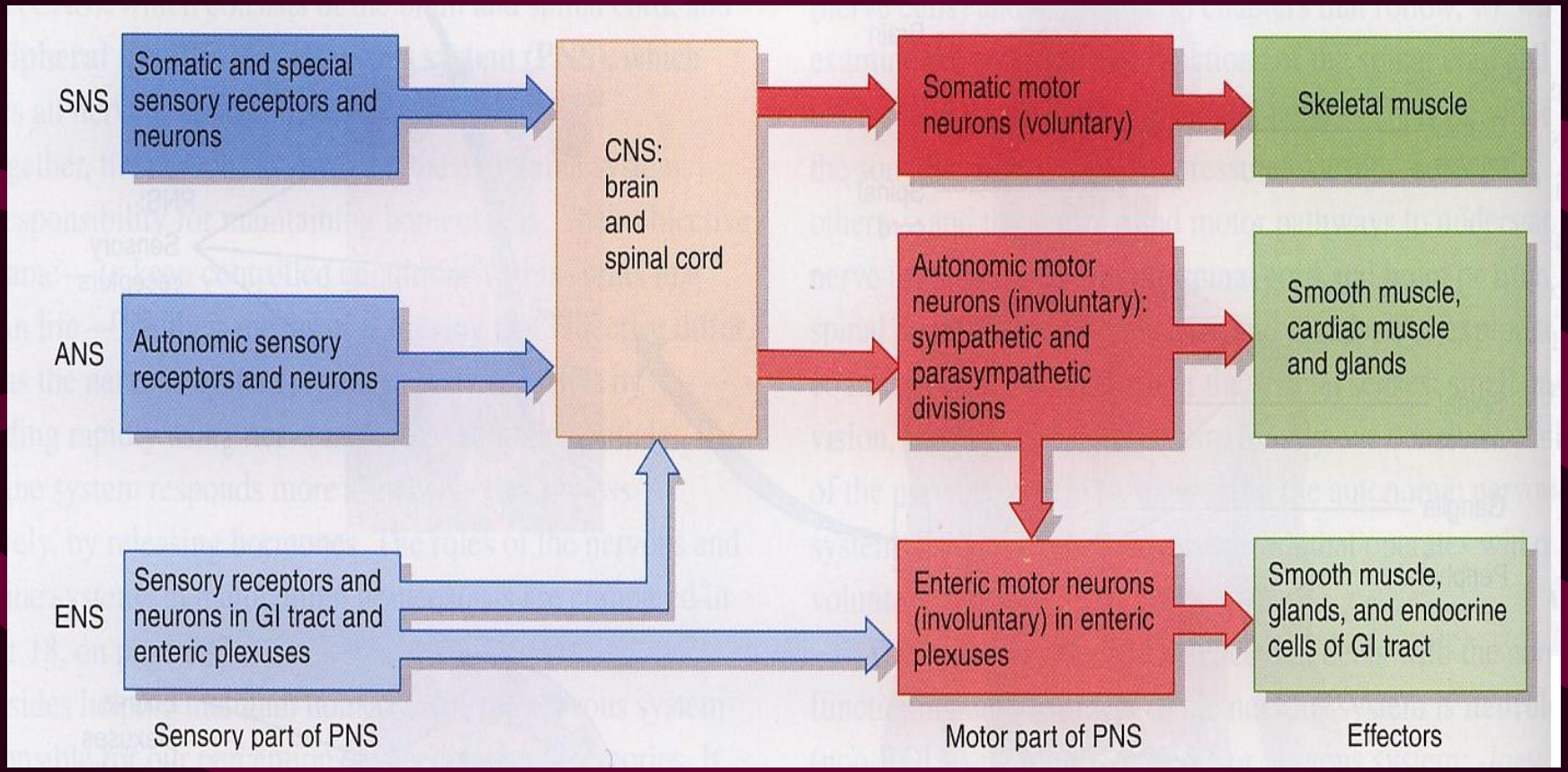
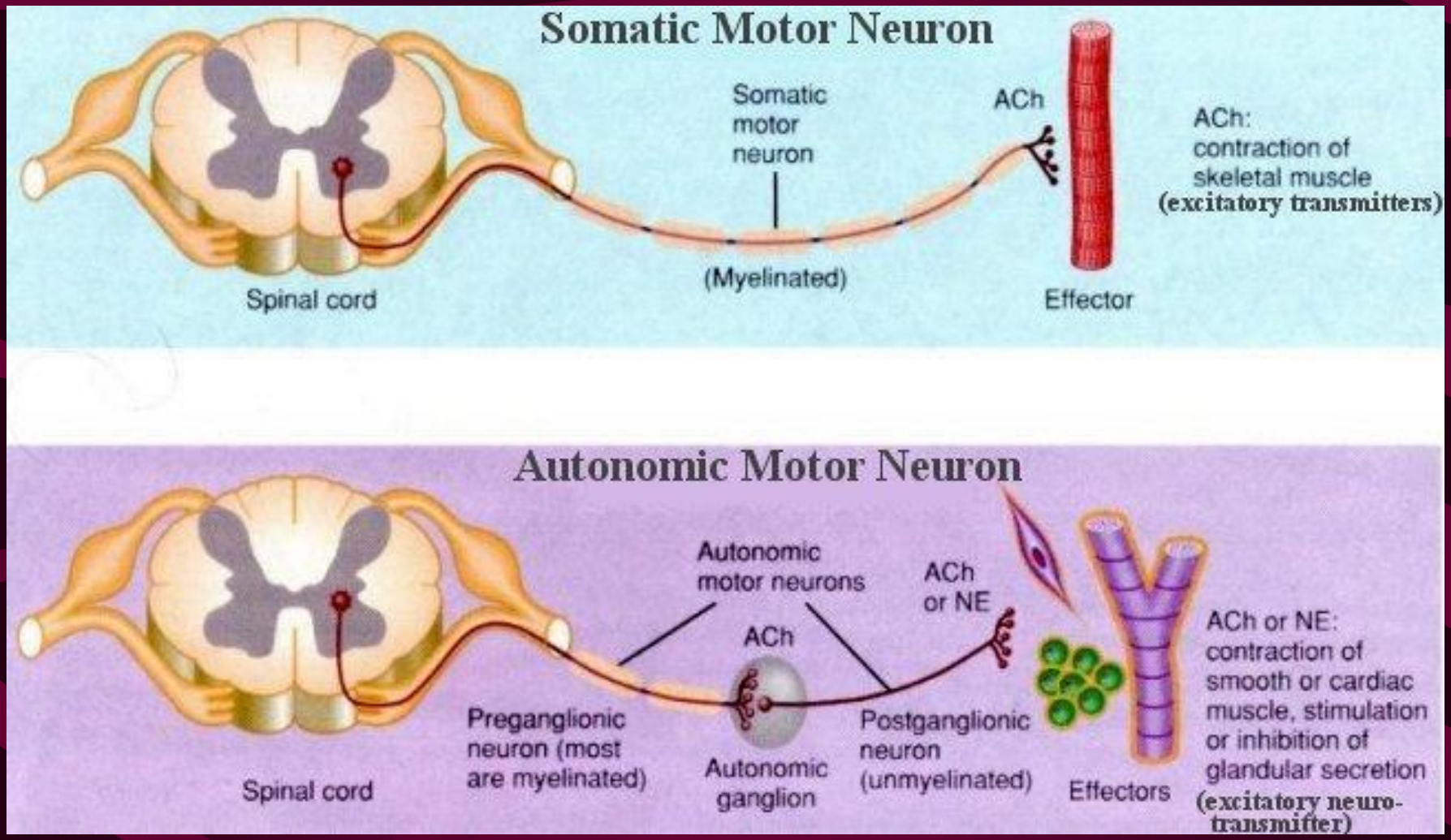
Organization of the nervous system



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 388, Figure 12.2

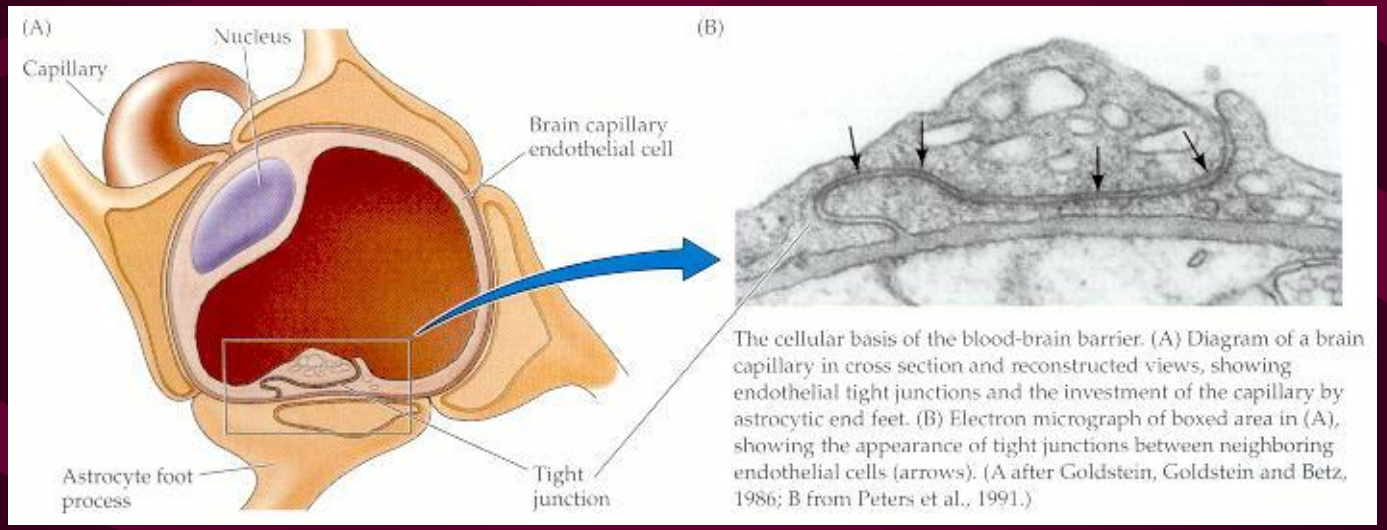

Somatic Motor Neuron
Somatic motor neuron
ACh
ACh: contraction of skeletal muscle (excitatory transmitters)
Spinal cord
(Myelinated)
Effector
Autonomic Motor Neuron
Autonomic motor neurons
ACh or NE
ACh
Preganglionic neuron (most are myelinated)
Postganglionic neuron (unmyelinated)
ACh or NE: contraction of smooth or cardiac muscle, stimulation or inhibition of glandular secretion (excitatory neuro-transmitter)
Spinal cord
Autonomic ganglion
Effectors

Facts about human brain

- weighs about 3 pounds (1.5 kg) or about 2% of the body's weight
- contains 1.1 trillion cells, including 100 billion neurons, 10x more glial cells
- neurons on the average have 5000 connections called synapse from other neurons
- brain uses 20-25% of the body's oxygen and glucose, uses 20% of blood flow but it is only 2% of the body's weight

Blood brain barrier

- BBB selectivity protects the brain
- Cerebrospinal fluid is a salty solution that is continuously secreted by the choroid plexus
- The choroid plexus is remarkably similar to kidney tissue and consist of capillaries and transporting epiphelium derived from the ependyma



The cellular basis of the blood-brain barrier. (A) Diagram of a brain capillary in cross section and reconstructed views, showing endothelial tight junctions and the investment of the capillary by astrocytic end feet. (B) Electron micrograph of boxed area in (A), showing the appearance of tight junctions between neighboring endothelial cells (arrows). (A after Goldstein, Goldstein and Betz, 1986; B from Peters et al., 1991.)

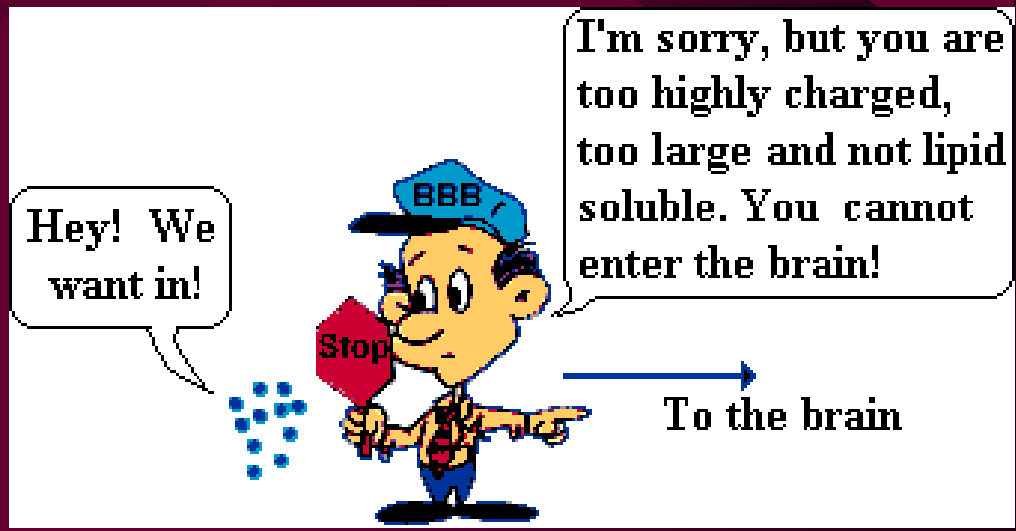
Blood brain barrier selectivity

- The choroid plexus cells selectively pump sodium and other solutes from plasma into the ventricles, creating an osmotic gradient that draws water along with the solutes

- free permeability (passive diffusion):
  - small molecules: H2O, O2, CO2, NH3, ethanol
  - lipid soluble molecules: steroid hormones

- carrier mediated transport:
  - glucose
  - amino acids

- pinocytosis



The BBB can be broken down by:

Hypertension (high blood pressure): high blood pressure opens the BBB

Development: the BBB is not fully formed at birth.

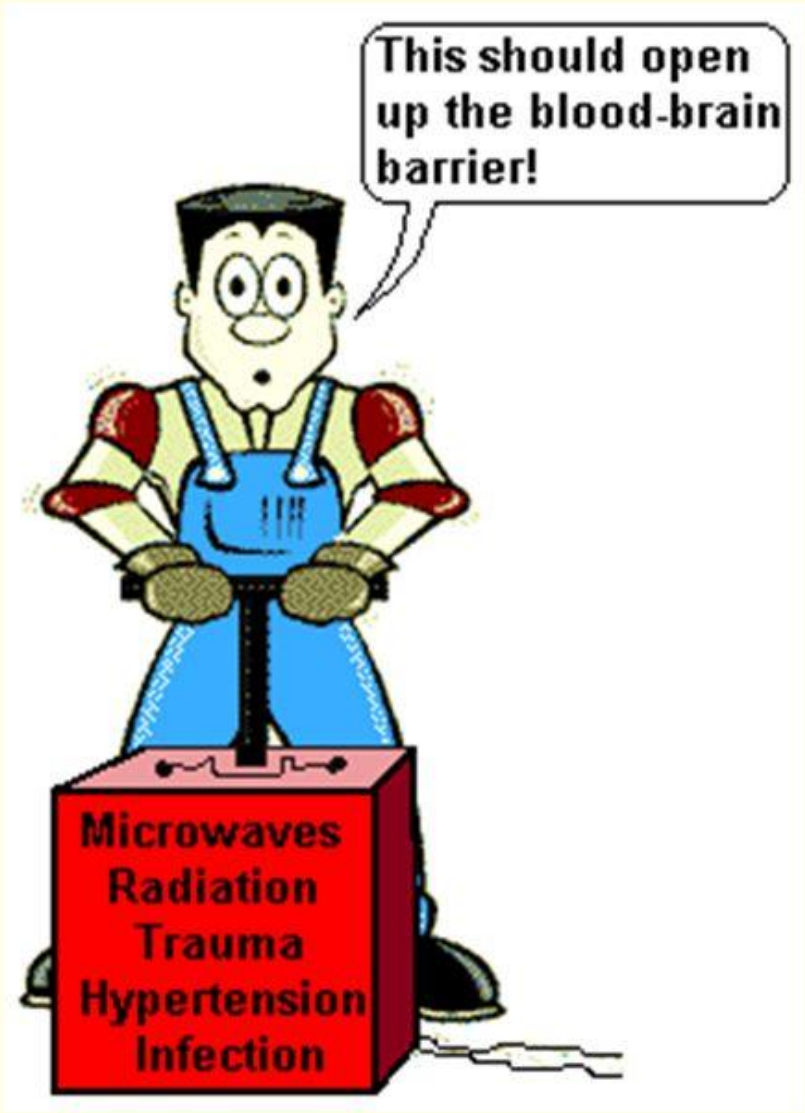
Hyperosmolity: a high concentration of a substance in the blood can open the BBB.

Microwaves: exposure to microwaves can open the BBB.

Radiation: exposure to radiation can open the BBB.

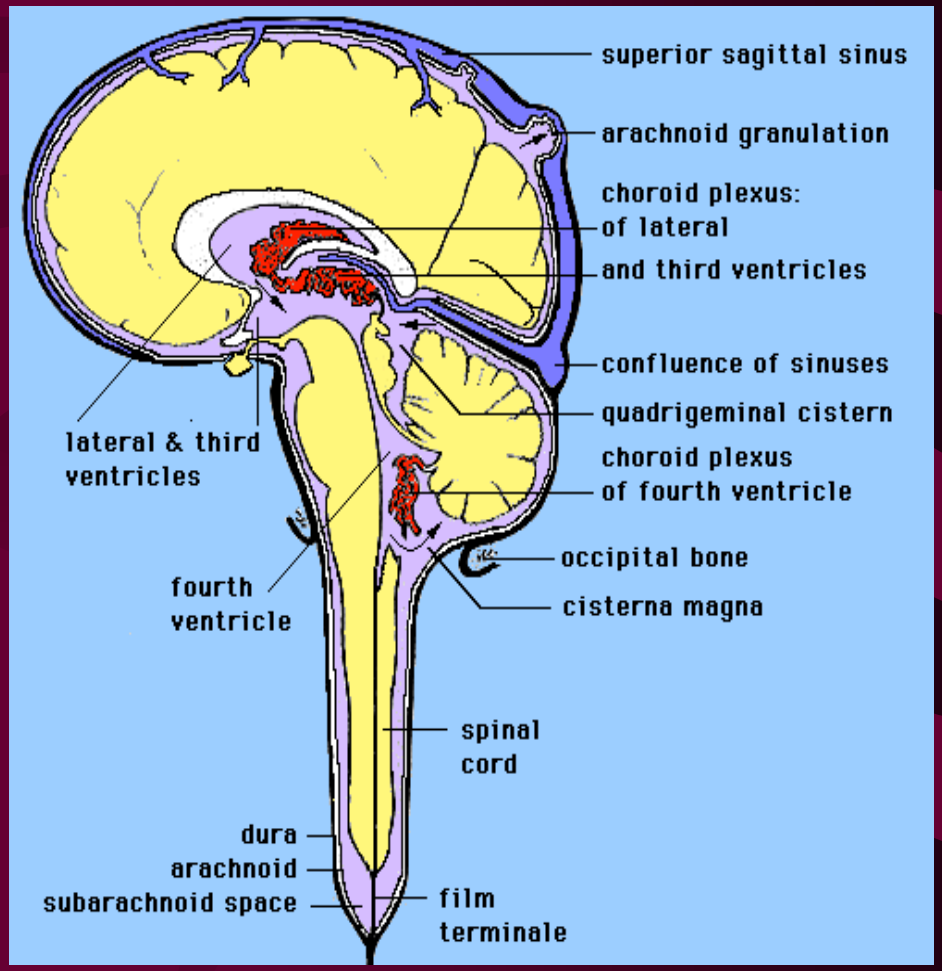
Infection: exposure to infectious agents can open the BBB.

Trauma, Ischemia, Inflammation, Pressure: injury to the brain can open the BBB.



CSF Production

- 70 % CSF produced in choroid plexuses of lateral, third and fourth ventricles
- produced at rate of 500 ml/day or approximately 20ml/hour (0.3-0.5 ml/kg/hr)
- eliminated by being absorbed into the arachnoid villi --> dural sinus --> jugular system

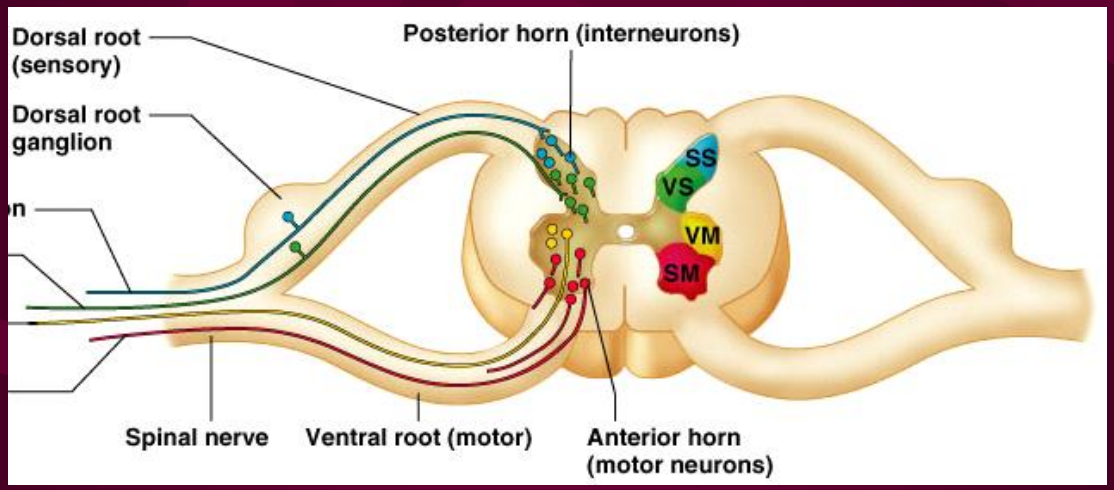


CSF Functions

- provide mechanical protection
- maintain a stable extracellular environment for the brain
- remove some waste products
- nutrition
- convey messages? (hormones/releasing factors/neurotransmitters)

Spinal Cord

- The spinal cord is the major pathway for information flowing back and forth between brain and skin, joints, and muscles of the body
- Gray matter – H-shaped central portion
  - consists of cell bodies and axons of neurons
  - two pairs of "horns"
    - Dorsal (posterior) horns – cells transmit sensory information
    - Ventral (anterior) horns – contains alpha motor neurons with axons terminating on skeletal muscle
  - Interneurons (*Renshaw cells*) – in ventral horn



- The simplest reflex arc is one with a single synapse between the afferent and efferent neurons

- Such arcs are monosynaptic, and reflexes occurring in them are called **monosynaptic reflexes**

- Reflex arcs in which one or more interneuron is interposed between the afferent and efferent neurons are called **polysynaptic reflexes**

Polysynaptic reflex-the withdrawal reflex

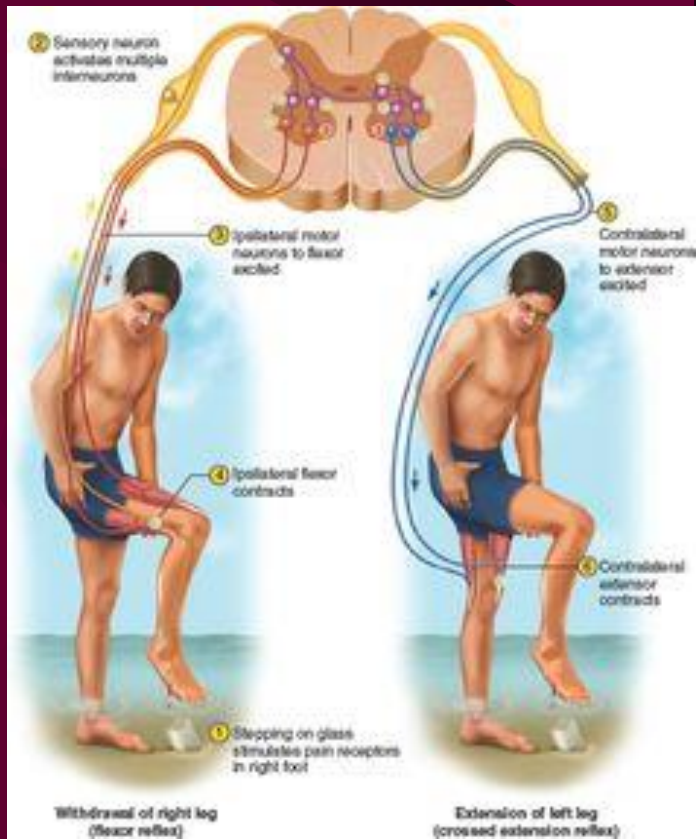
- When injurious stimuli are applied to the skin, there is reflex withdrawal of the skin from the source of the injury

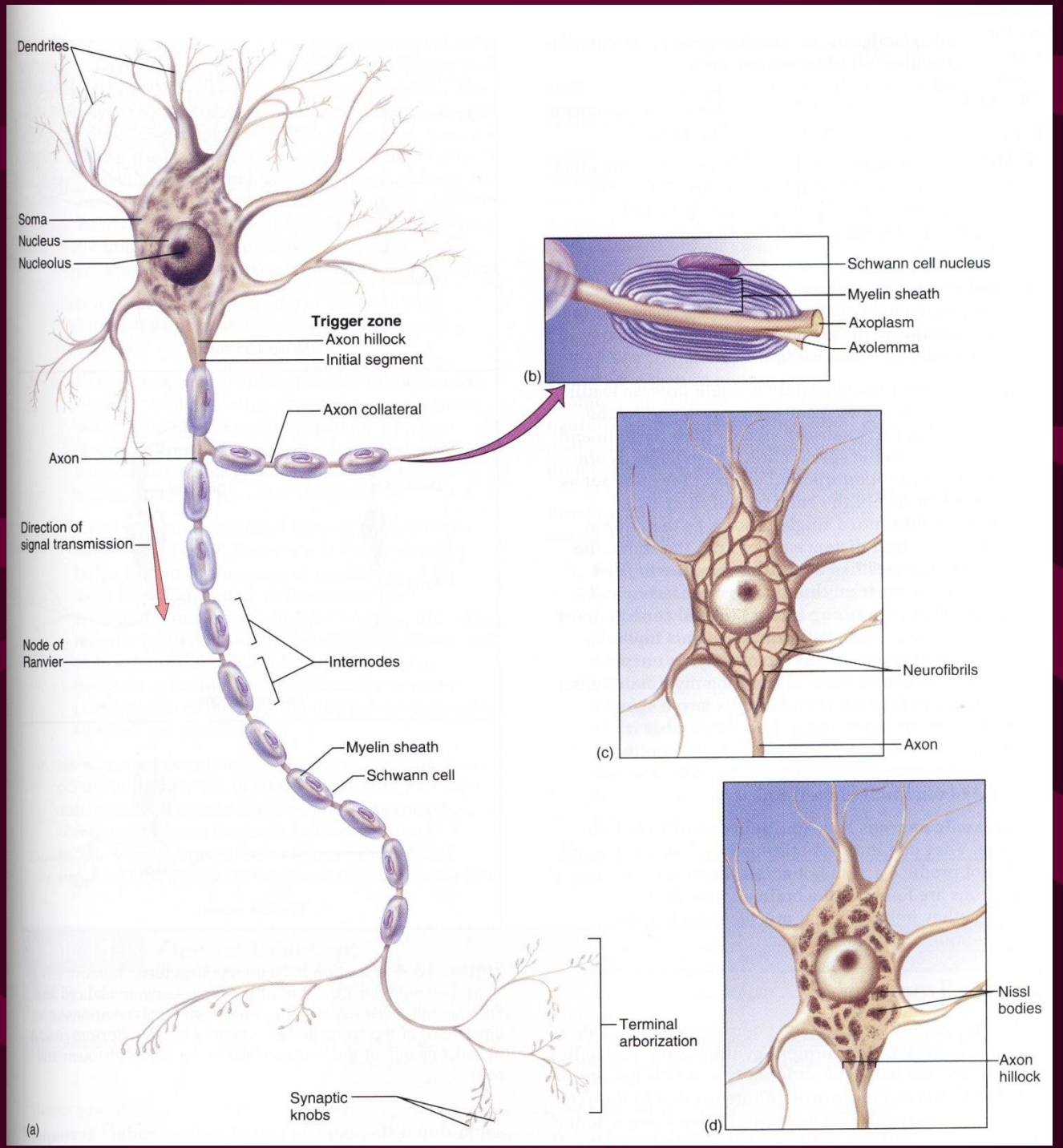
- The stimuli that elicit this response are:

- excessive force sufficient to penetrate or cause damage to the skin,

- excessive heat that would denature proteins in the tissues are applied to the skin,

-other physical or chemical stimuli that cause injury





Saladin; Figure 13.3

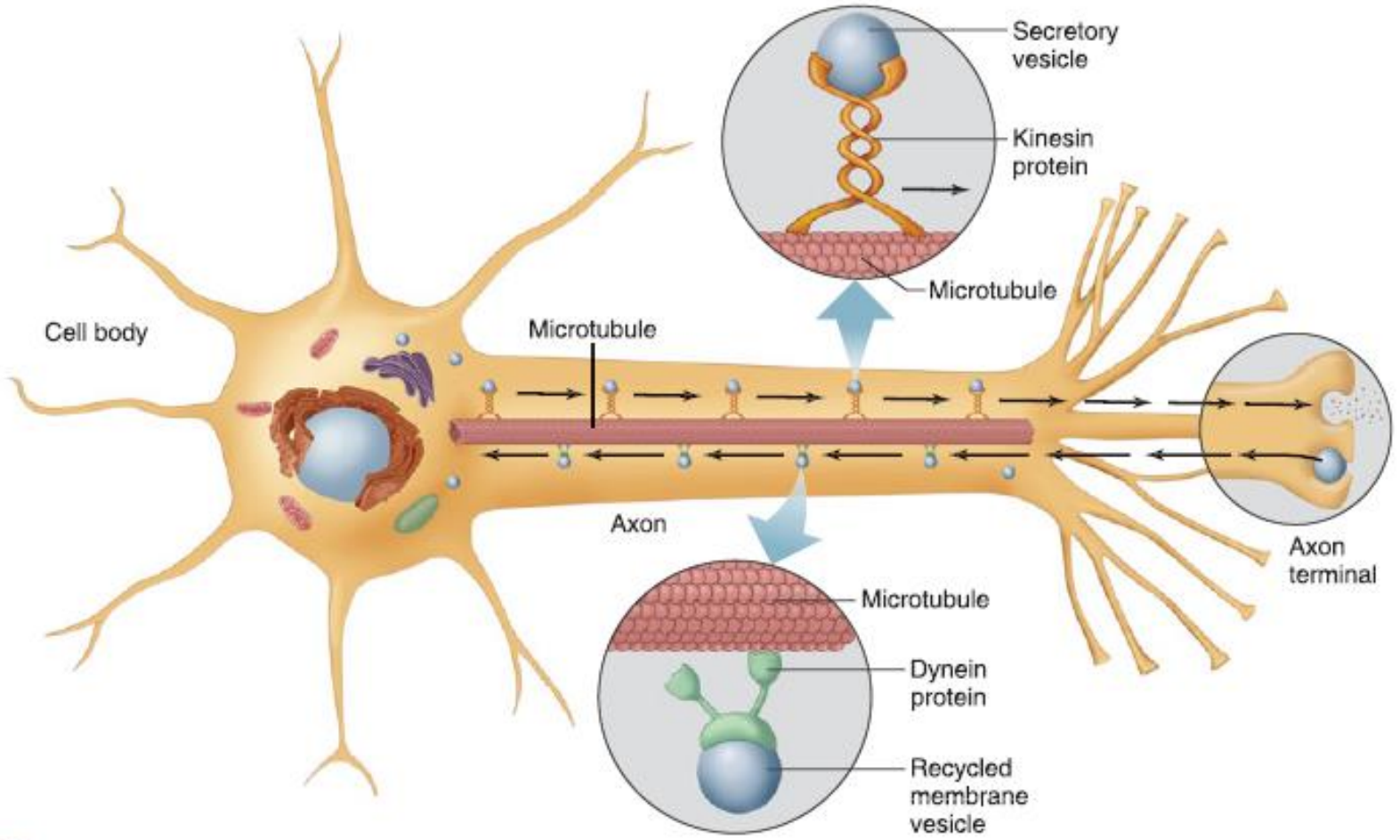


FIGURE 4–4 **Axonal transport along microtubules by dynein and kinesin.** Fast and slow axonal orthograde transport occurs along microtubules that run along the length of the axon from the cell body to the terminal. Retrograde transport occurs from the terminal to the cell body. (From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Electrical signals in neurons

- **Propagation of nerve impulses**
  - nerve impulses propagate more rapidly along myelinated axon than along unmyelinated axons
  - larger-diameter axon propagate impulses faster then small ones
  - temperature
  - synapses
  - toxin
  - local anesthetic

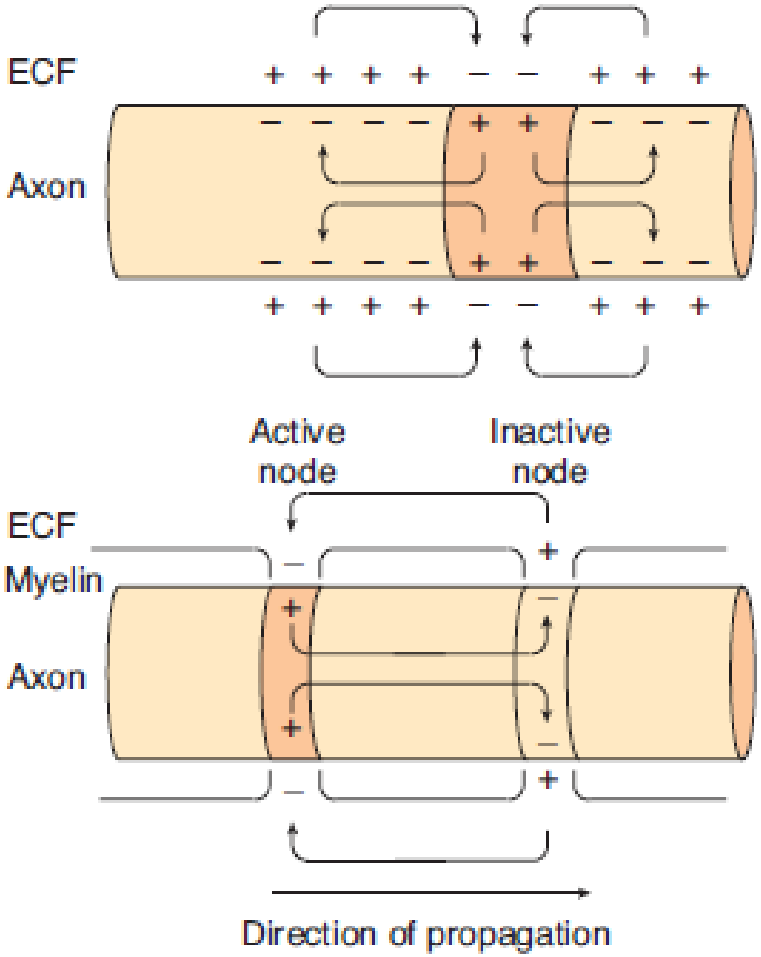


FIGURE 4–10 **Local current flow (movement of positive charges) around an impulse in an axon. Top:** Unmyelinated axon. **Bottom:** Myelinated axon. Positive charges from the membrane ahead of and behind the action potential flow into the area of negativity represented by the action potential ("current sink"). In myelinated axons, depolarization jumps from one node of Ranvier to the next (saltatory conduction).

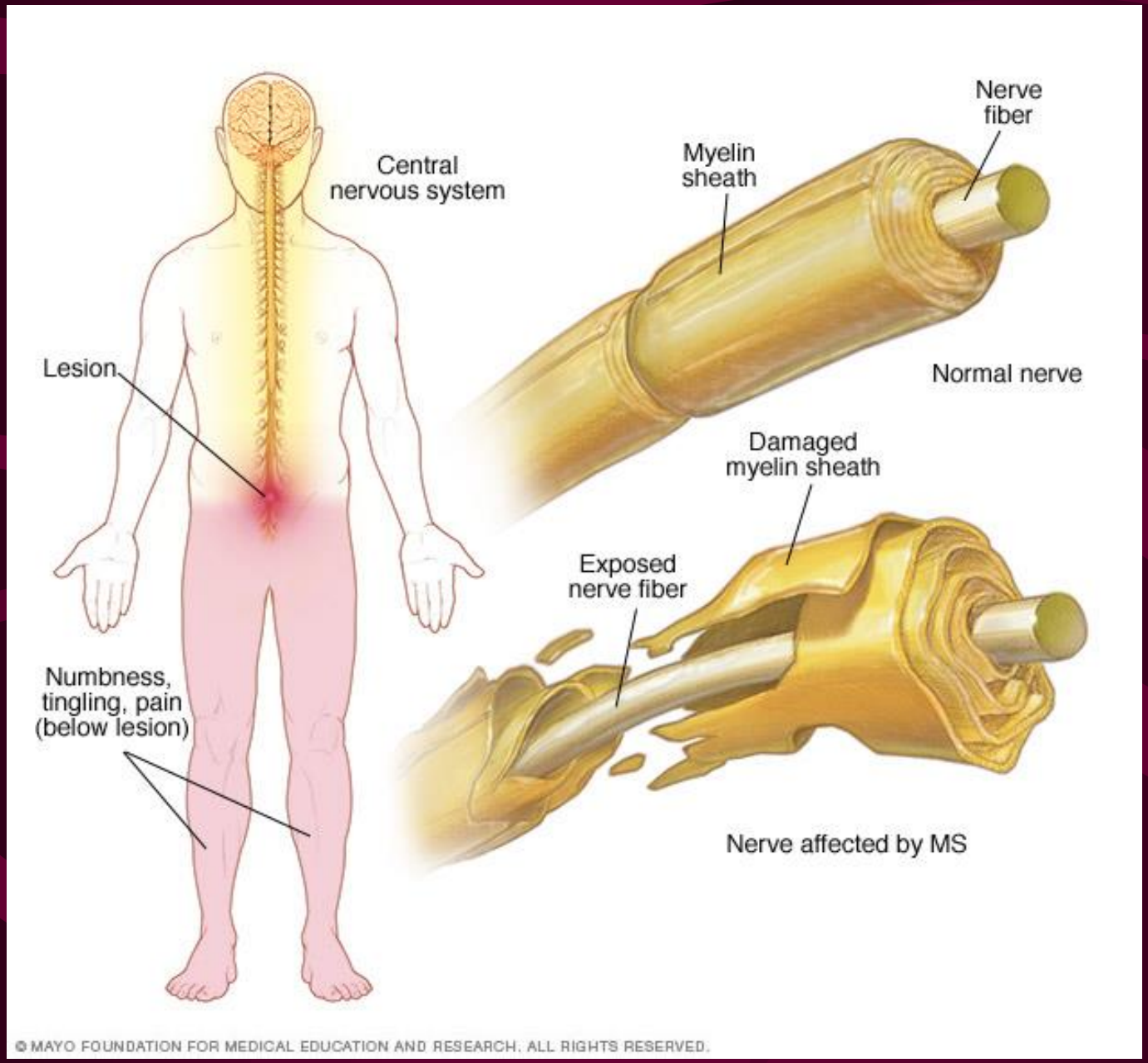
TABLE 4–1 Nerve fiber types in mammalian nerve.[a]

Fiber Type	Function	Fiber Diameter (μm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period (ms)
A					
α	Proprioception; somatic motor	12–20	70–120		
β	Touch, pressure	5–12	30–70	0.4–0.5	0.4–1
γ	Motor to muscle spindles	3–6	15–30		
δ	Pain, cold, touch	2–5	12–30		
B	Preganglionic autonomic	<3	3–15	1.2	1.2
C					
Dorsal root	Pain, temperature, some mechano-reception	0.4–1.2	0.5–2	2	2
Sympathetic	Postganglionic sympathetic	0.3–1.3	0.7–2.3	2	2

[a]A and B fibers are myelinated; C fibers are unmyelinated.

TABLE 4–3 Relative susceptibility of mammalian A, B, and C nerve fibers to conduction block produced by various agents.

Susceptibility to:	Most Susceptible	Intermediate	Least Susceptible
Hypoxia	B	A	C
Pressure	A	B	C
Local anesthetics	C	B	A


Central
nervous system
Lesion
Numbness,
tingling, pain
(below lesion)
Nerve
fiber
Myelin
sheath
Normal nerve
Damaged
myelin sheath
Exposed
nerve fiber
Nerve affected by MS
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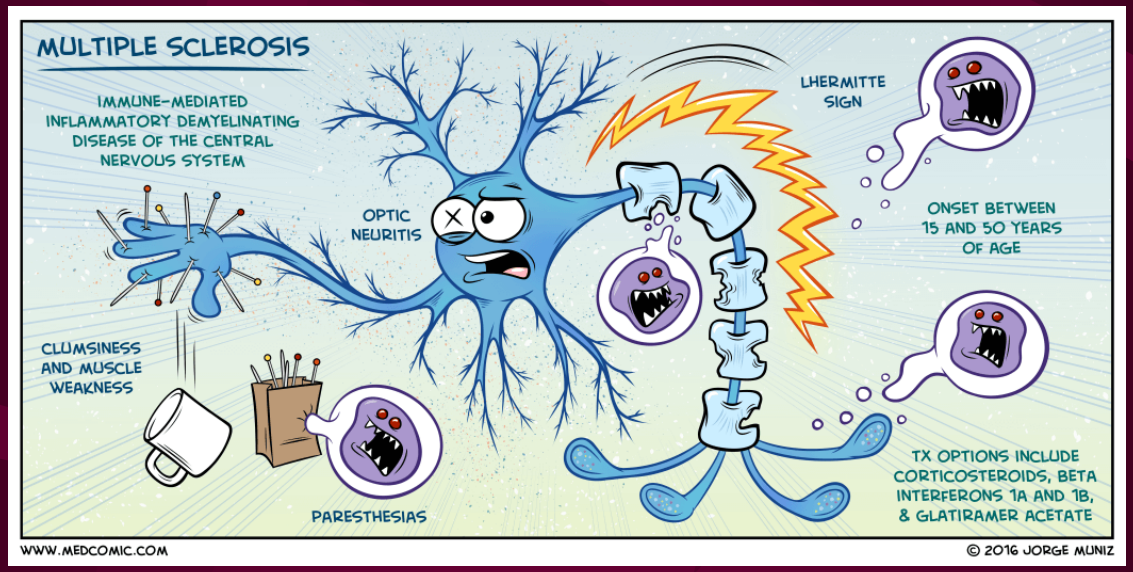
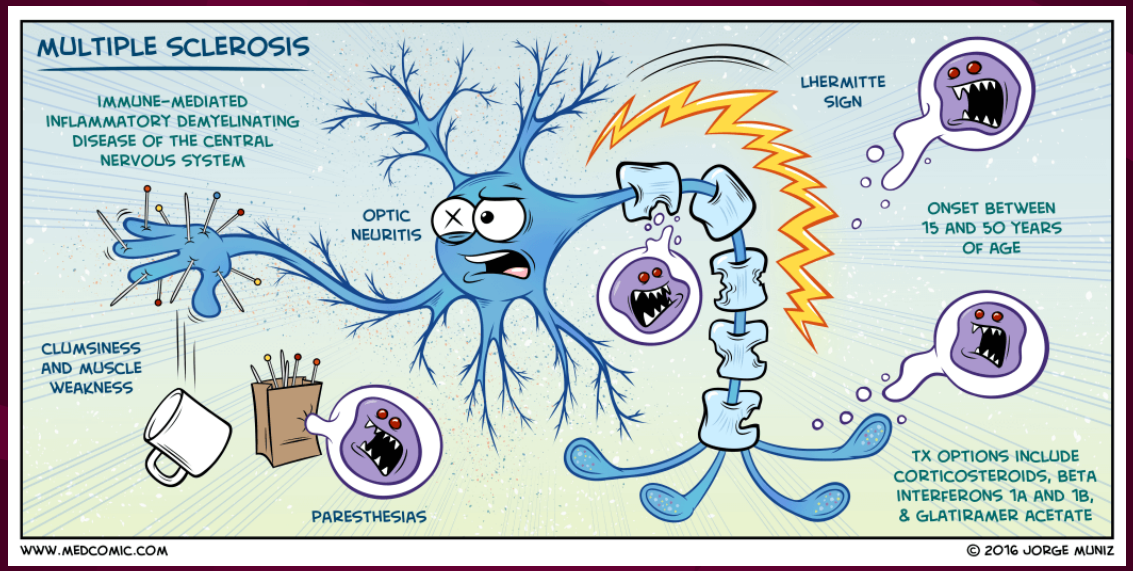
Multiple Sclerosis

- **Normal conduction of action potentials relies on the insulating properties of myelin.**
  - Thus, defects in myelin can have major adverse neurological conseqences
  - One example is multiple sclerosis, an autoimmune disease that afect over 3 million people worldwide, usually striking between the ages of 20 and 50.



Multiple Sclerosis-risk factors

- **Age**
- **Sex.** Women are about twice as likely as men are to develop MS
- **Family history.** If one of parents or siblings has had MS, patient is at higher risk of developing the disease
- **Certain infections.** A variety of viruses have been linked to MS, including Epstein-Barr, the virus that causes infectious mononucleosis



Multiple Sclerosis-risk factors

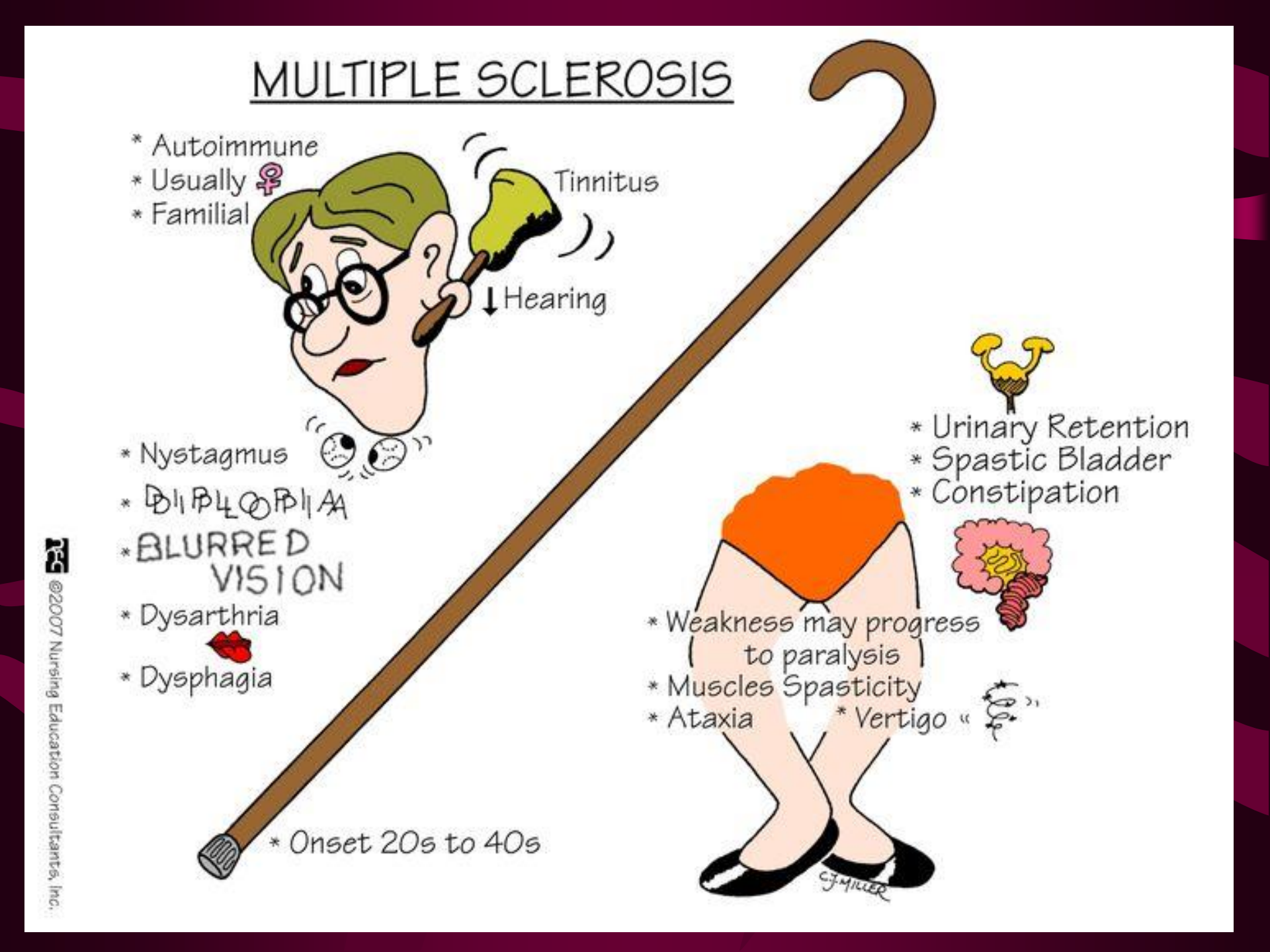
- **Race.** White people, particularly those of Northern European descent, are at highest risk of developing MS. People of Asian, African or Native American descent have the lowest risk.

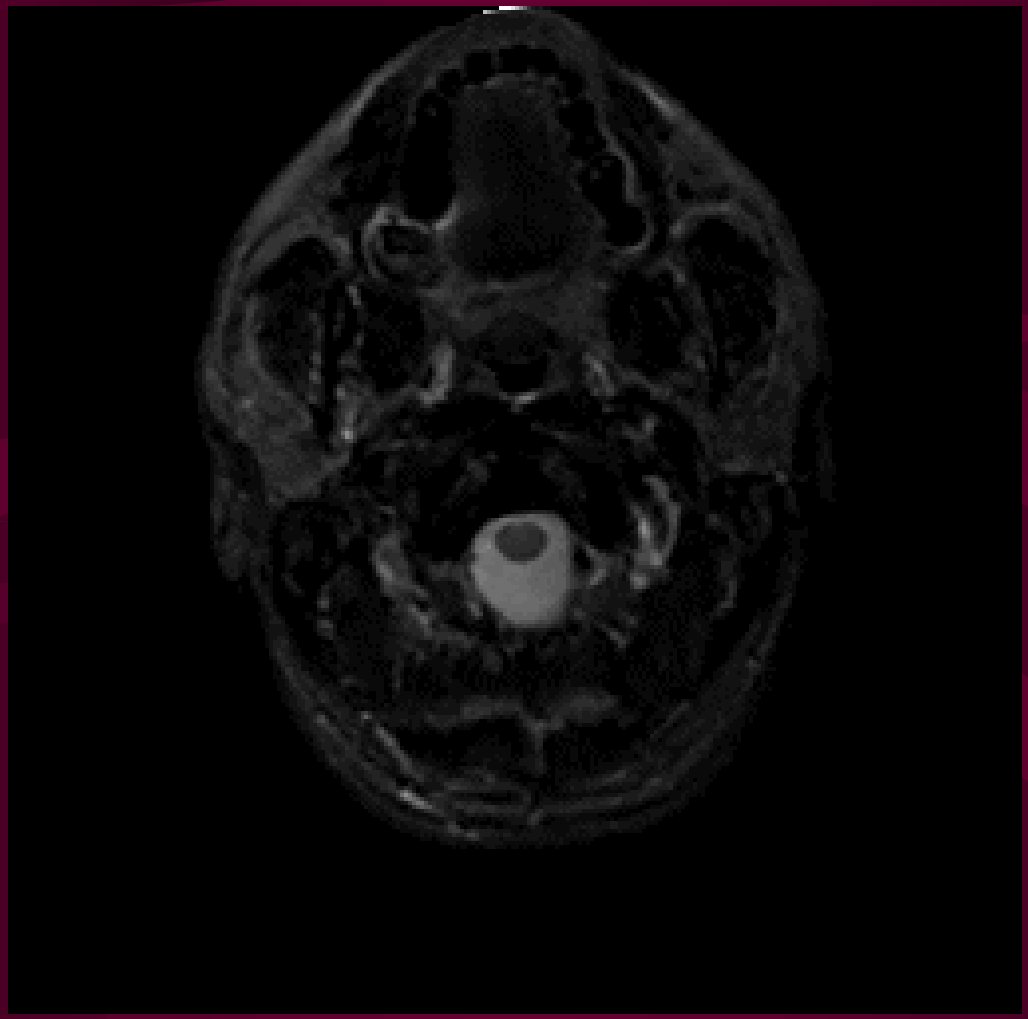
- **Climate.** MS is far more common in countries with temperate climates, including Canada, the northern United States, New Zealand, southeastern Australia and Europe.

- **Certain autoimmune diseases.** You have a slightly higher risk of developing MS if you have thyroid disease, type 1 diabetes or inflammatory bowel disease.

- **Smoking.** Smokers who experience an initial event of symptoms that may signal MS are more likely than nonsmokers to develop a second event that confirms relapsing-remitting MS

MULTIPLE SCLEROSIS





Multiple Sclerosis – treatment options

- Medications to Modify the Disease
  - Beta interferons
    - Interferon beta-1b (Betaseron)
    - Interferon beta-1a (Avonex, Rebif)
  - Glatiramer
- Medications used to treat the symptoms of MS
  - Corticosteroids
  - Muscle relaxants
    - Tizanidine (Zanaflex)
    - Baclofen (Lioresal)
  - Medications to reduce fatique
    - Amantadine (Symmetrel)
    - Modafinil (Provigil)
- Physical and Occupational Therapy

Electrical signals in neurons

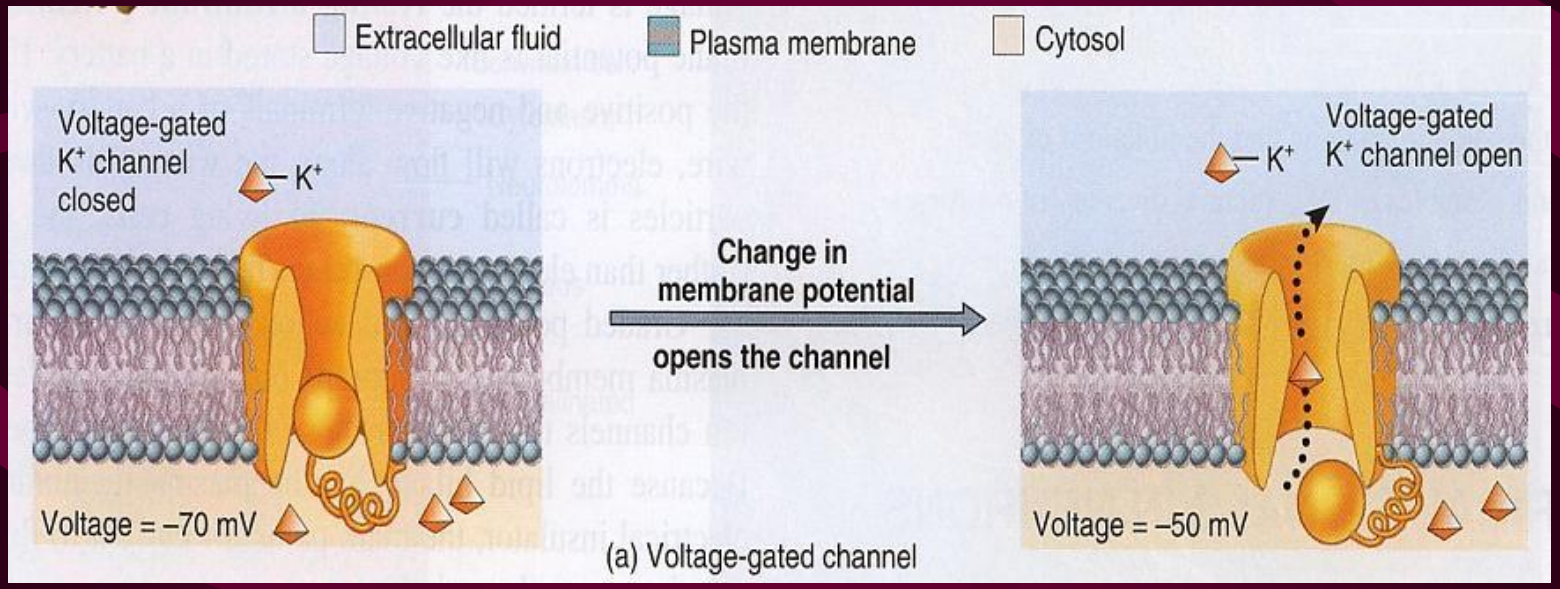
- Ion channels
  - Ion channels are selective.
  - Ion channels may be open or closed.
  - Types of ion channels
    - In leakage channels
    - A voltage-gated channel
    - A ligand-gated channel
    - A mechanically gated channel

Electrical signals in neurons

- In leakage channels, the gates randomly alternate between open and closed position. Typically, plasma membranes have many more potassium ion (K^+) leakage channels than sodium ion (Na^+) leakage channels. Thus, the membranes permeability to K^+ is much higher than its permeability to Na^+.

Electrical signals in neurons

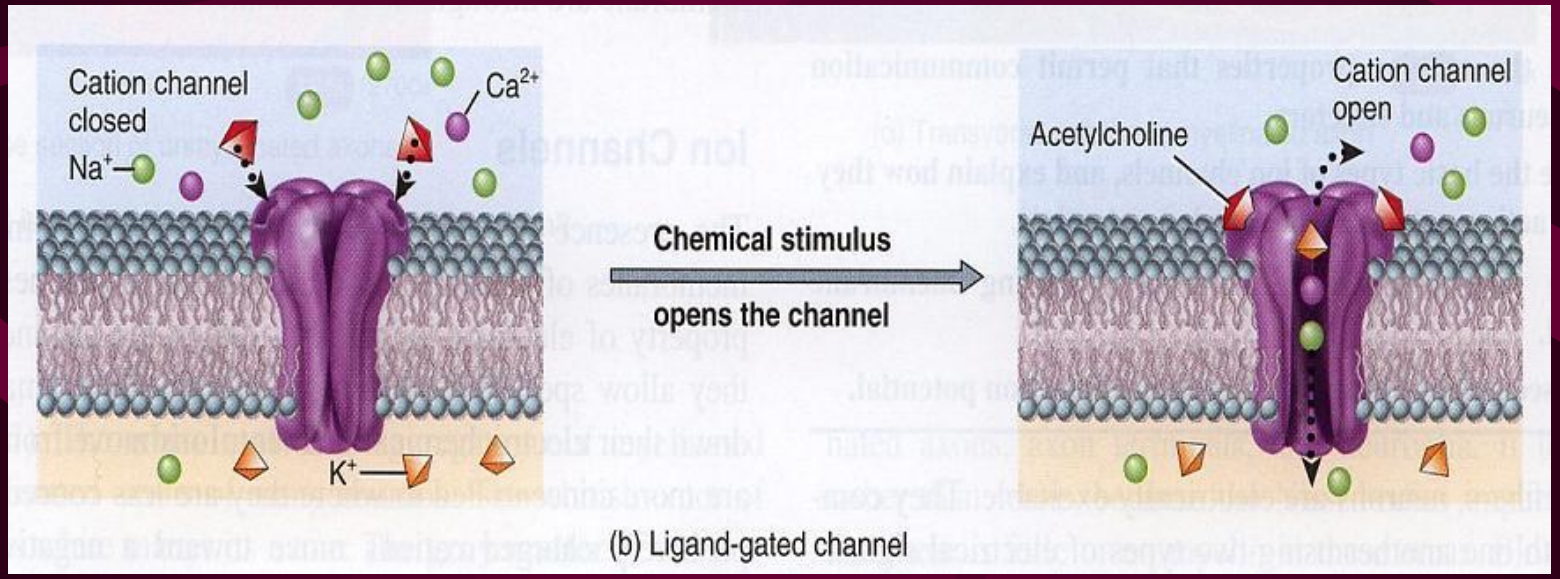
- A voltage-gated channel open in response to a change in membrane potential (voltage). Voltage-gated channels participate in the generation and conduction of action potential



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 396, Figure 12.8

Electrical signals in neurons

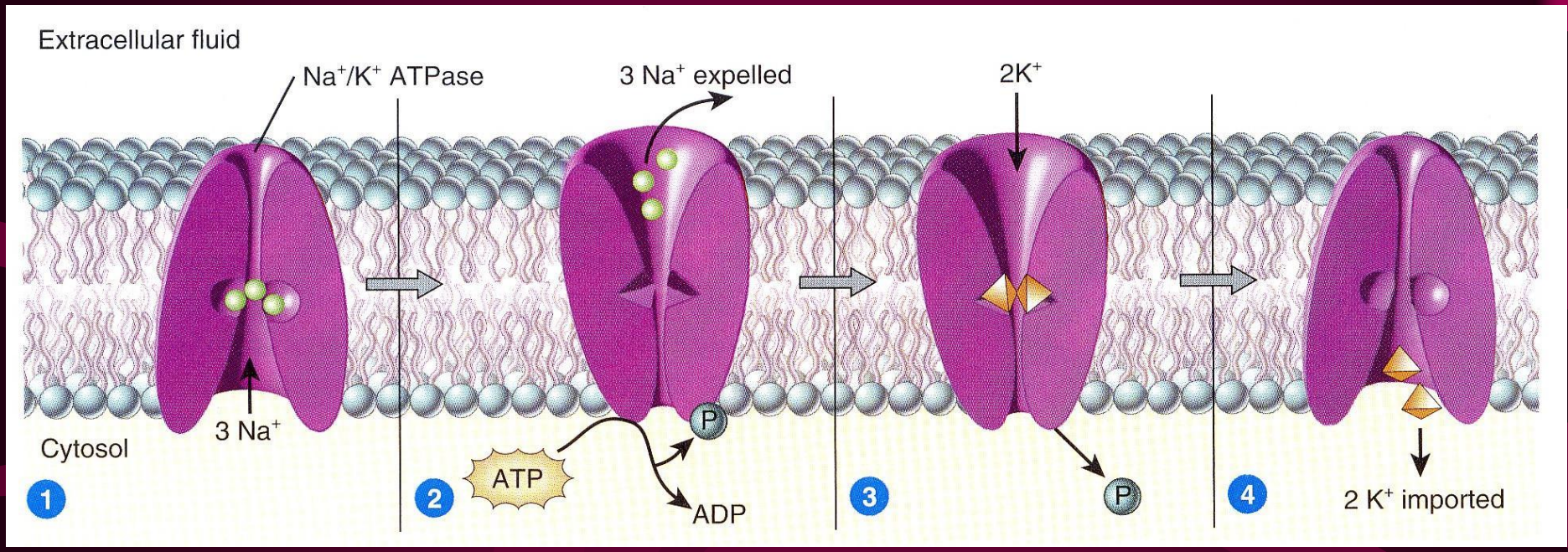
- A ligand-gated channel opens and closes in response to a specific chemical stimulus. It wide variety of chemical ligands – including neurotransmitters, hormones, and particular ions – can open or close ligand-gated channels. The neurotransmitter acetylocholine, for example, opens cation-channels that allow Na^+ and Ca^{2+} to diffuse inward and K^+ to diffuse outward.



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 396, Figure 12.8

Electrical signals in neurons

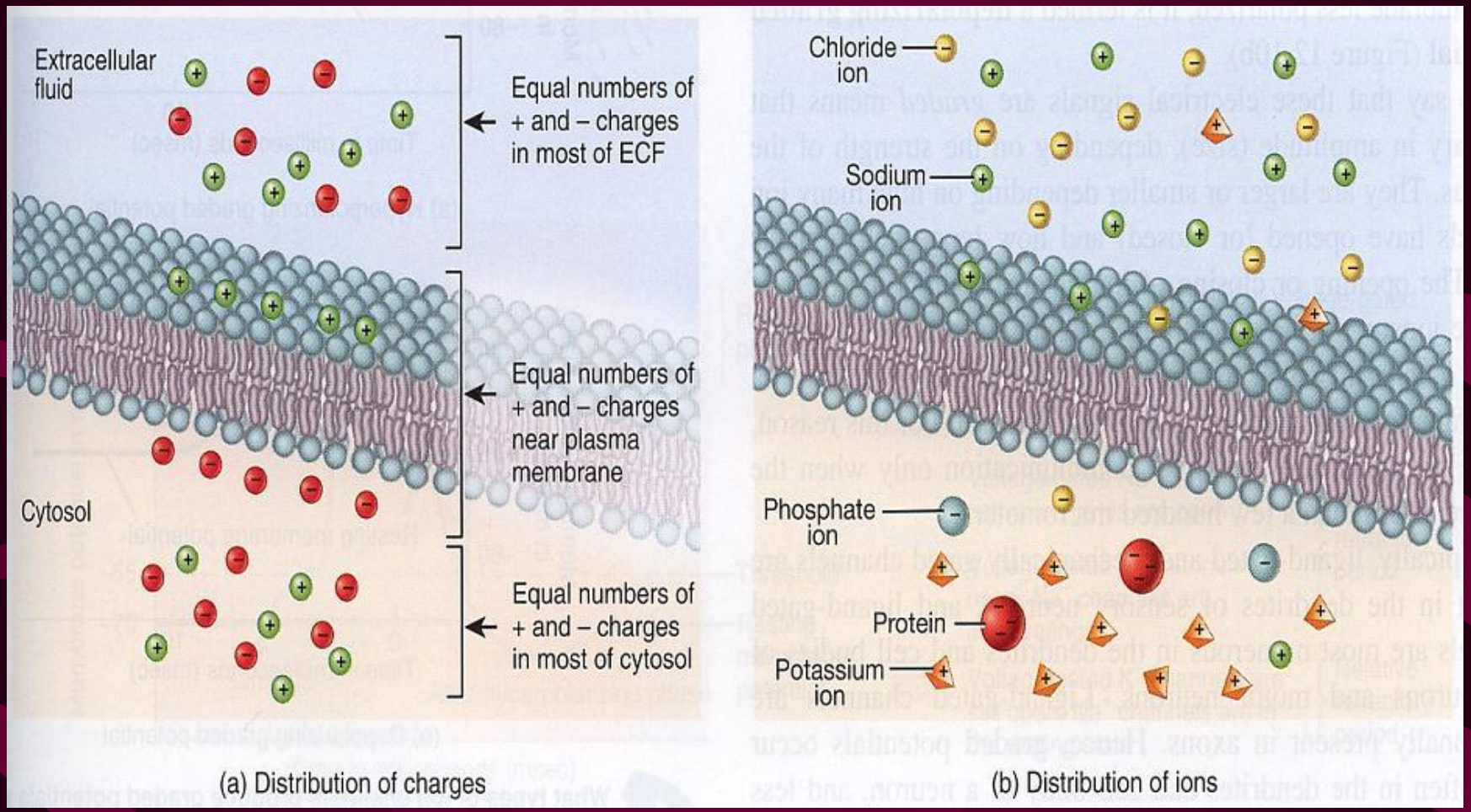
- A mechanically gated channel open or closes in response to mechanical stimulation in the form vibration (such as sound waves), pressure (such a touch), or tissue stretching. The force distorts the channel from resting position, opening the gate.


Extracellular fluid
Na+/K+ ATPase
3 Na+ expelled
2K+
3 Na+
Cytosol
P
ATP
ADP
P
2 K+ imported
1
2
3
4

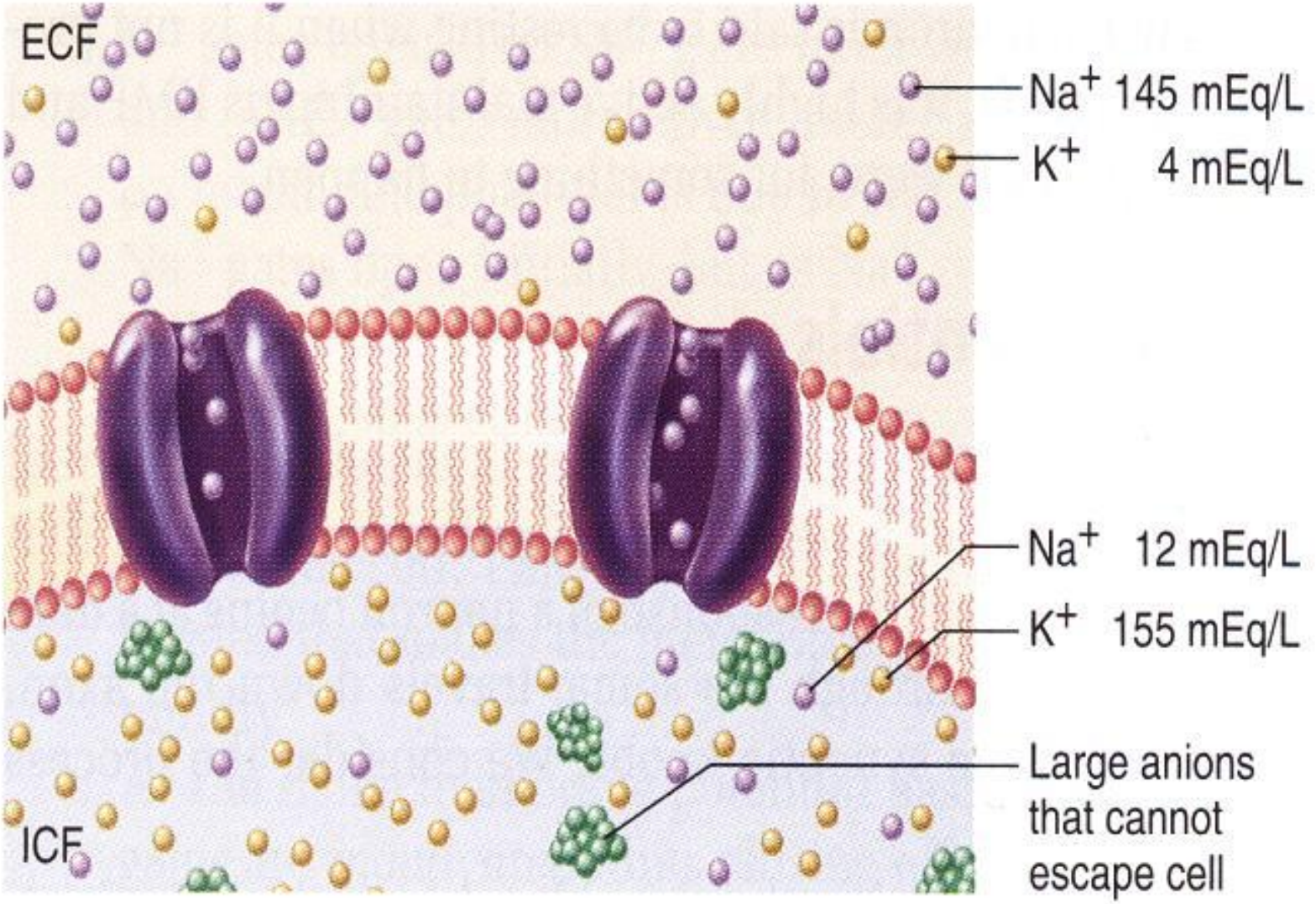
Digitalis purpurea

Electrical signals in neurons

- **Resting membrane potential**
  - resting membrane potential is expressed as the measured potential difference across the cell membrane in millivolts (mV)
  - in neurons, the resting membrane potential ranges from -40 to -90mV. A typical value is -70mV
  - the minus sign indicates that the inside is negative relative to the outside
  - a cell that exhibits a membrane potential is said to be polarized



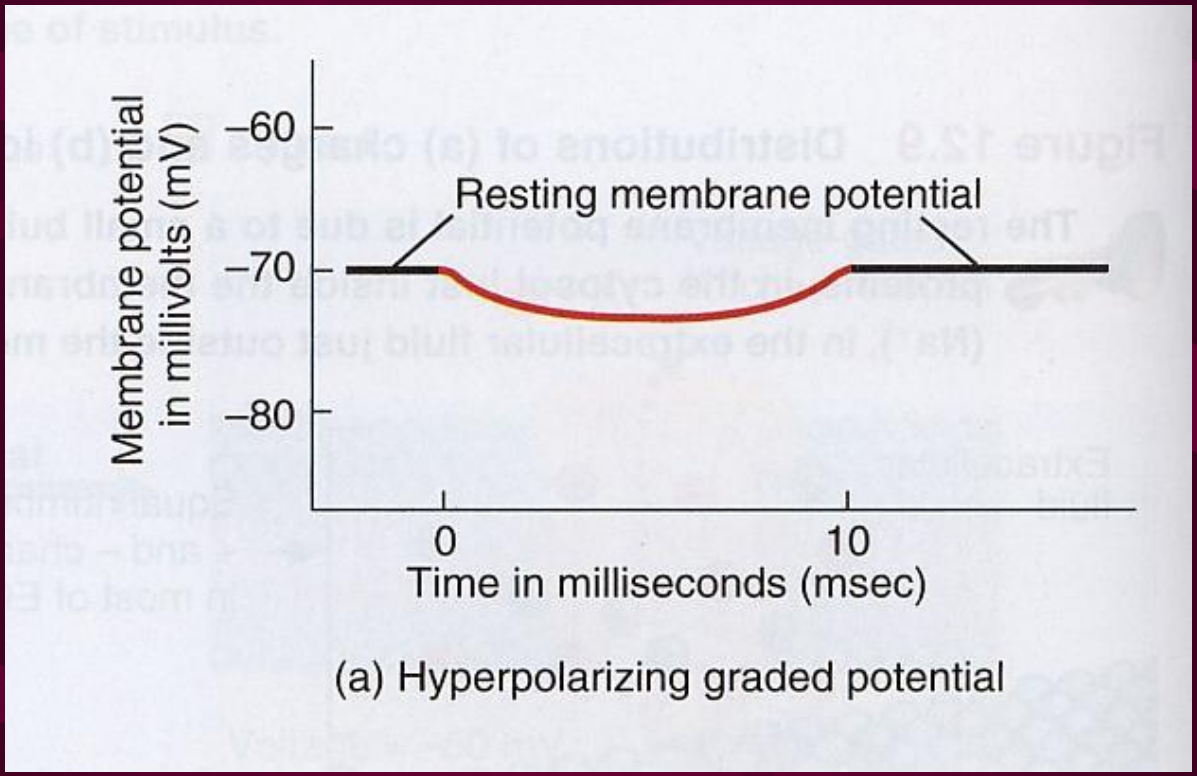
Tortora & Grabowski – Principles of Anatomy & Physiology; Page 397, Figure 12.9



Ionic Basis of the Resting Membrane Potential

Electrical signals in neurons

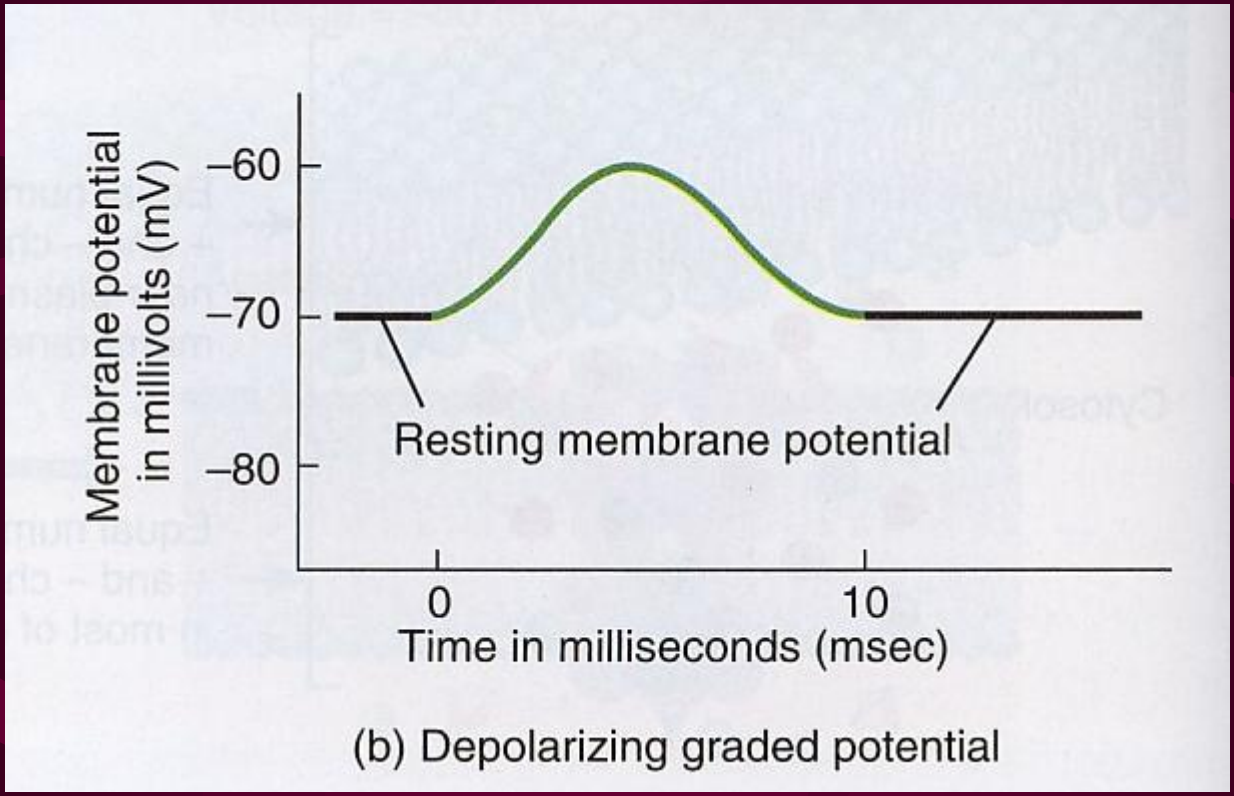
- Graded potential
  - When the response makes the membrane even more polarized (a greater difference in the change between inside and outside) it is termed a hyperpolarizing graded potential.



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 398, Figure 12.10

Electrical signals in neurons

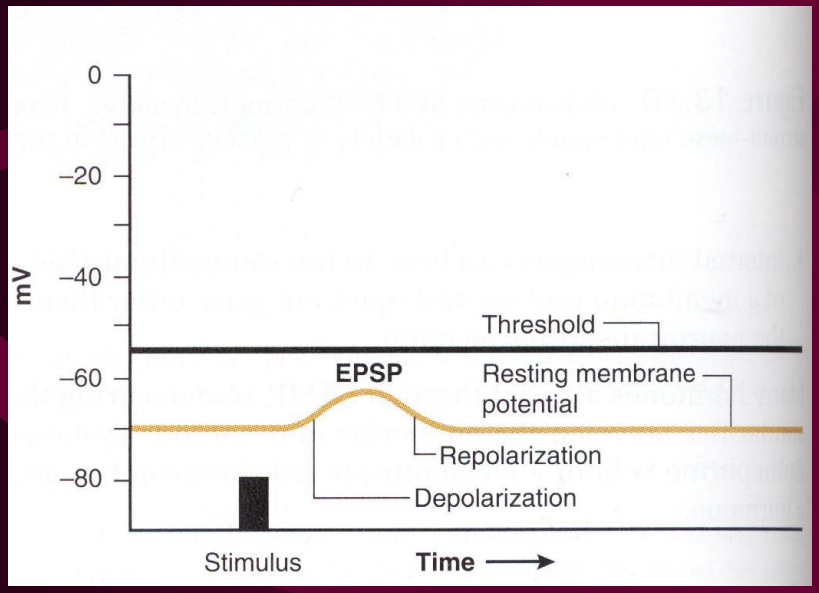
- Graded potential
  - When the response makes the membrane less polarized, it is termed a depolarizing graded potential .

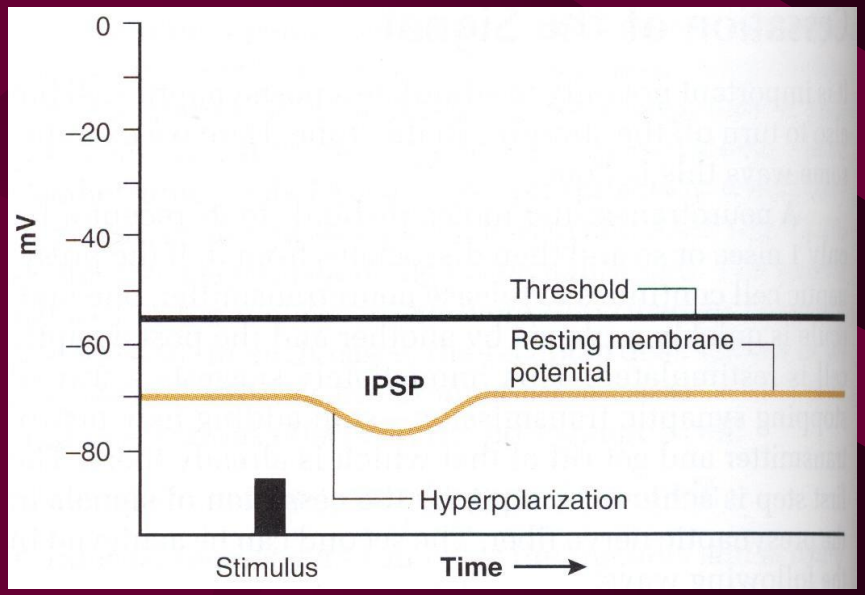


Tortora & Grabowski – Principles of Anatomy & Physiology; Page 398, Figure 12.10

Signal transmission at synapses

- Excitatory and inhibitory synaptic potential
  - EPSP – a depolarizing postsynaptic potential is called an **excitatory postsynaptic potential**
  - IPSP – a hyperpolarizing postsynaptic potential is termed an **inhibitory postsynaptic potential**

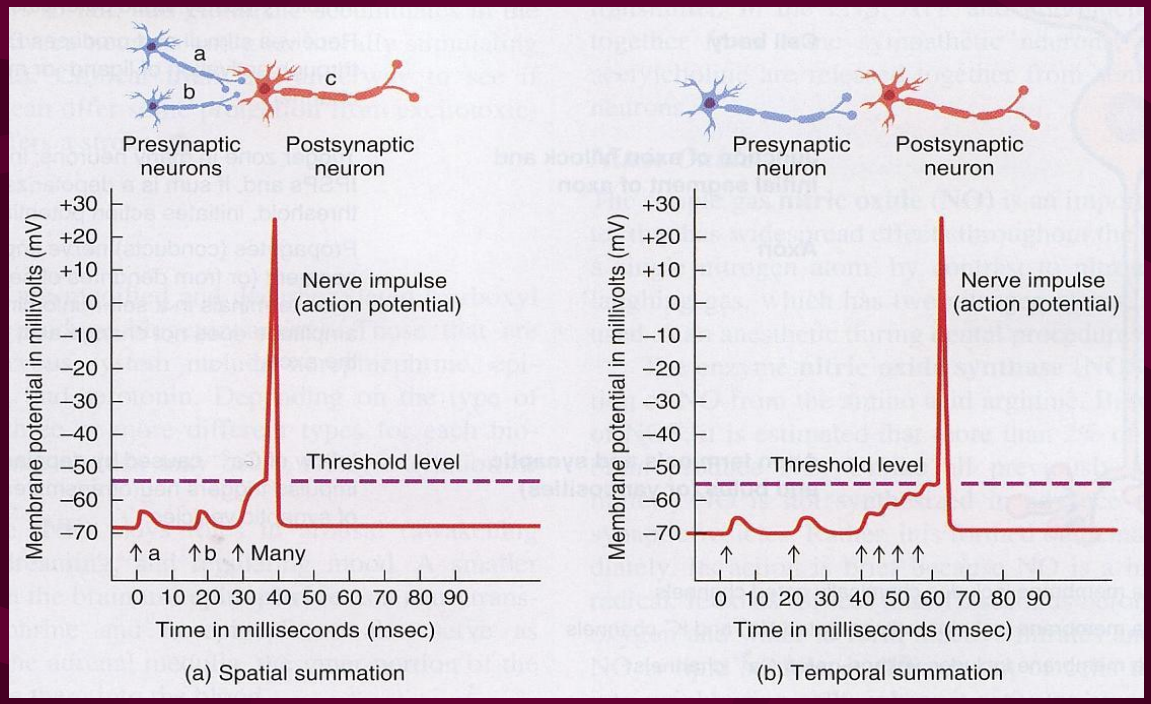




Saladin; Page 478, Figure 13.21

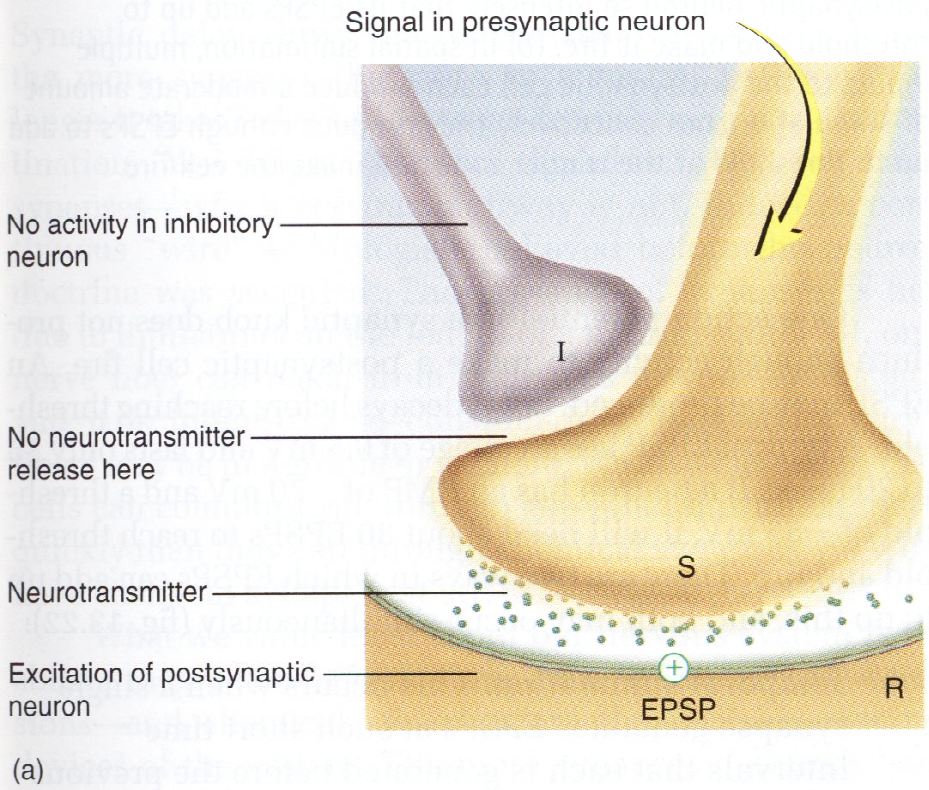
Signal transmission at synapses

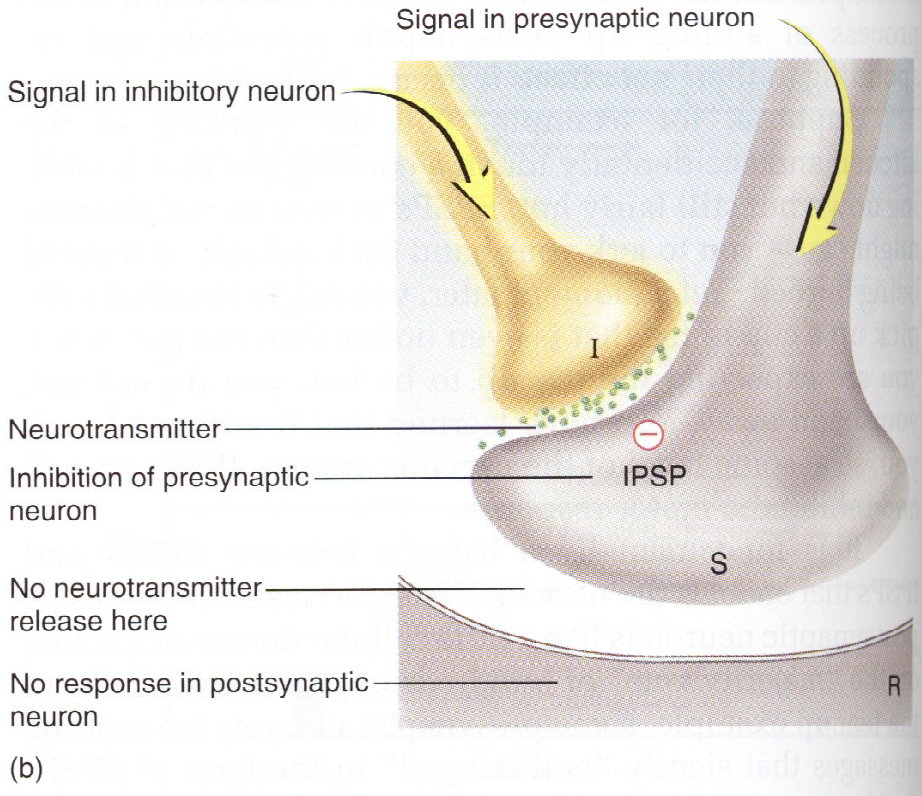
- Summation at synapses
  - **temporal summation** - occurs when two excitatory inputs arrive at a postsynaptic neurons in rapid succession.
  - **spatial summation** – occurs when two excitatory inputs arriver at a postsynaptic neuron simultaneously.



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 407, Figure 12.15

Presynaptic Inhibition





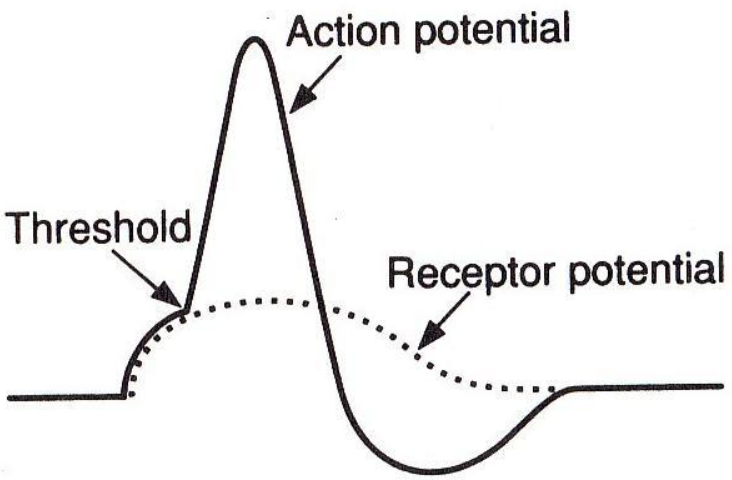
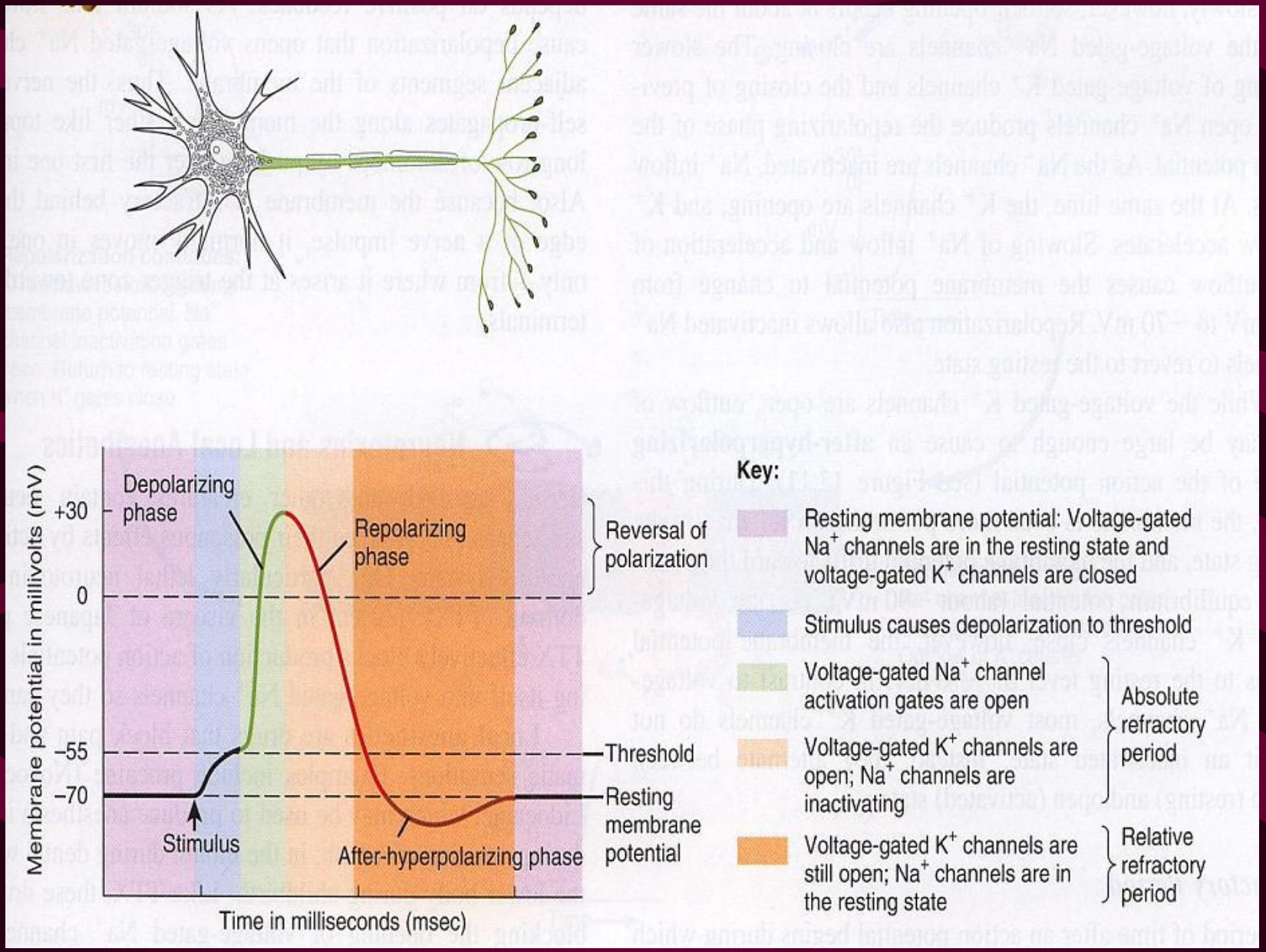


Figure 2-2. Receptor (generator) potential and how it may lead to an action potential.

Costanzo; Page 39, Figure 2-2

Electrical signals in neurons

- **Action potentials** (depolarizing phase, threshold, repolarizing phase)
  - is a very rapid change in membrane potential that occurs when a nerve cell membrane is stimulated.
  - specifically, the membrane potential goes from the resting potential (typically -70mV) to some positive value (typically about +30mV) in a very short period of time (just a few milliseconds).
  - action potential have stereotypical size and shape, are propagating and are all-or-none.



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 399, Figure 12.11

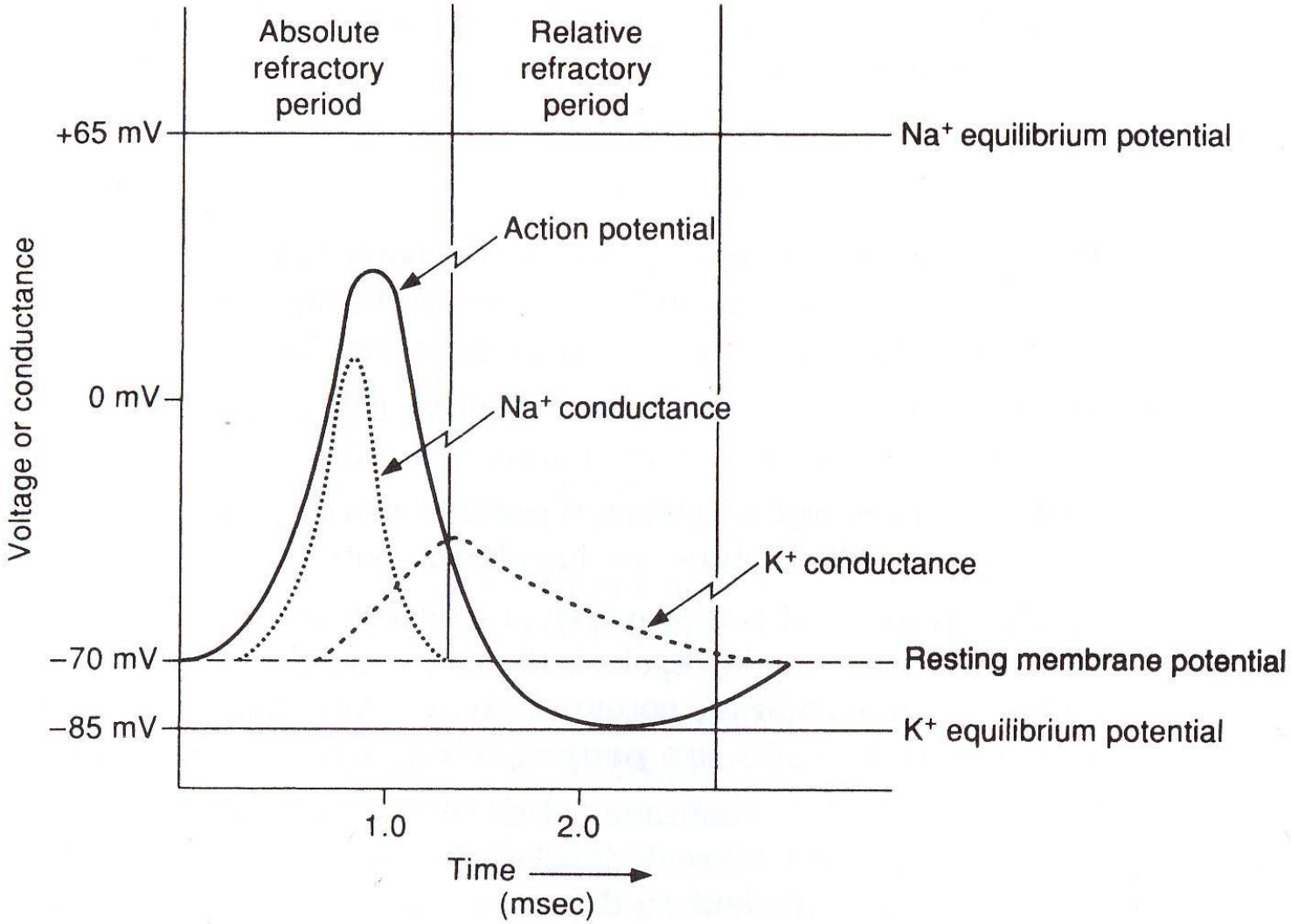
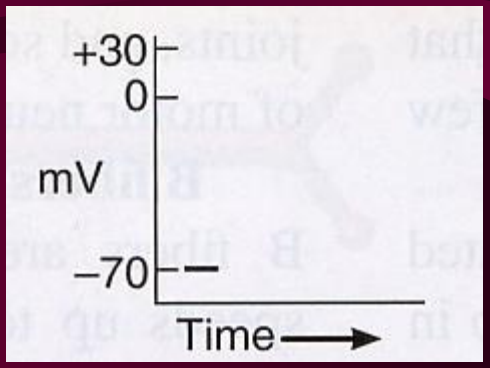


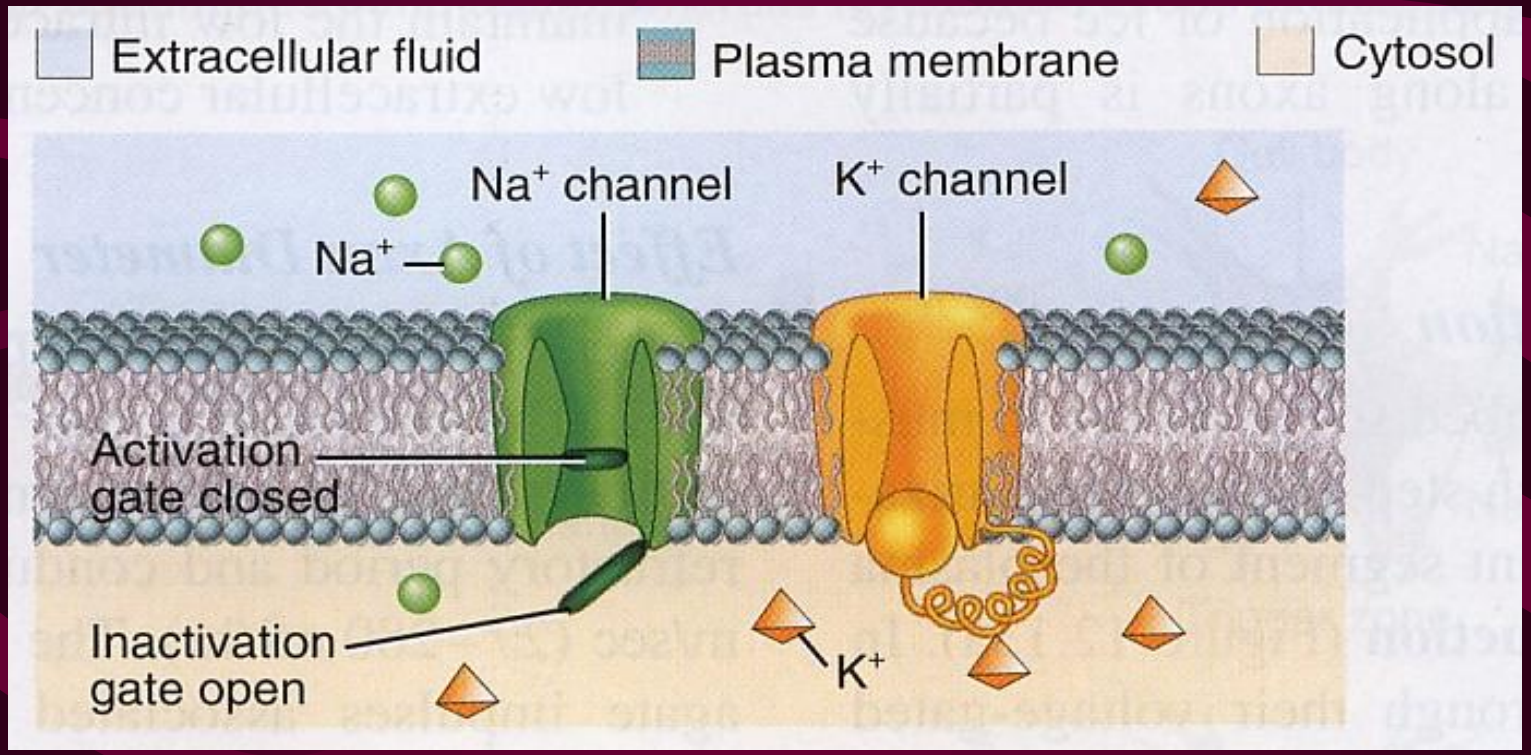
Figure 1-6. Nerve action potential and associated changes in Na^+ and K^+ conductance.

Costanzo; Page 12, Figure 1-6

1. Resting state:

All voltage-gated Na^+ and K^+ channels are closed.

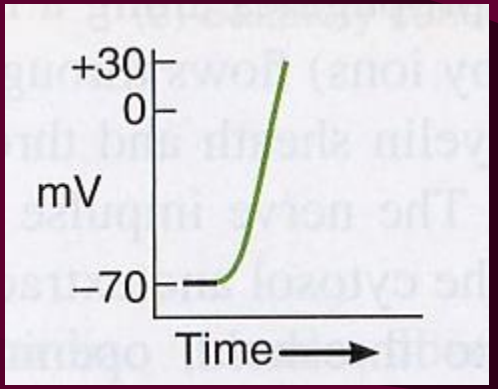


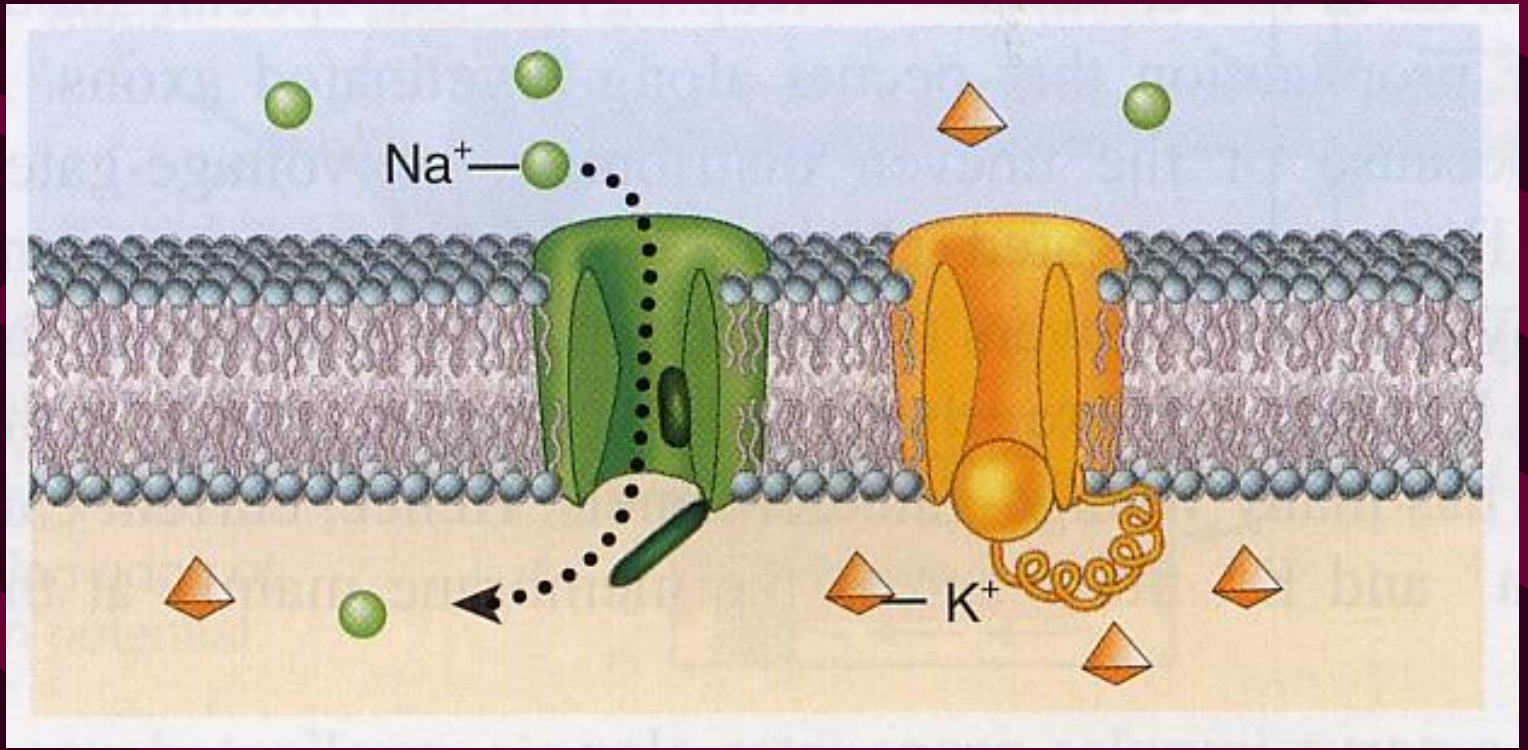


Tortora & Grabowski – Principles of Anatomy & Physiology; Page 401, Figure 12.12

2. Depolarizing phase:

Depolarization to threshold opens Na^+ channel activation gates. Na^+ inflow further depolarizes the membrane, opening more Na^+ channel activation gates.

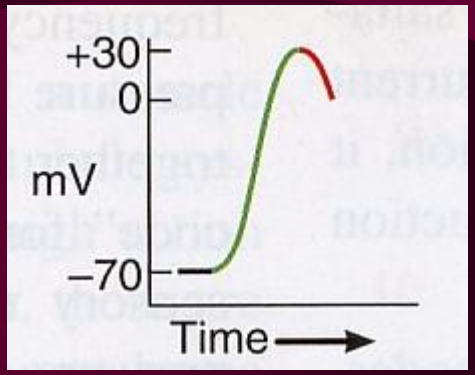


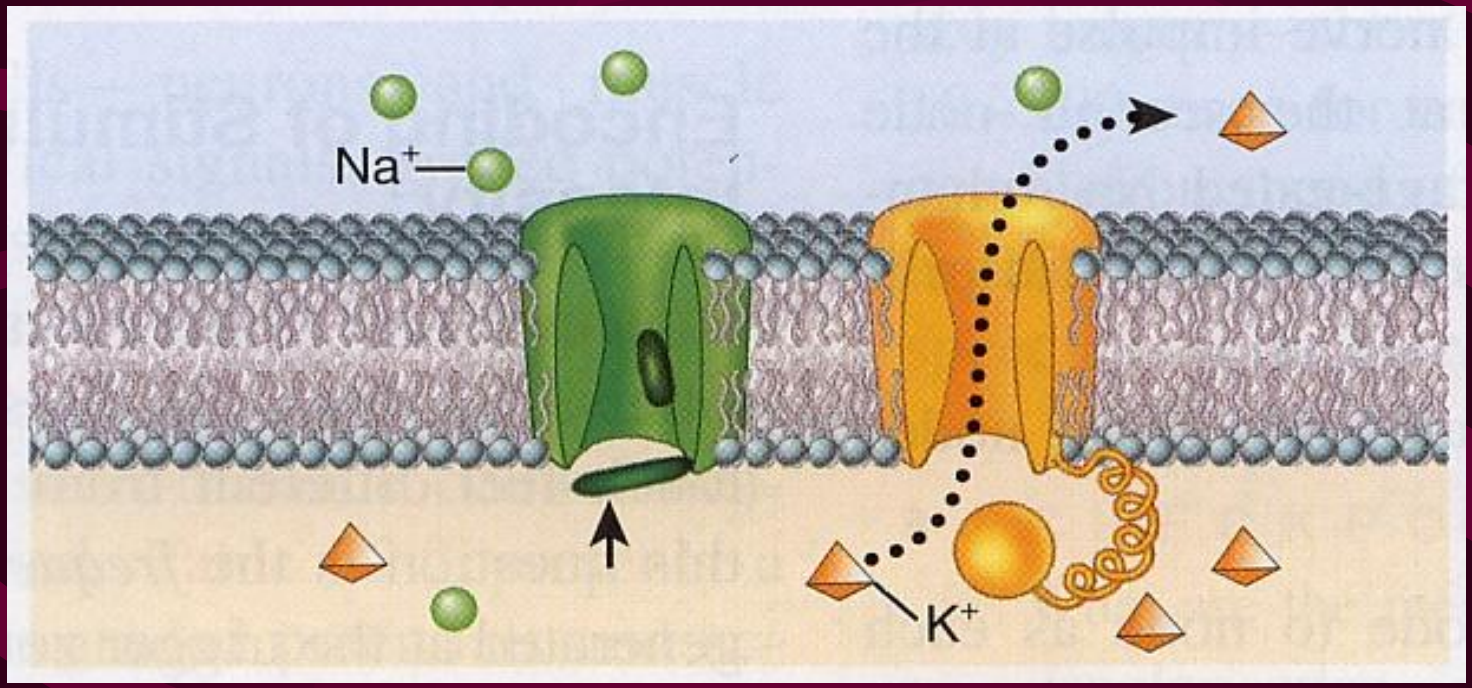


Tortora & Grabowski – Principles of Anatomy & Physiology; Page 401, Figure 12.12

3. Repolarizing phase:

Na^+ channel inactivation gates close and K^+ channels open. Outflow of K^+ causes repolarization.

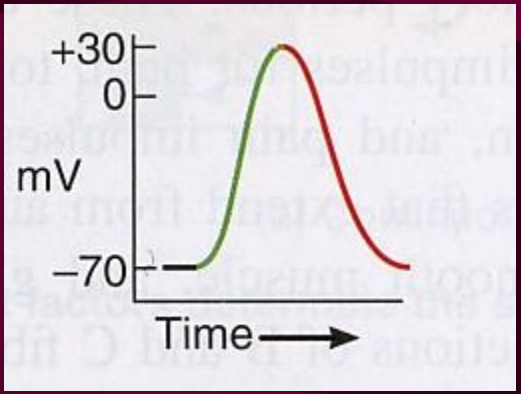


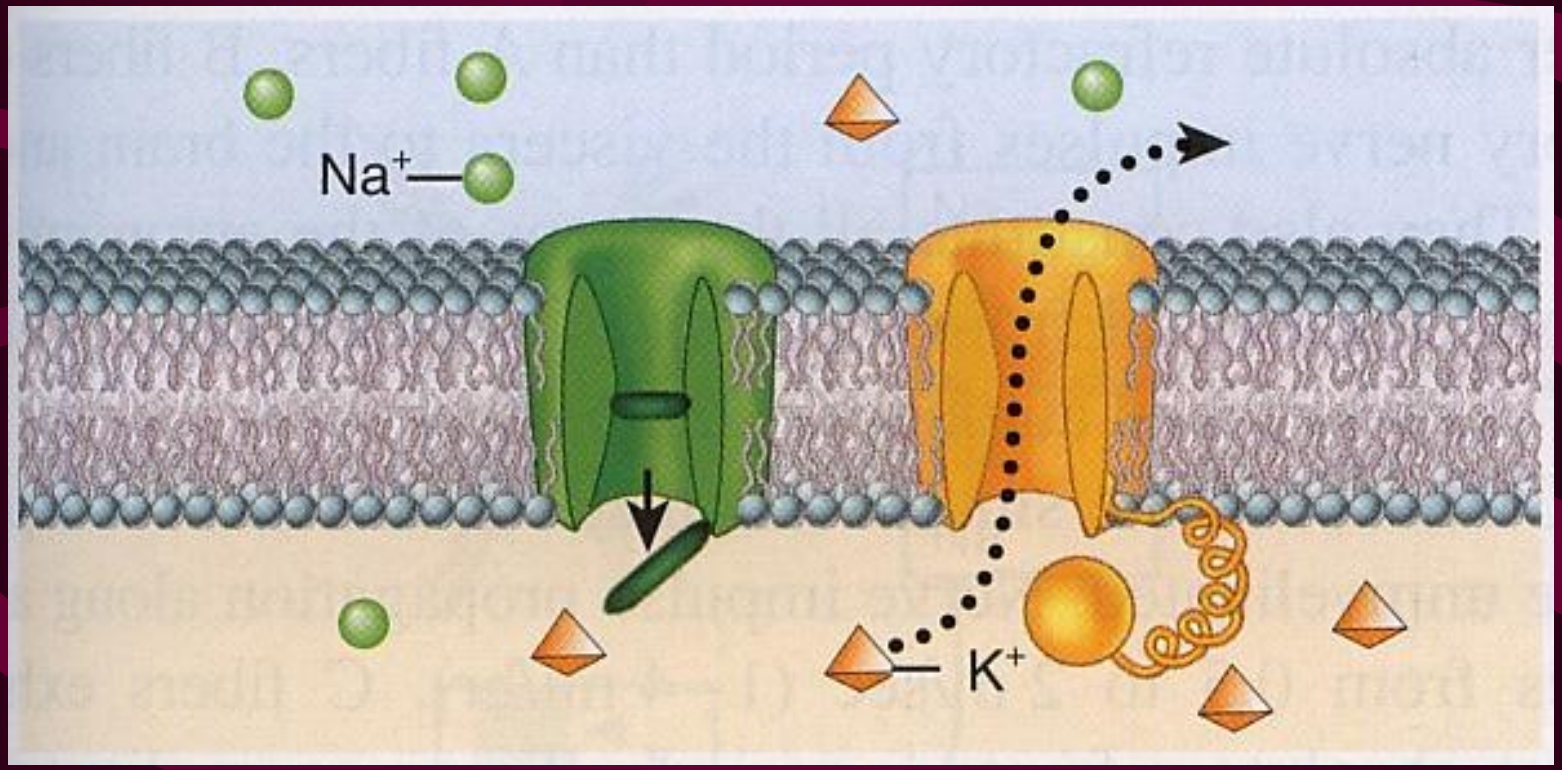


Tortora & Grabowski – Principles of Anatomy & Physiology; Page 401, Figure 12.12

4. Repolarization continues:

K^+ outflow restores resting membrane potential. Na^+ channel inactivation gates open. Return to resting state when K^+ gates close.

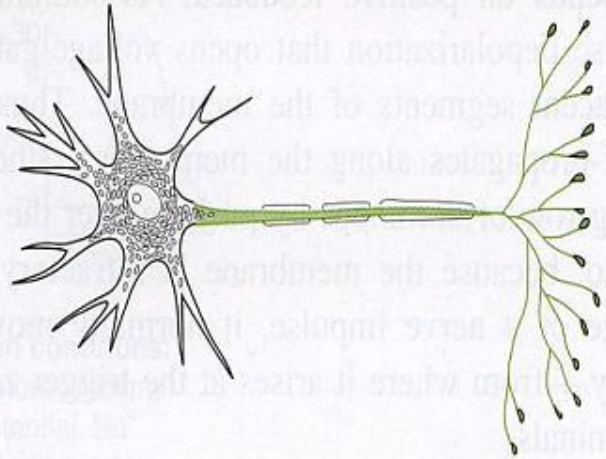


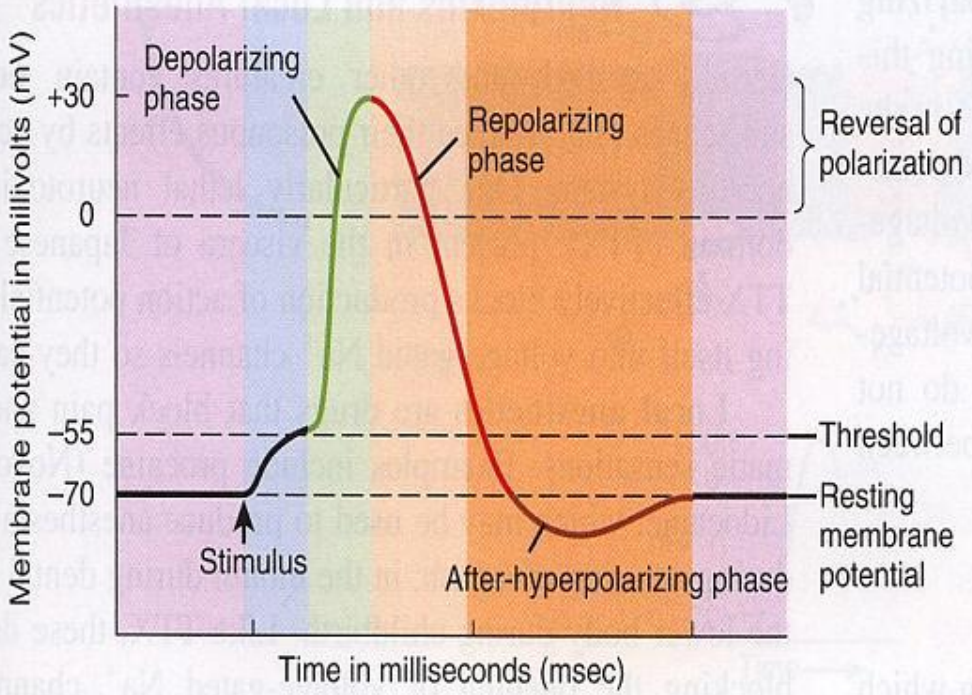


Tortora & Grabowski – Principles of Anatomy & Physiology; Page 401, Figure 12.12

Electrical signals in neurons

- **Refractory period**
  - the period of time after an action potential begins during which an excitable cell cannot generate another action potential.
  - absolute refractory period
  - relative refractory period





Tortora & Grabowski – Principles of Anatomy & Physiology; Page 399, Figure 12.11

Comparison of Graded Potentials and Action Potentials

Characteristic	Graded Potentials	Action Potentials
Origin	Arise mainly in dendrites and cell body (some arise in axons)	Arise at trigger zones and propagate along the axon.
Types of channels	Ligand-gated or mechanically gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Not propagated; localized and thus permit communication over a few micrometers.	Propagate and thus permit communication over long distance.
Amplitude	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All-or-none; typically about 100 mV.
Duration	Typical longer, ranging from several msec to several min.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of an action potential) or depolarizing (excitatory to generation of an action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present, thus spatial and temporal summation can occur.	Present, thus summation cannot occur.

Pain

Pain may be classified in several ways, but one general division is between pain coming from the skin, muscle, bones and joints (***somatic pain***) and pain originating in the viscera (***visceral pain***).

Pain

Pain has been classified into two major types: fast pain and slow pain.

***Fast pain*- is felt within about 0.1 second after stimulus is applied,** is also described by many *alternative names, such as sharp pain, acute pain and electric pain*

Slow pain - **begins only after 1 second or more and then increases slowly over many second** and sometimes even minutes, also goes by many names, such as *slow burning pain, aching pain, throbbing pain, nauseous,* and *chronic pain*

Pain receptors

Nociceptors (nocere, to injure) are receptors that respond to a variety of strong noxious stimuli (chemical, mechanical or thermal).

- nociceptors are sometimes called pain receptors.

the pain receptors in the skin and other tissue are all free nerve endings.

- nociceptive pain is mediated by free nerve endings, that respond to a variety of chemical, mechanical and thermal stimuli with the help of membrane ion channel.
- for example, the membrane channels called ***vanilloid receptors*** respond to damaging heat from a stove or other source, as well as to ***capsaicin***, the chemical that makes hot chili peppers burn your mouth.

Pain receptors

- at the oposite end of the temperature spectrum, researchers recently identified a membrane protein that responds both to coild and to *menthol*, one reason mint-favored foods feel cool.
- nociceptor activation is modulated by local chemicals that are released upon tissue injury, such as K^+, *histamine*, and *prostaglandins* released from damaged, *serotonin* released from platelets activated by tissue damage, and a peptide known as *substance P* secreted by primary sensory neurons.

Some analgesics relieve pain primarily by decreasing the sodium and potassium transfers at the neuron level, thereby slowing or stopping pain transmission. Examples—local anesthetics, anticonvulsants used for neuropathic pain, migraines.

Pain

- afferent signals from nociceptors are carried to the CNS in three types of primary sensory fibers: ***Aβ*** (beta), ***AΔ*** (delta), and ***C*** fibers
- two sensations may be perceived when nociceptors are activated pain and itch.
- nociceptors use two separate pathway for transmitting pain signals into the CNS.

the two pathways mainly correspond to the two types of pain: ***a fast-sharp pain pathway*** and ***a slow-chronic pain pathway***.

Pain

2 types of nerve fiber pathways

1. Acute pain fibers (A-delta fibers)
   - thin myelinated fibers
   - conduct pain rapidly
   - sensation of sharp pain
   - sensation does not continue after stimulus is removed

Pain

Types of nerve fiber pathways

2. Chronic pain fibers (C fibers)
   - slower than acute fibers
   - sensation of dull ache
   - can be intense and long-lasting
   - resists relief

Pain

Pain inhibiting neurotransmitters

- Enkephalins

  inhibit acute and chronic pain impulses

- Serotonin

  stimulates neurons to release enkephalins.

- Endorphins

  more effective in inhibiting chronic pain impulses.

Pain threshold and pain tolerance

- **The pain threshold** is the point at which a stimulus is perceived as pain. Perceptual dominance- intense pain at one location may cause an increase in the pain threshold in another location

- **The pain tolerance** is expressed as duration of time or the intensity of pain that an individual will endure before initiation overt pain responses.

  It is influenced by
  - person's cultural prescriptions
  - expectations
  - role behaviours
  - physical and mental health

- Pain tolerance is generally decreased:
  - with repeated exposure to pain,
  - by fatigue, anger, boredom, apprehension,
  - sleep deprivation

- Tolerance to pain may be increased:
  - by alcohol consumption,
  - medication, hypnosis,
  - warmth, distracting activities,
  - strong beliefs or faith

Pain tolerance varies greatly is among people and in the same person over time

A decrease in pain tolerance also evident in the elderly, and women appear to be more tolerant to pain than men

Age and perception of pain

Children and the elderly may experience or express pain differently than adults

Infants in the first 1 to 2 days of life are less sensitive to pain (or they simply lack the ability to verbalise the pain experience). A full behavioural response to pain is apparent at 3 to 12 month of life

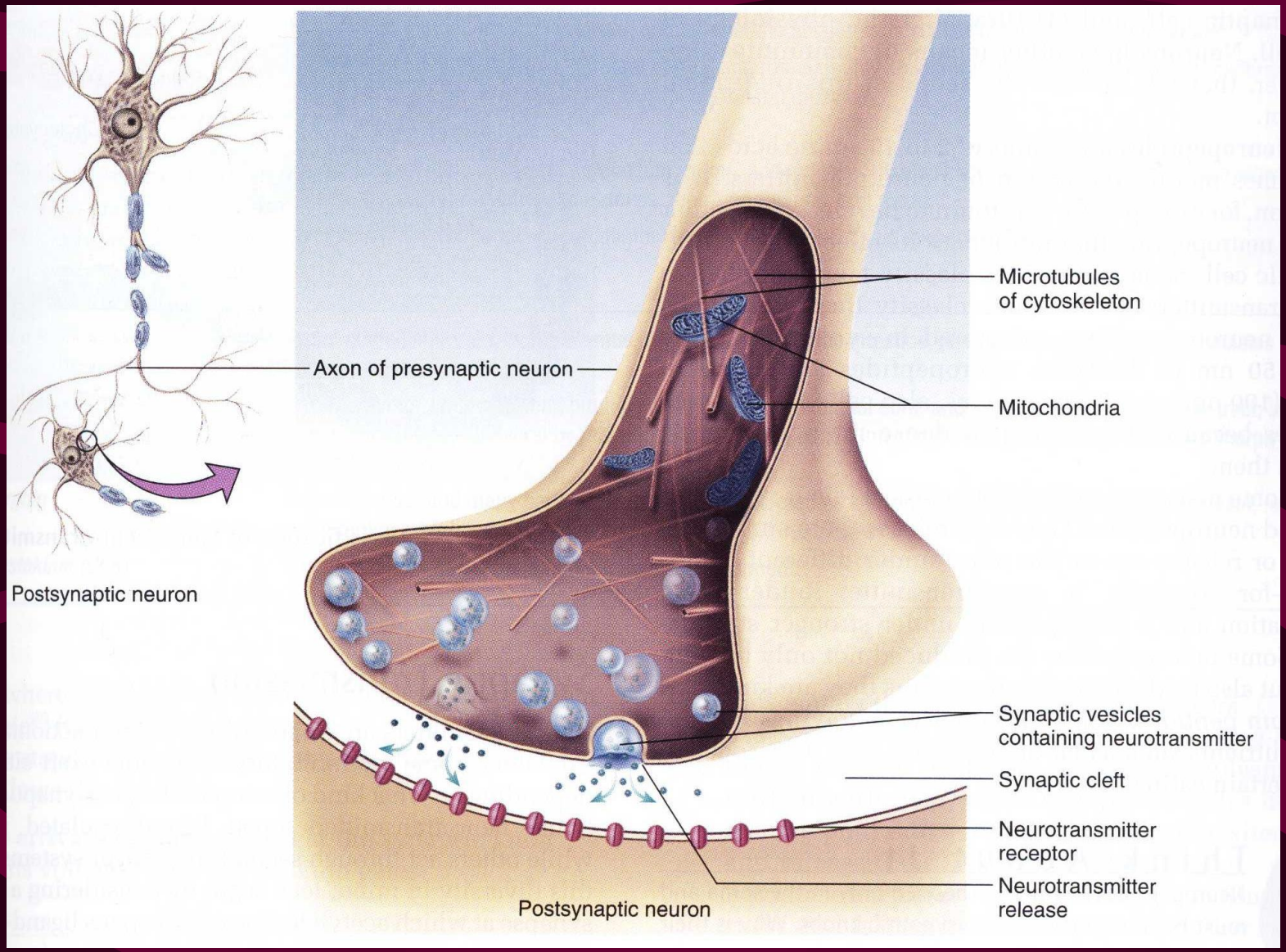
Older children , between the ages of 15 and 18 years, tend to have a lower pain threshold than do adults

Pain threshold tends to increase with ageing

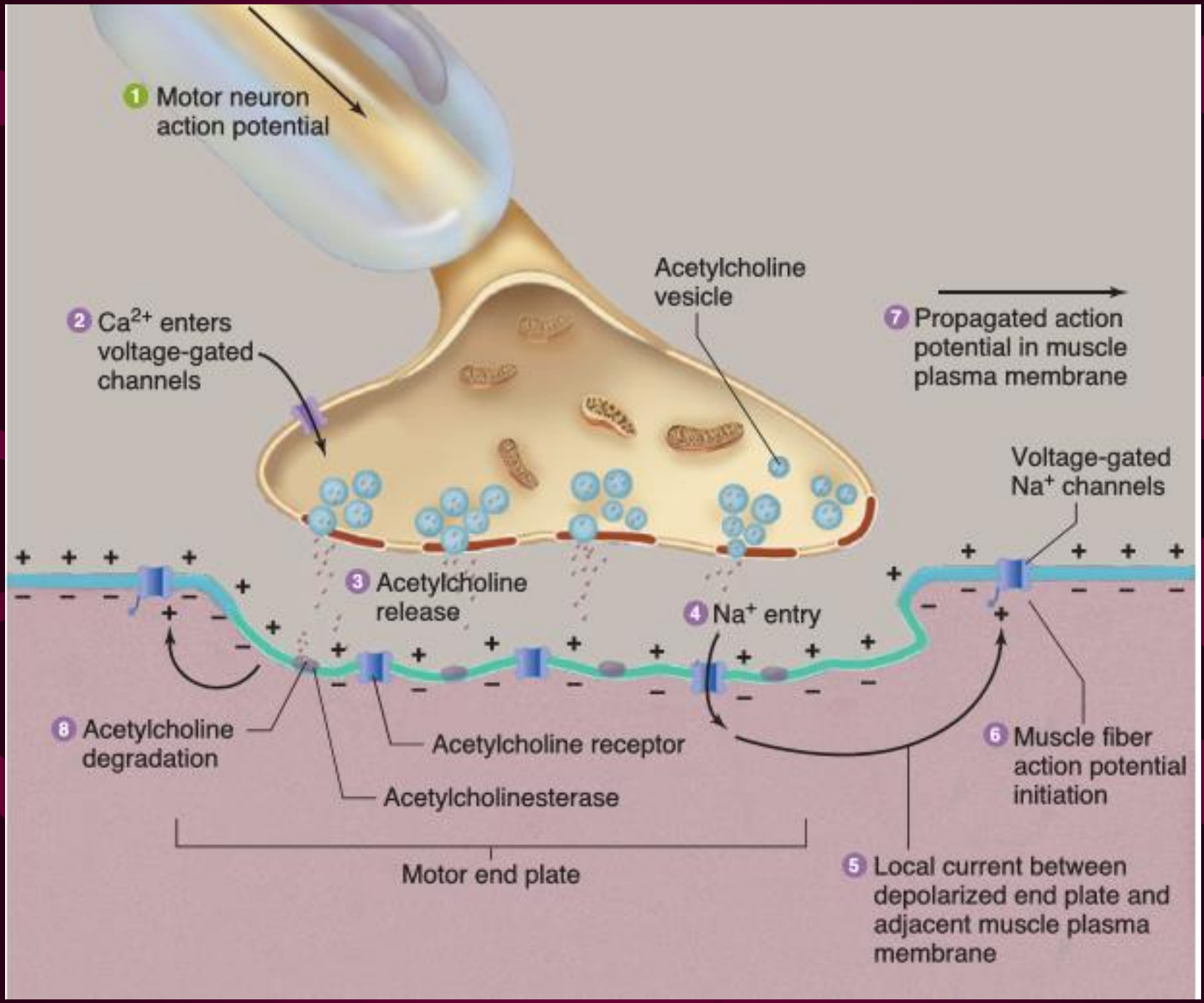
This change is probably caused by peripheral neuropathies and changes in the thickness of the skin

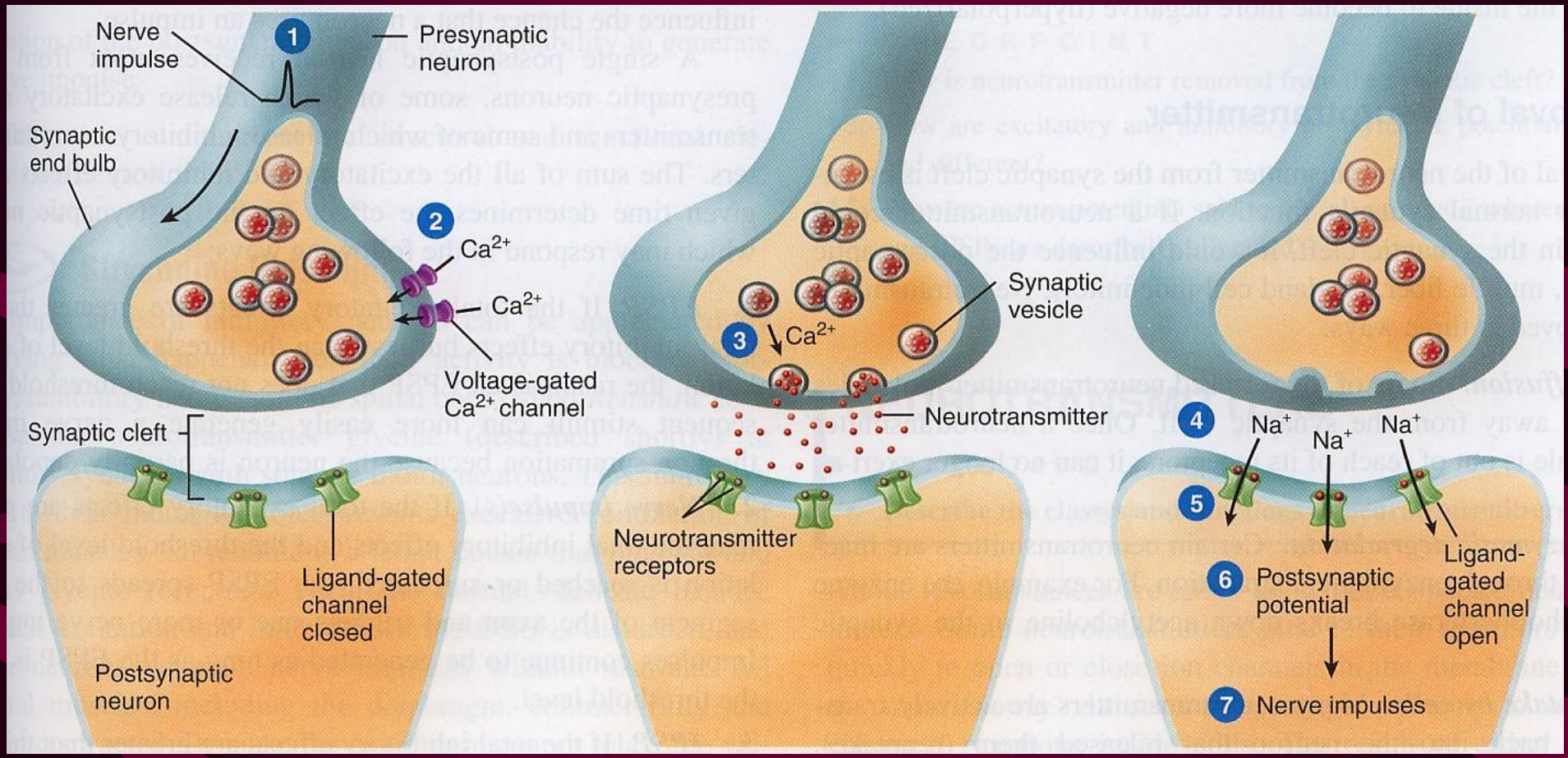
Signal transmission at synapses

- The role of synapses – synapses determine the directions that the nervous signals will spread in to the nervous system.
- Physiologic anatomy of synapses (presynaptic terminals, synaptic cleft, postsynaptic neuron).
- The major type of synapses
  - **the chemical synapse** (transmitters, "one-way" conduction)
  - **the electrical synapse** (action potentials conduct directly between adjacent cells through gap junctions)



Saladin; Page 473, Figure 13.17


1 Motor neuron action potential
2 Ca^{2+} enters voltage-gated channels
Acetylcholine vesicle
7 Propagated action potential in muscle plasma membrane
Voltage-gated Na^+ channels
3 Acetylcholine release
4 Na^+ entry
8 Acetylcholine degradation
Acetylcholine receptor
Acetylcholinesterase
6 Muscle fiber action potential initiation
Motor end plate
5 Local current between depolarized end plate and adjacent muscle plasma membrane



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 405, Figure 12.14

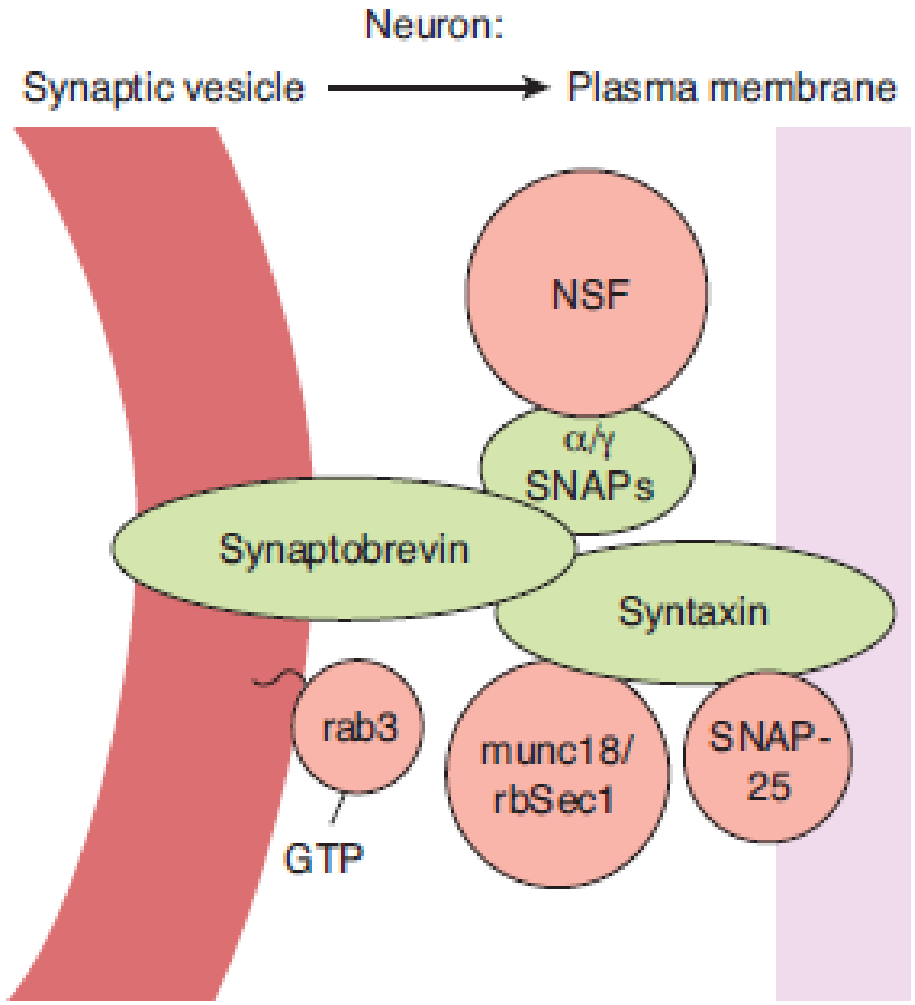
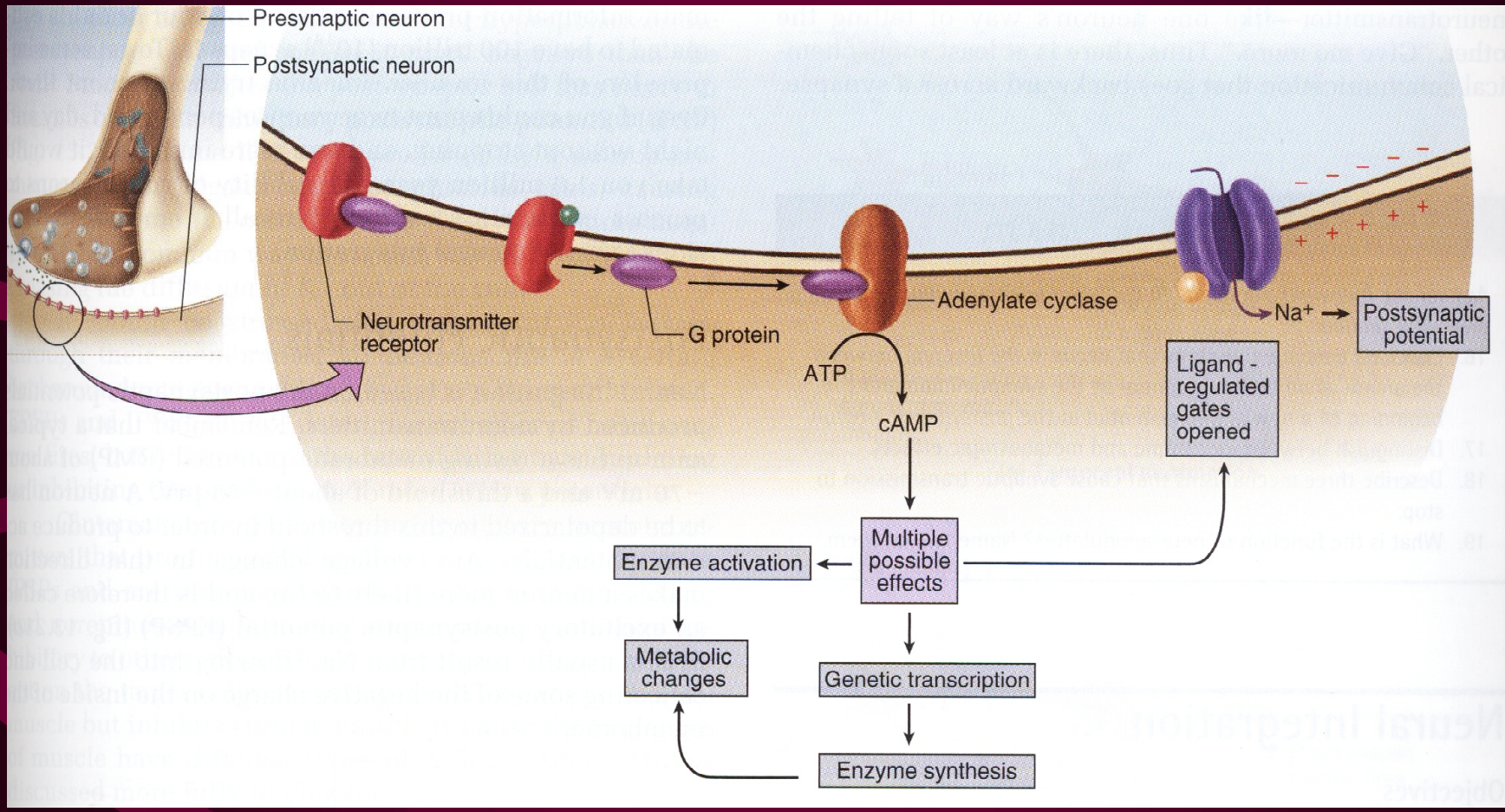
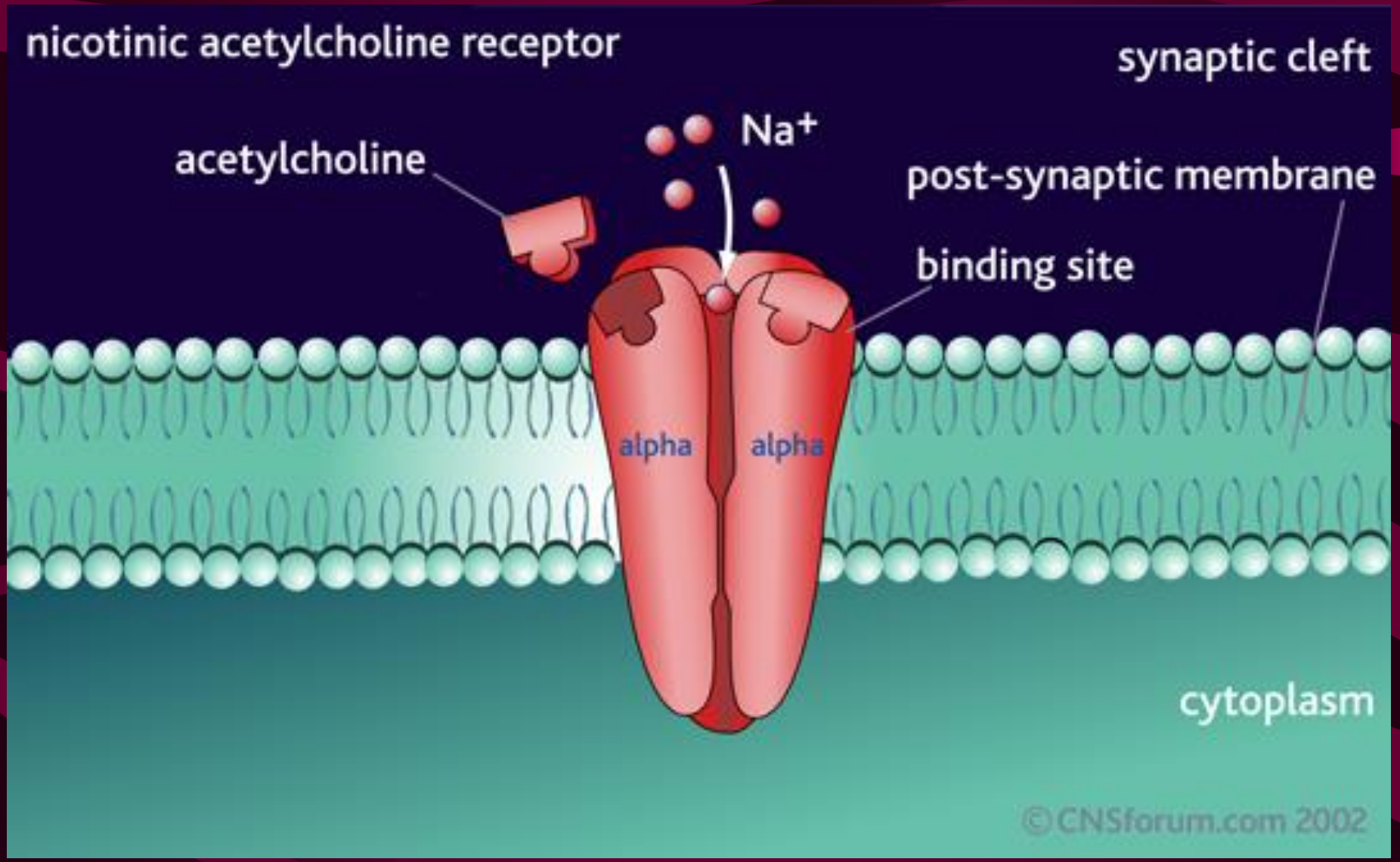
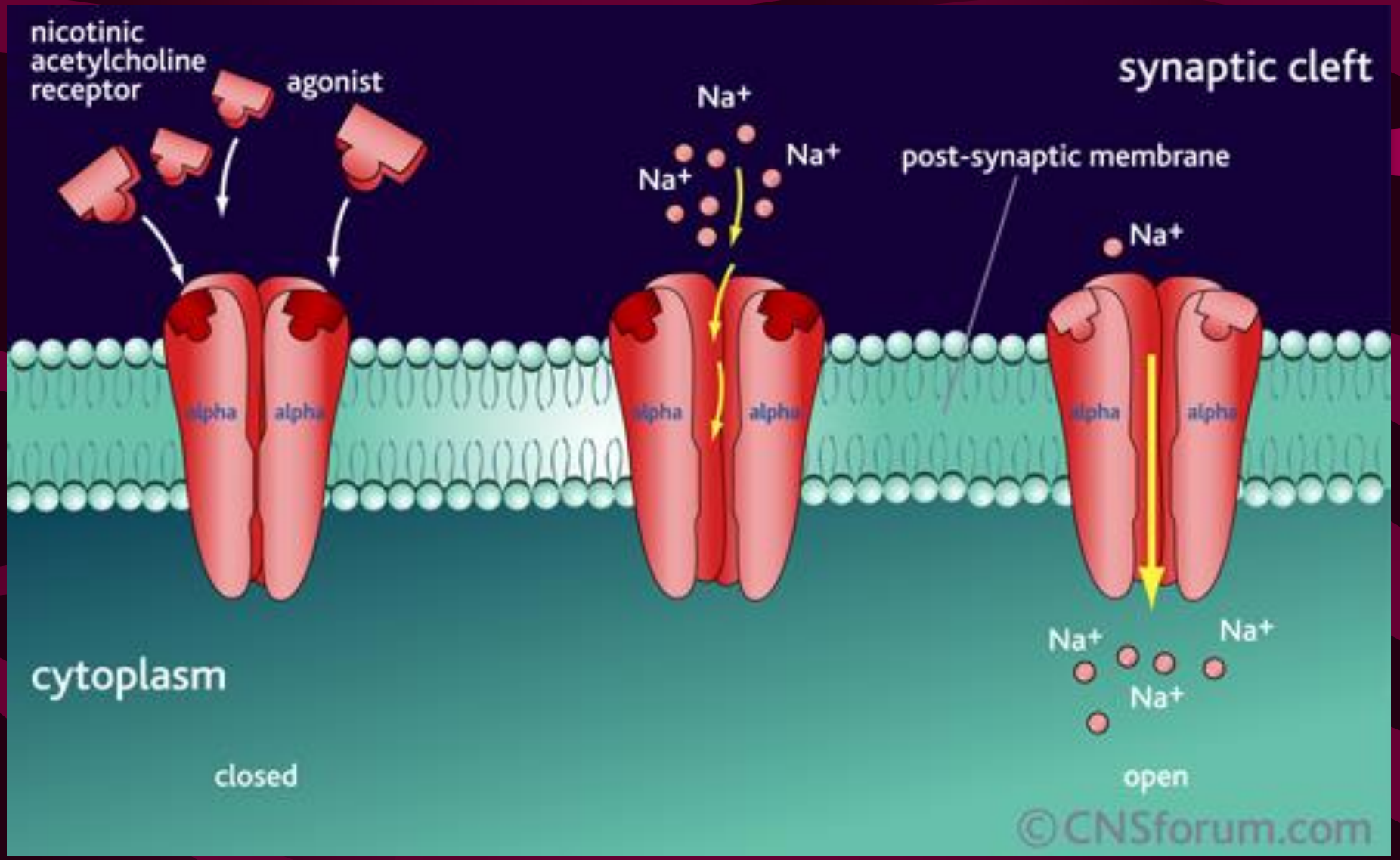


FIGURE 6–5 Main proteins that interact to produce synaptic vesicle docking and fusion in nerve endings. (Reproduced with permission from Ferro-Novick S, John R: Vesicle fusion from yeast to man. Nature 1994;370:191. Copyright by Macmillan Magazines.)


Presynaptic neuron
Postsynaptic neuron
Neurotransmitter receptor
G protein
Adenylate cyclase
ATP
cAMP
Na+
Postsynaptic potential
Ligand - regulated gates opened
Multiple possible effects
Enzyme activation
Metabolic changes
Genetic transcription
Enzyme synthesis


nicotinic acetylcholine receptor
synaptic cleft
Na+
acetylcholine
post-synaptic membrane
binding site
alpha
alpha
cytoplasm
© CNSforum.com 2002


nicotinic
acetylcholine
receptor
agonist
synaptic cleft
Na+
Na+
Na+
post-synaptic membrane
Na+
alpha
alpha
alpha
alpha
alpha
alpha
cytoplasm
Na+
Na+
Na+
closed
open
©CNSforum.com

Signal transmission at synapses

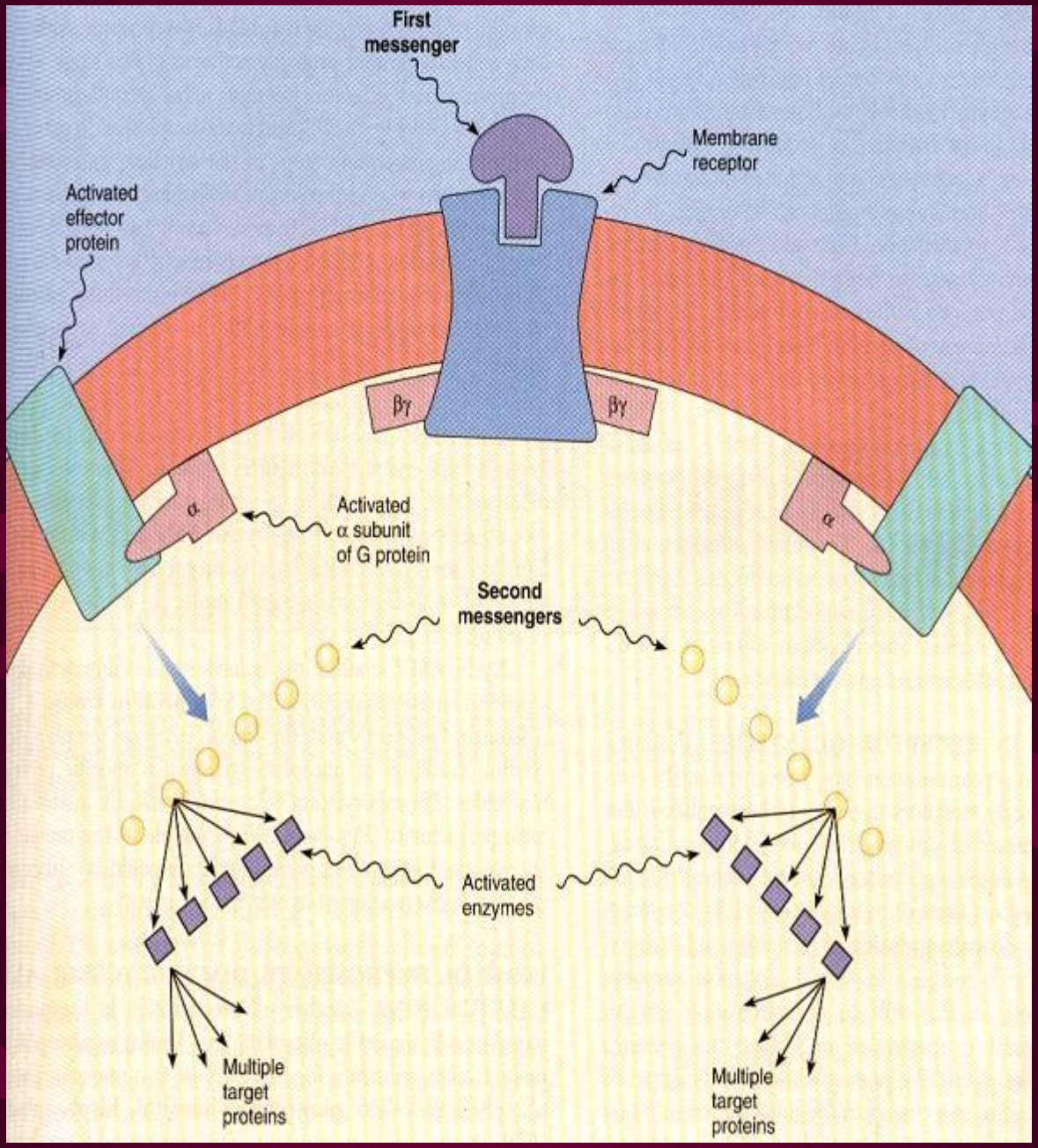
- **Second-messengers** may activate certain enzymes that catalyze the phosphorylation of certain proteins, which in turn produce the physiological response of the cell to the extracellular signal (first messenger)

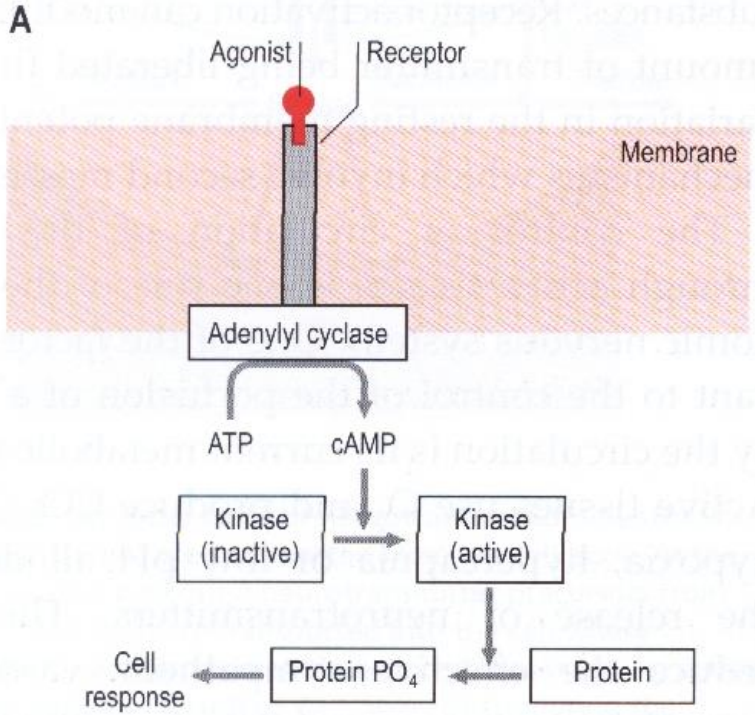
Signal transmission at synapses

- **Binding of a signal molecule – into an intracellular response that modifies the behavior of target cell**
  - Phase I – binding of first messenger (transmitter) to the receptor (T+R)
  - Phase II – transduction of a signal into the intracellular compartment. T+R complex interacts with a specific G-protein; T+R+G complex binds GTP, which activates α subunit of G protein
  - Phase III – activated α subunit of G protein activates (or inhibits) a specific enzyme (eg. adenylate cyclase or phospholipase C), which causes synthesis of **second messenger**

Signal transmission at synapses

- When a first messenger binds to a G-protein coupled receptor, the receptor changes its conformation and activates several G-protein α subunits. Each α subunit breaks away from the $\gamma\beta$ complex, and activates a single effector protein, which, in turn, generates many intracellular second-messenger molecules. One second messenger activates many enzymes, and each activated enzyme can regulate many target proteins (amplification).


First messenger
Membrane receptor
Activated effector protein
βγ
βγ
α
Activated α subunit of G protein
α
Second messengers
Activated enzymes
Multiple target proteins
Multiple target proteins



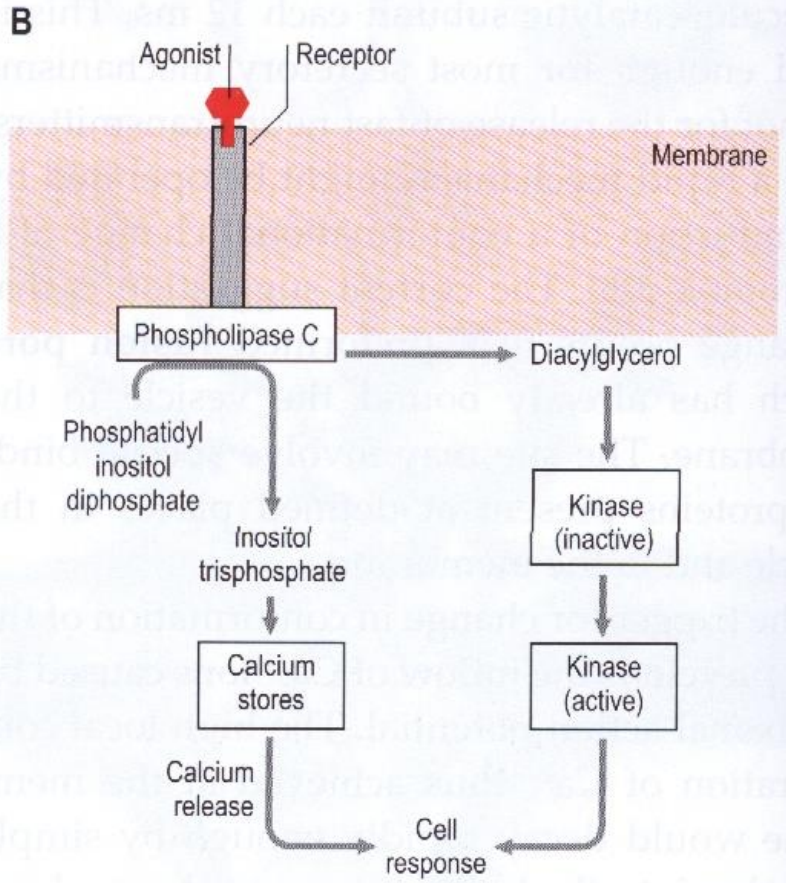
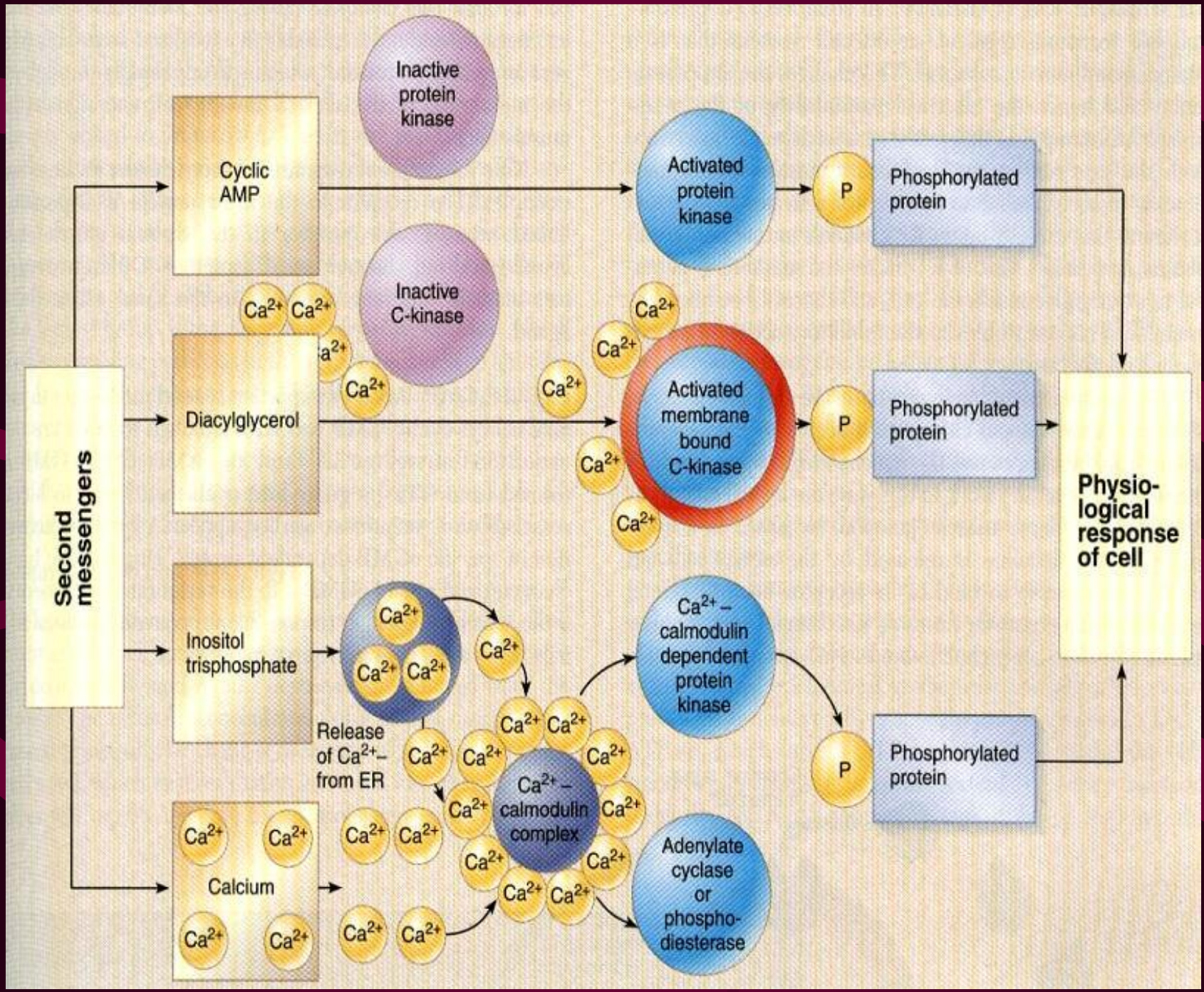


Fig. 3.2.7 Two second messenger mechanisms found in the autonomic nervous system. The effector response results from the *formation of the second messengers cAMP* (**A**) *and inositol trisphosphate or diacylglycerol* (**B**).


Second messengers
Cyclic AMP
Inactive protein kinase
Activated protein kinase
P
Phosphorylated protein
Diacylglycerol
Inactive C-kinase
Activated membrane bound C-kinase
P
Phosphorylated protein
Physio-logical response of cell
Inositol trisphosphate
Release of Ca2+– from ER
Ca2+ – calmodulin dependent protein kinase
P
Phosphorylated protein
Calcium
Ca2+ – calmodulin complex
Adenylate cyclase or phospho-diesterase

Signal transmission at synapses

- Neurotransmitters
  - **excitatory** – neurotransmitters that make membrane potential less negative (for example norepinephrine, dopamine, epinephrine, serotonin, histamine)
  - **inhibitory** – neurotransmitters that make membrane more negative (for example Gamma aminobutyric (GABA) and glycine).

GABA (gamma-aminobutyric acid)

- is secreted by nerve terminals in the spinal cord, cerebellum, basal ganglia, and many areas of the cortex
- it is believed always to cause inhibition

Glycine

- is secreted mainly at synapses in the spinal cord
- it is believed to always act as an inhibitory transmitter

Neuropeptide

Neuropeptides – are built from peptides which is a kind of organic molecule

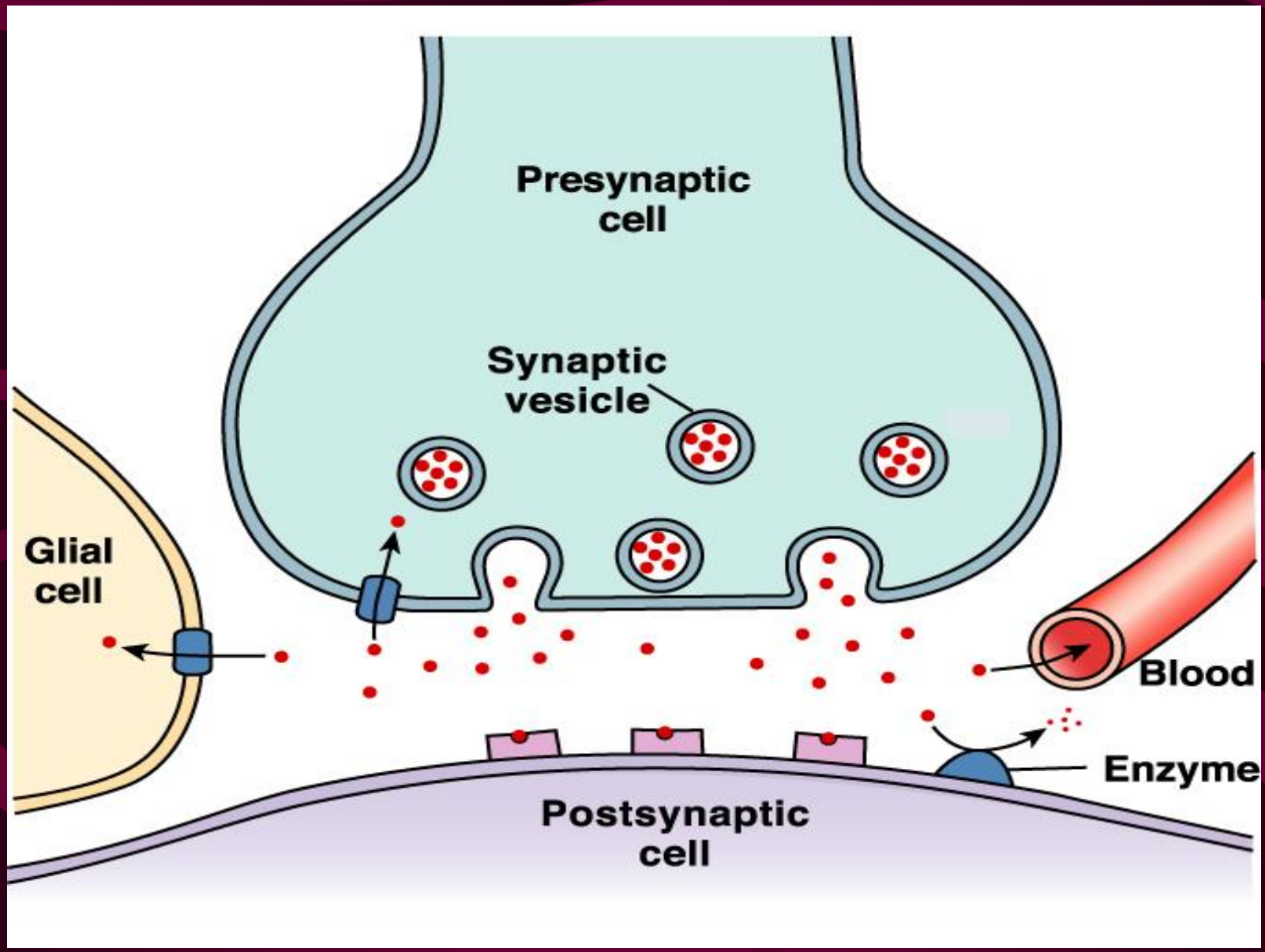
Opiods – buffer stress, provide soothing & reduce pain, & produce pleasure - these include the endorphines

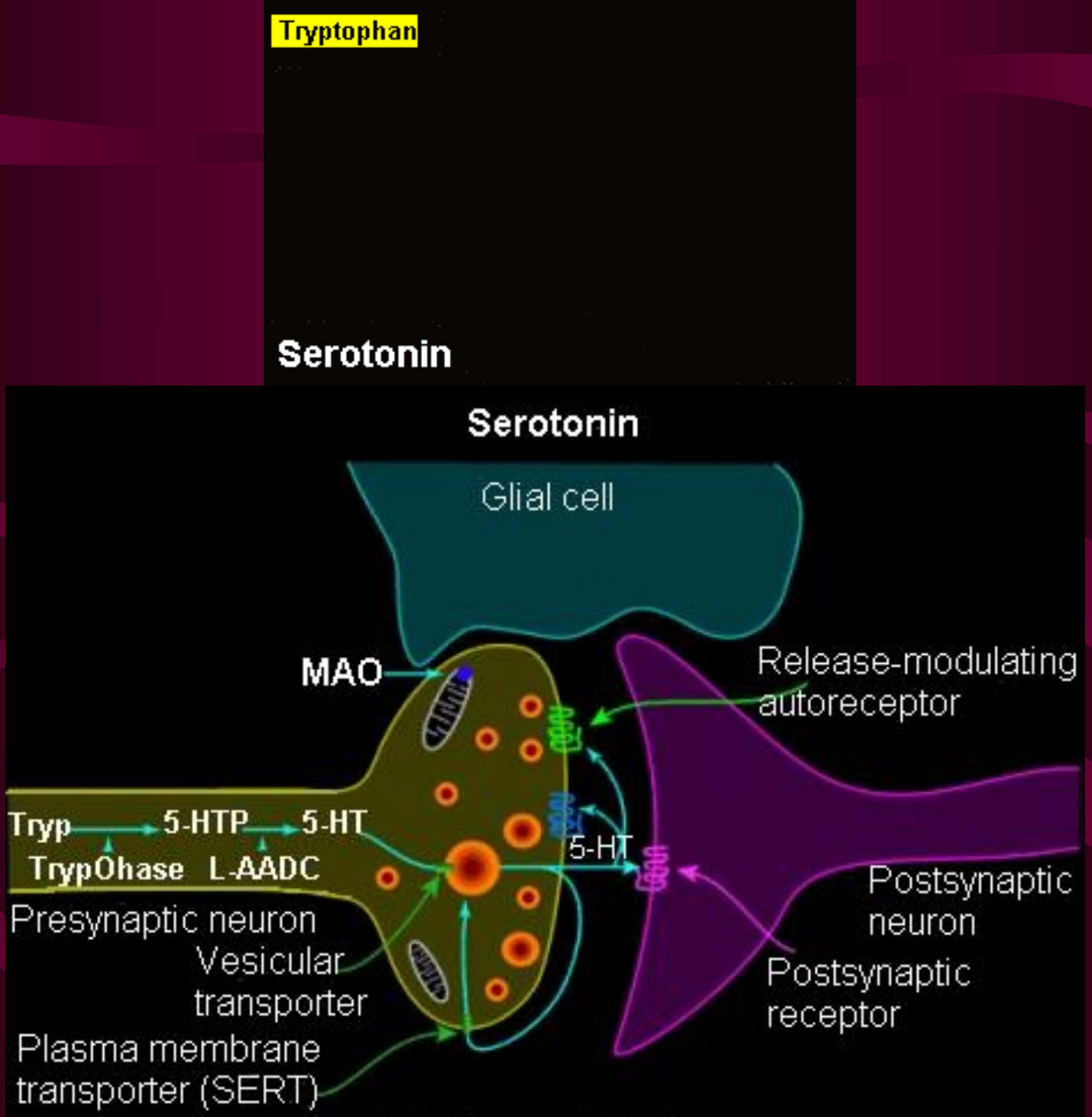
Oxytocin – promote nurturing behaviors toward children & bonding in couples. Associated with blissful closeness & love. Women typically have more oxytocin than men

Vasopressin – supports pair bonding & in men it may promote aggressiveness towards sexual rivals

Removal of Neurotransmitter

- Removal of the neurotransmitter from the synaptic cleft is essential for normal synaptic function. Neurotransmitter is removed in three ways:
  - **Diffusion**. Some of the released neurotransmitter molecules diffuse away from the synaptic cleft.
  - **Enzymatic degradation**. Certain neurotransmitters are inactivated through enzymatic degradation. For example, the enzyme acetylocholinesterase breaks down acetylocholine in the synaptic cleft.
  - **Uptake by cells**. Many neurotransmitters are actively transported back into the neuron that released them (reuptake).


Presynaptic cell
Synaptic vesicle
Glial cell
Blood
Enzyme
Postsynaptic cell

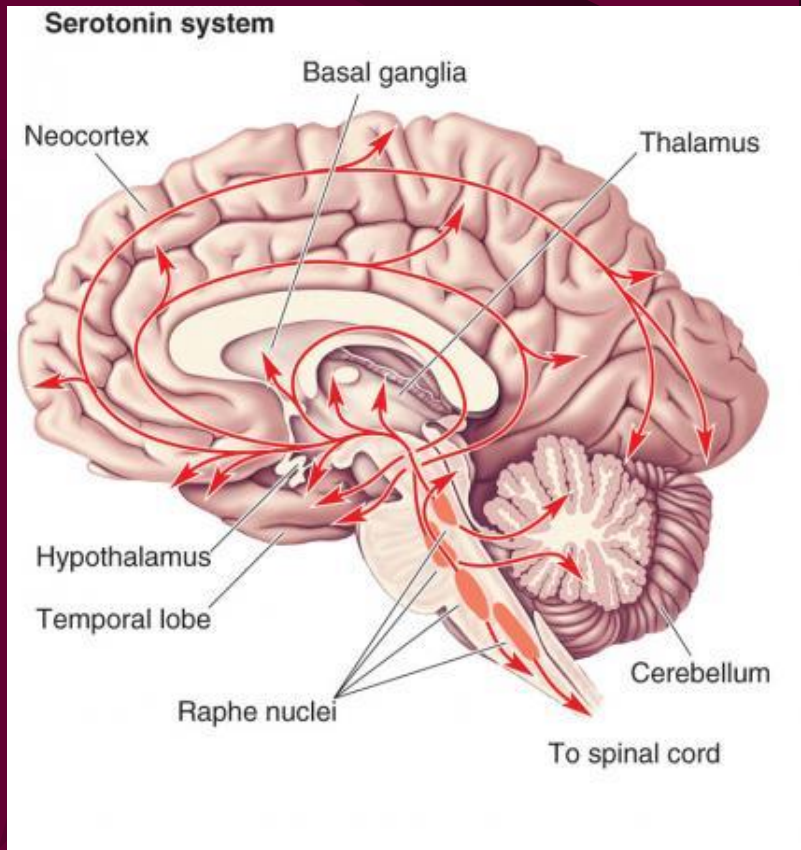

Tryptophan
Serotonin
Serotonin
Glial cell
MAO
Release-modulating autoreceptor
Tryp
5-HTP
5-HT
TrypOhase
L-AADC
5-HT
Presynaptic neuron
Vesicular transporter
Plasma membrane transporter (SERT)
Postsynaptic neuron
Postsynaptic receptor

Serotonin

Function: 1. lower nuclei: pain, locomotion
2. upper nuclei: sleep-wake cycle, mood and emotional behaviors, such as aggression and depression

Neurons originate: raphe nuclei along brain stem midline

Neurons terminate:
1. lower nuclei project to spinal cord
2. upper nuclei project to most of brain



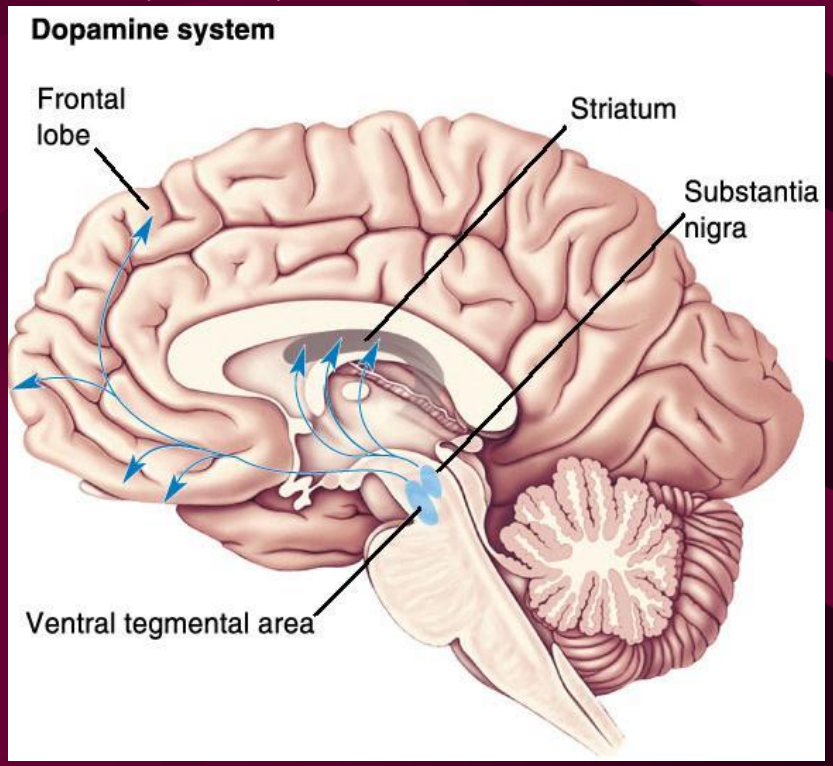
Tyrosine

The Catecholamines

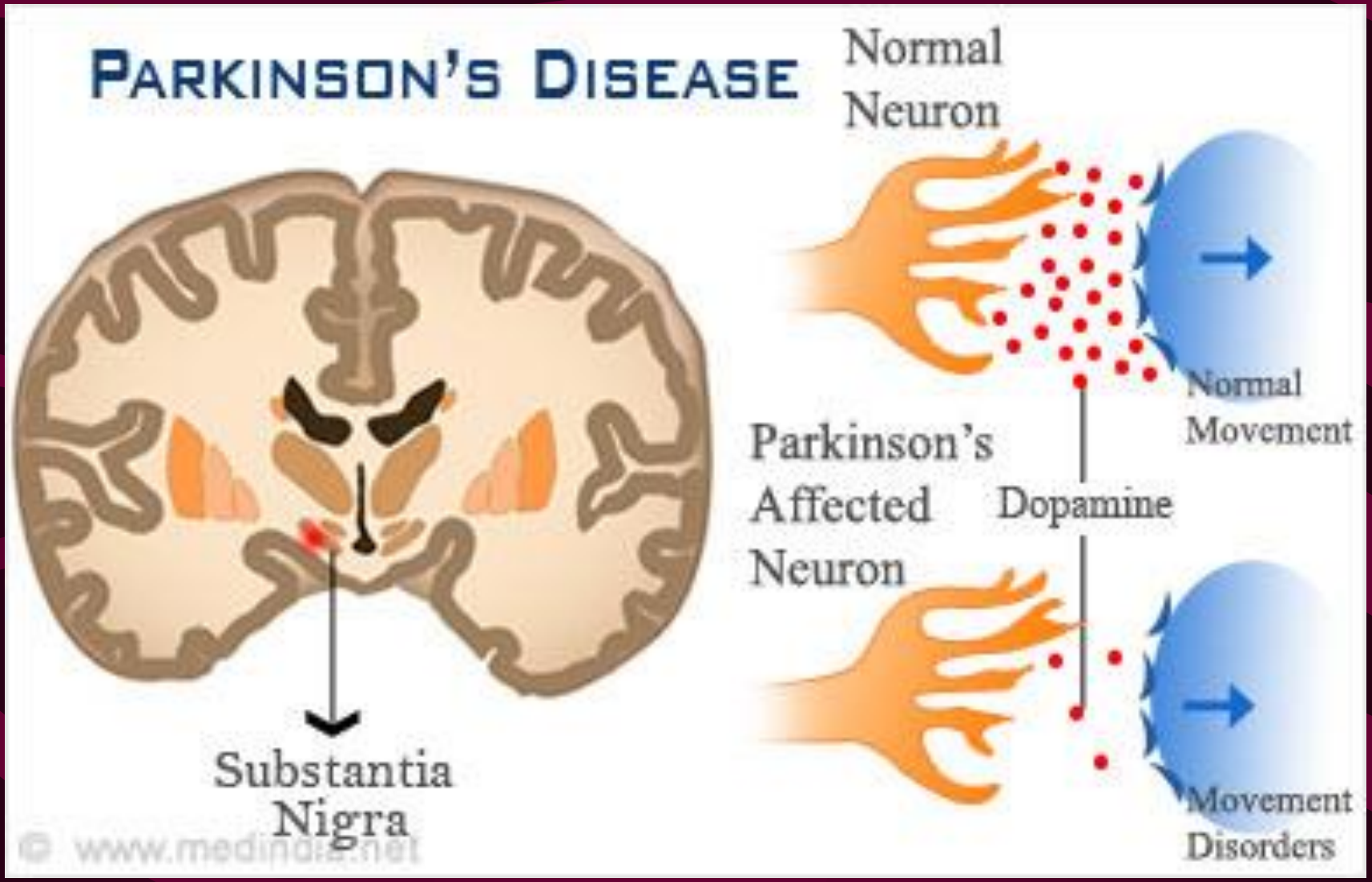
Dopamine

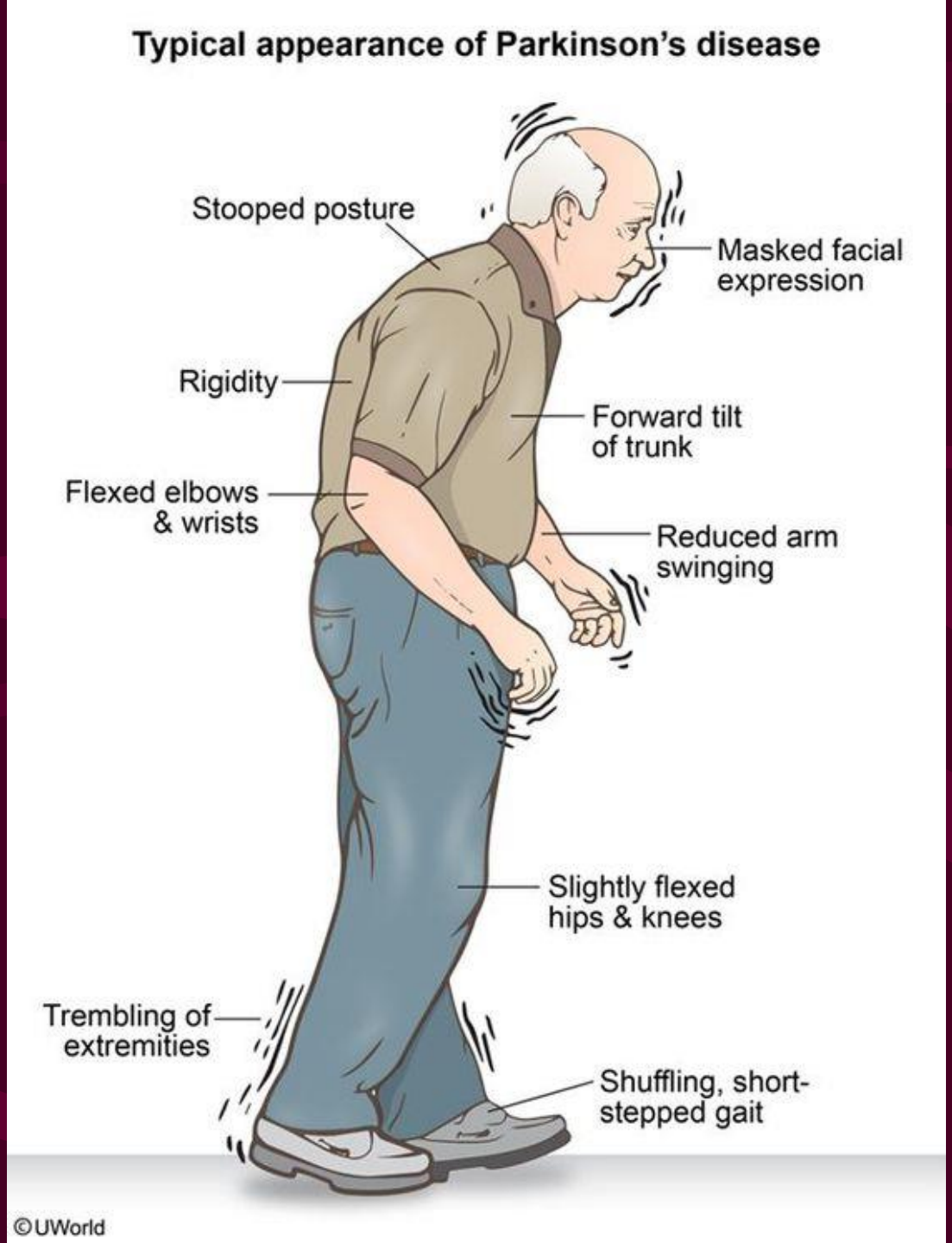
Function: 1. motor control
2. " reward" centers linked to addictive behaviors

Neurons originate: 1. substantia nigra in midbrain
2. ventral tegmentum in midbrain



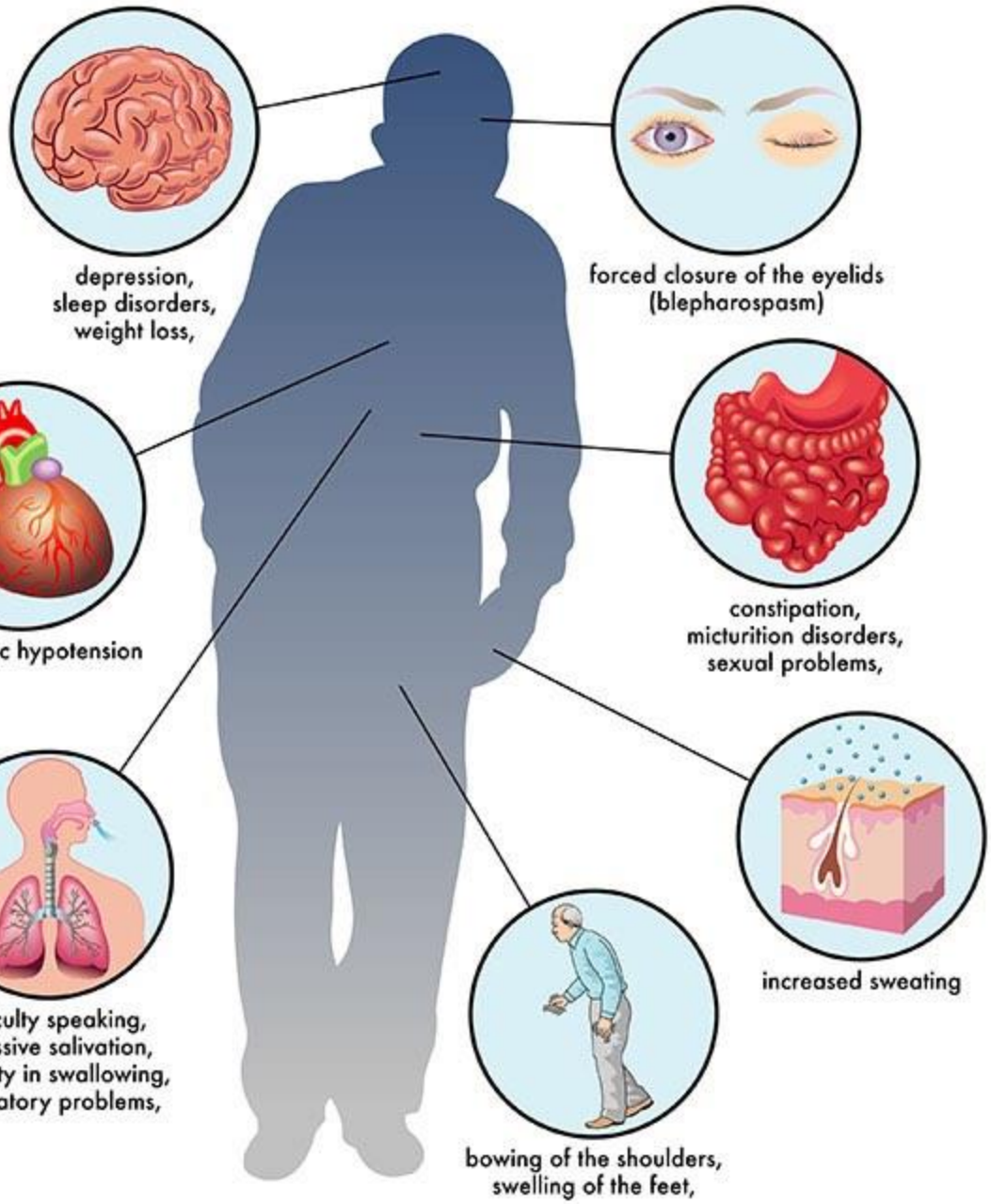
Neurons terminate: 1. cortex
2. cortex and part of limbic system


PARKINSON'S DISEASE
Normal Neuron
Normal Movement
Parkinson's Affected Neuron
Dopamine
Movement Disorders
Substantia Nigra
© www.medindia.net


Typical appearance of Parkinson's disease
Stooped posture
Masked facial expression
Rigidity
Forward tilt of trunk
Flexed elbows & wrists
Reduced arm swinging
Slightly flexed hips & knees
Trembling of extremities
Shuffling, short-stepped gait
©UWorld

Parkinson's disease

non-motor disorders caused by Parkinson's disease



Parkinson's disease-risk factors

- **Age.** People usually develop the disease around age 60 or older.
- **Sex.** Men are more likely to develop Parkinson's disease than are women.
- **Heredity.** Having a close relative with Parkinson's disease increases the chances that you'll develop the disease. However, your risks are still small unless you have many relatives in your family with Parkinson's disease.
- **Exposure to toxins.** Ongoing exposure to herbicides and pesticides may put you at a slightly increased risk of Parkinson's disease.

Parkinson's disease-diagnose

- No specific test exists to diagnose Parkinson's disease. Doctor trained in nervous system conditions (neurologist) will diagnose Parkinson's disease based on your medical history, a review of your signs and symptoms, and a neurological and physical examination.

- Imaging tests — such as MRI, ultrasound of the brain, SPECT and PET scans — may also be used to help rule out other disorders. Imaging tests aren't particularly helpful for diagnosing Parkinson's disease.

- In addition to neurological examination, doctor may give patient's carbidopa-levodopa, a Parkinson's disease medication.

Parkinson's Disease - treatment

The medications used in the treatment of Parkinson's disease seek to restore the balance between dopamine-based and acetylcholine-based neurotransmitter systems in the brain.

Medications	Mechanism
levodopa	dopamine replacement
carbidopa	slows metabolic breakdown of levodopa
bromocriptine, pergolide, pramimpexole, ropinerole	dompamine agonists, boots receptors for dopamine
biperiden HCl, trihexyphenidyl HCl, benzotropine, mesylate, procyclidine HCl	anticholinergics, suppress acetylcholine neurotransmitter system.
amantadine	antiviral medication
selegiline	MAO-B inhibitor, slows breakdown of dopamine
tolcapone, entacapone	COMT inhibitors

Parkinson's Disease - treatment

Deep brain stimulation

In deep brain stimulation (DBS), surgeons implant electrodes into a specific part of brain. The electrodes are connected to a generator implanted in chest near collarbone that sends electrical pulses to brain and may reduce Parkinson's disease symptoms.

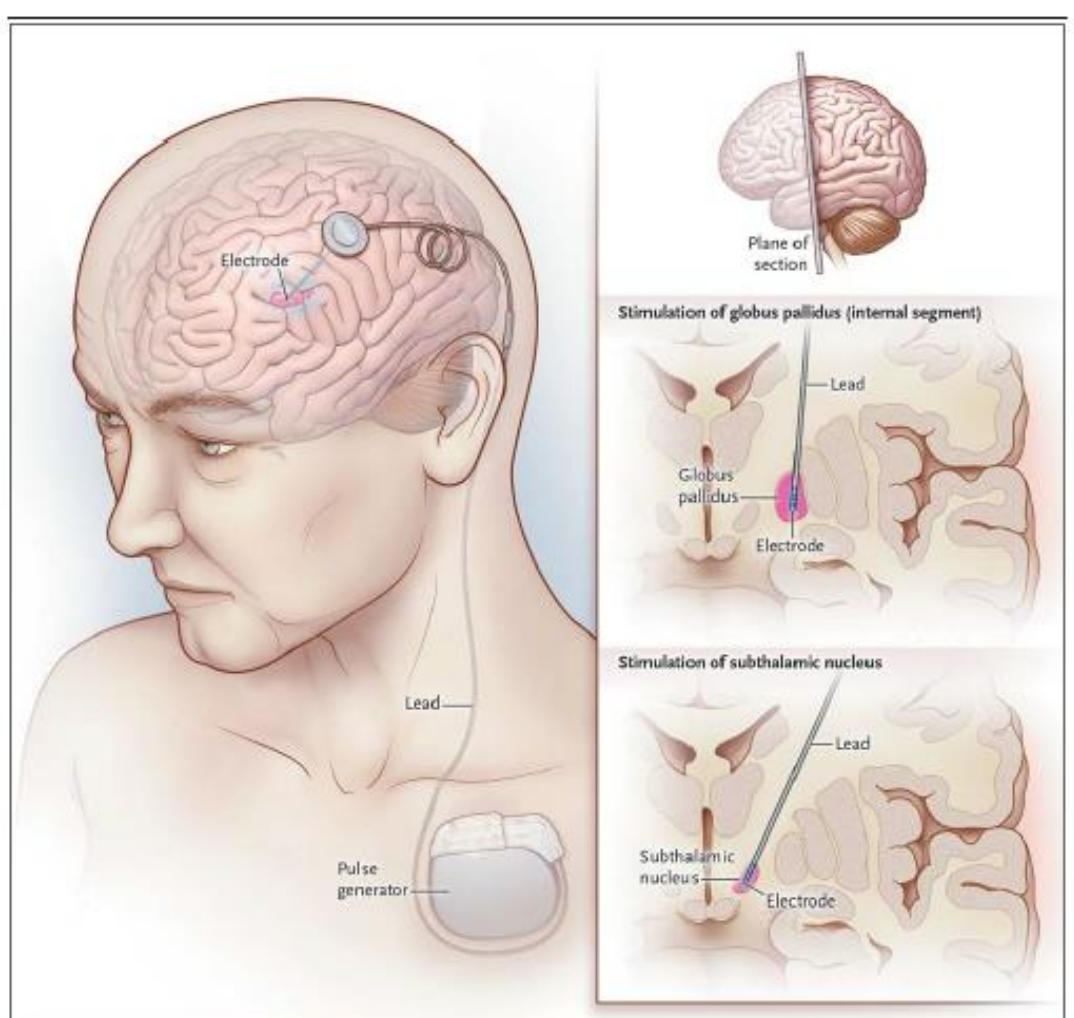


Figure 1. **Electrode Implantation for Deep-Brain Stimulation.**
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator.

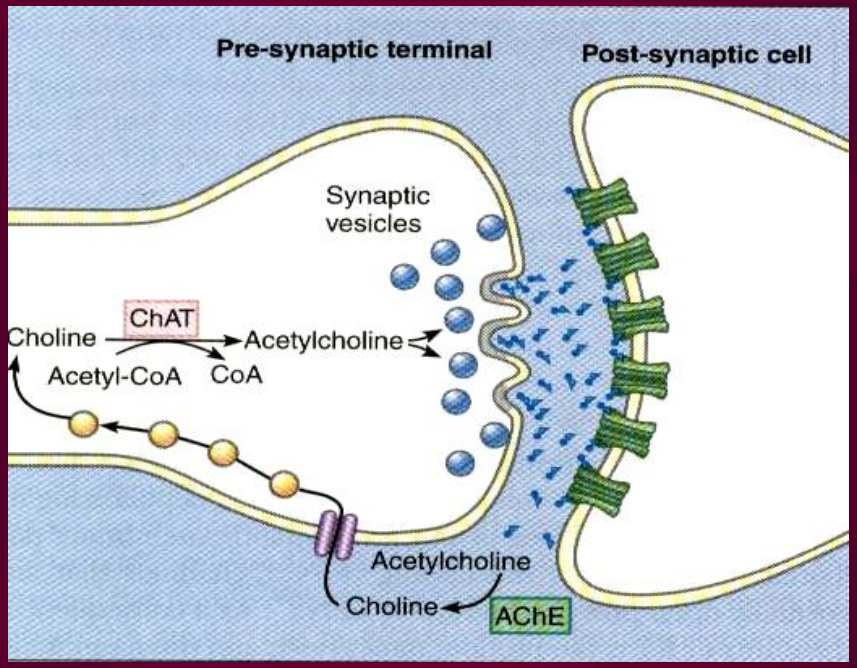
Acetylcholine metabolism

Acetylcholine

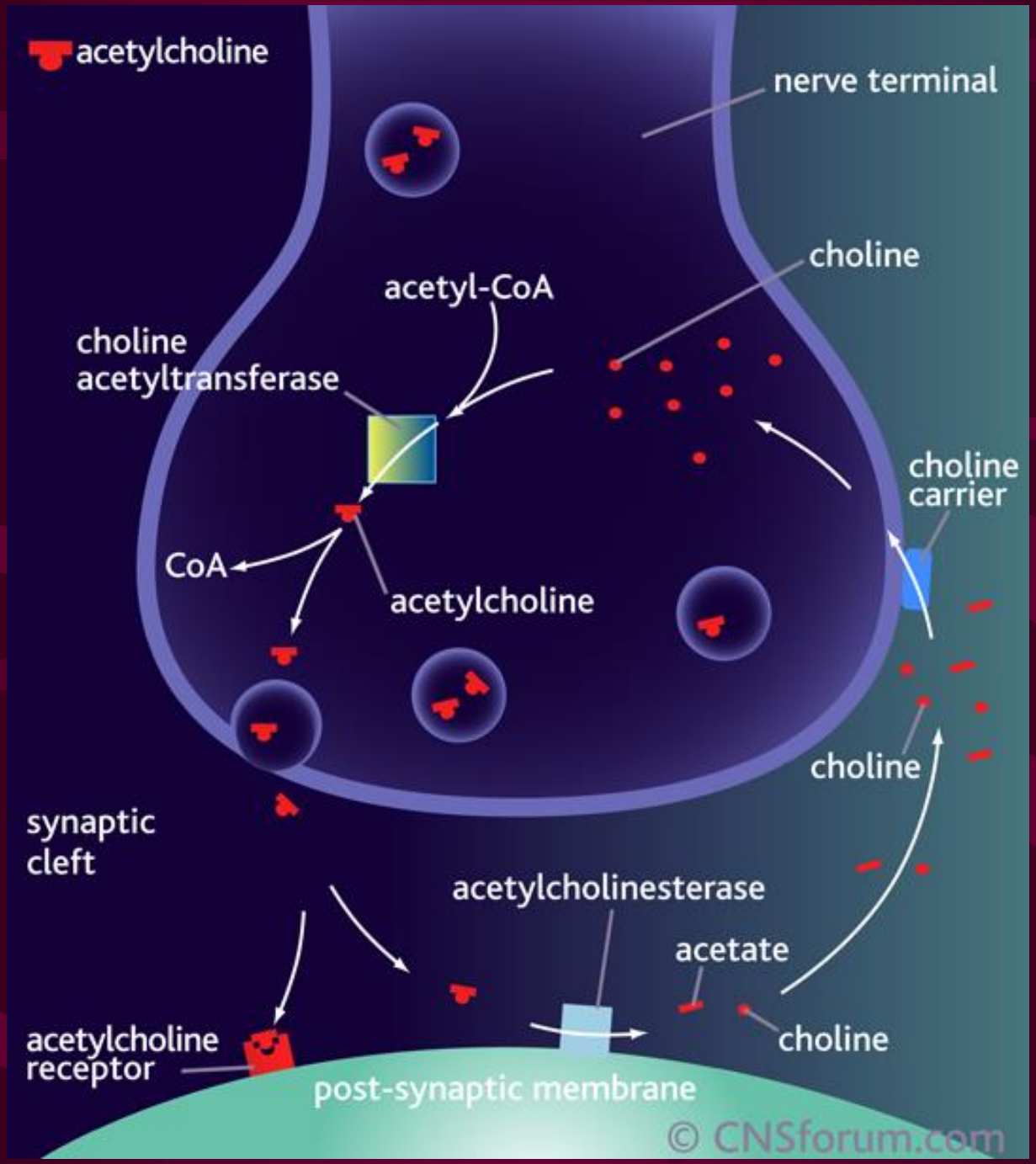
Choline acetyltransferase (ChAT)

Acetylcholinesterase (AchE)

Acetyl-CoA
+
Choline



Acetate
+
Choline


acetylcholine
nerve terminal
choline
acetyl-CoA
choline
acetyltransferase
choline
carrier
CoA
acetylcholine
choline
synaptic
cleft
acetylcholinesterase
acetate
acetylcholine
receptor
choline
post-synaptic membrane
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Acetylcholine

Function: sleep-wake cycles, arousal, learning, memory, sensory information passing through thalamus

Neurons originate: base of cerebrum, pons and midbrain

Neurons terminate: cerebrum, hippocampus, thalamus

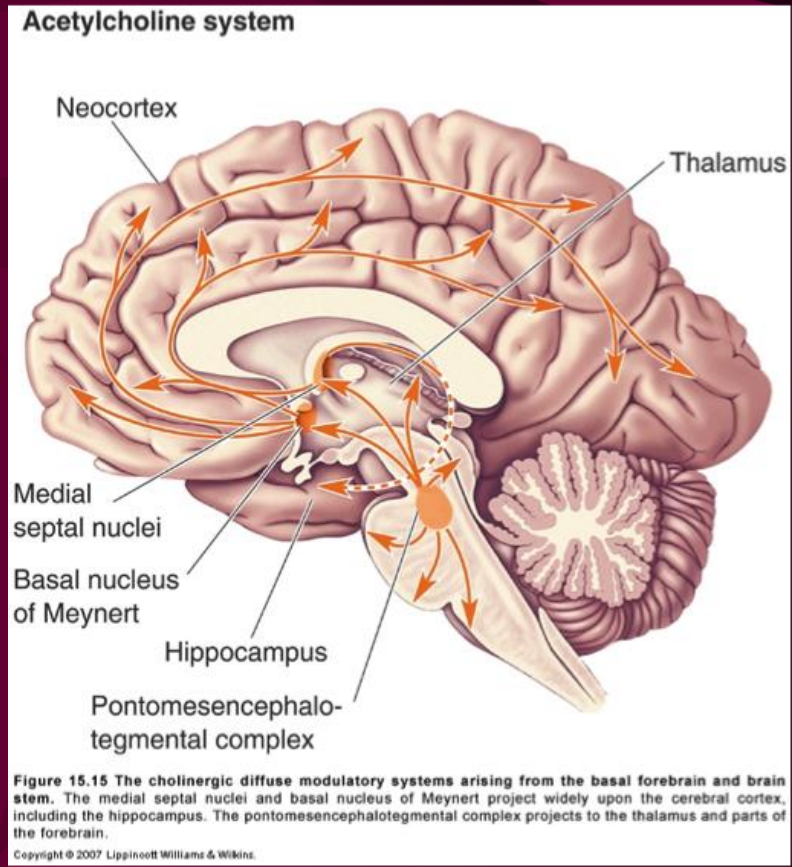
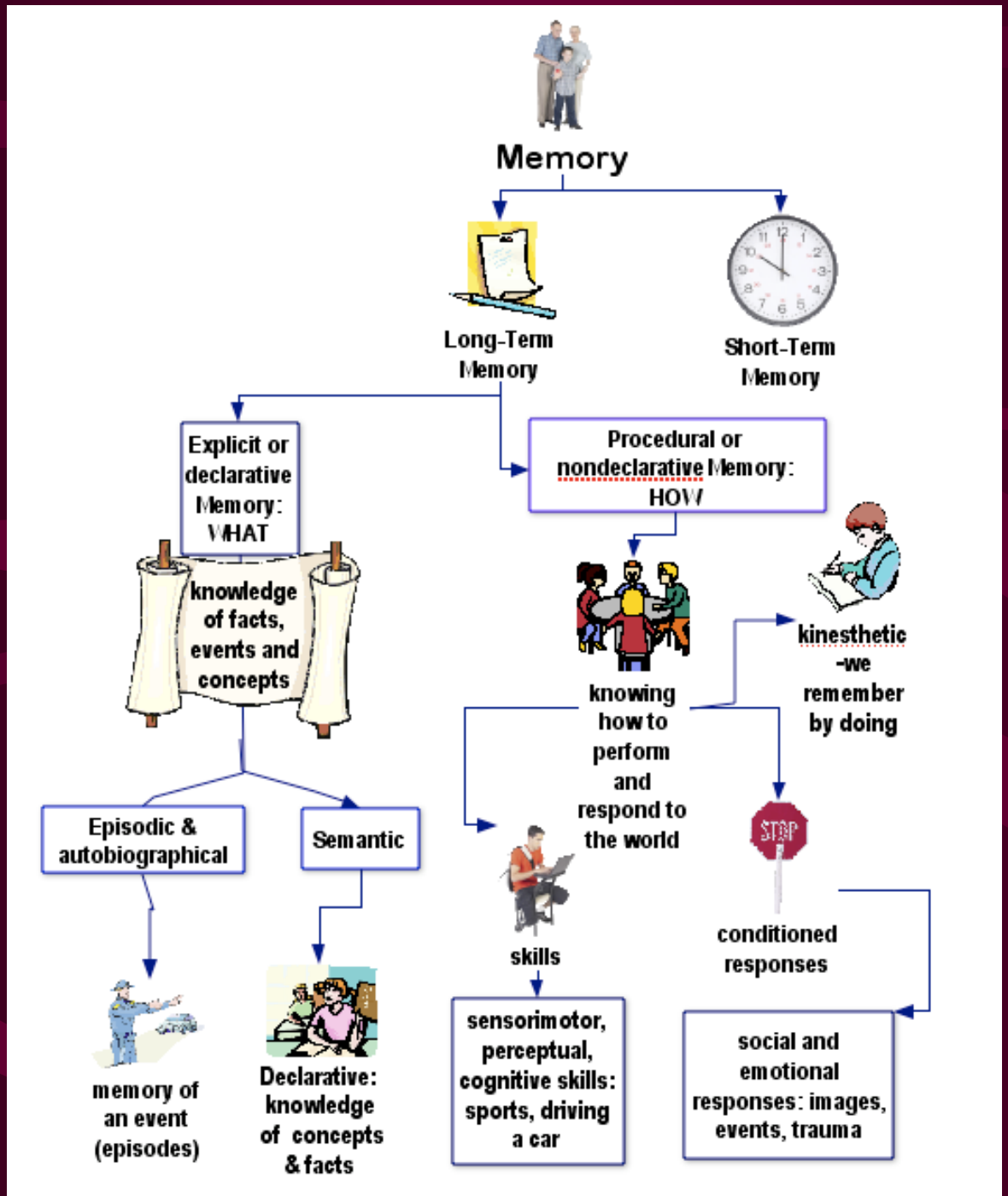
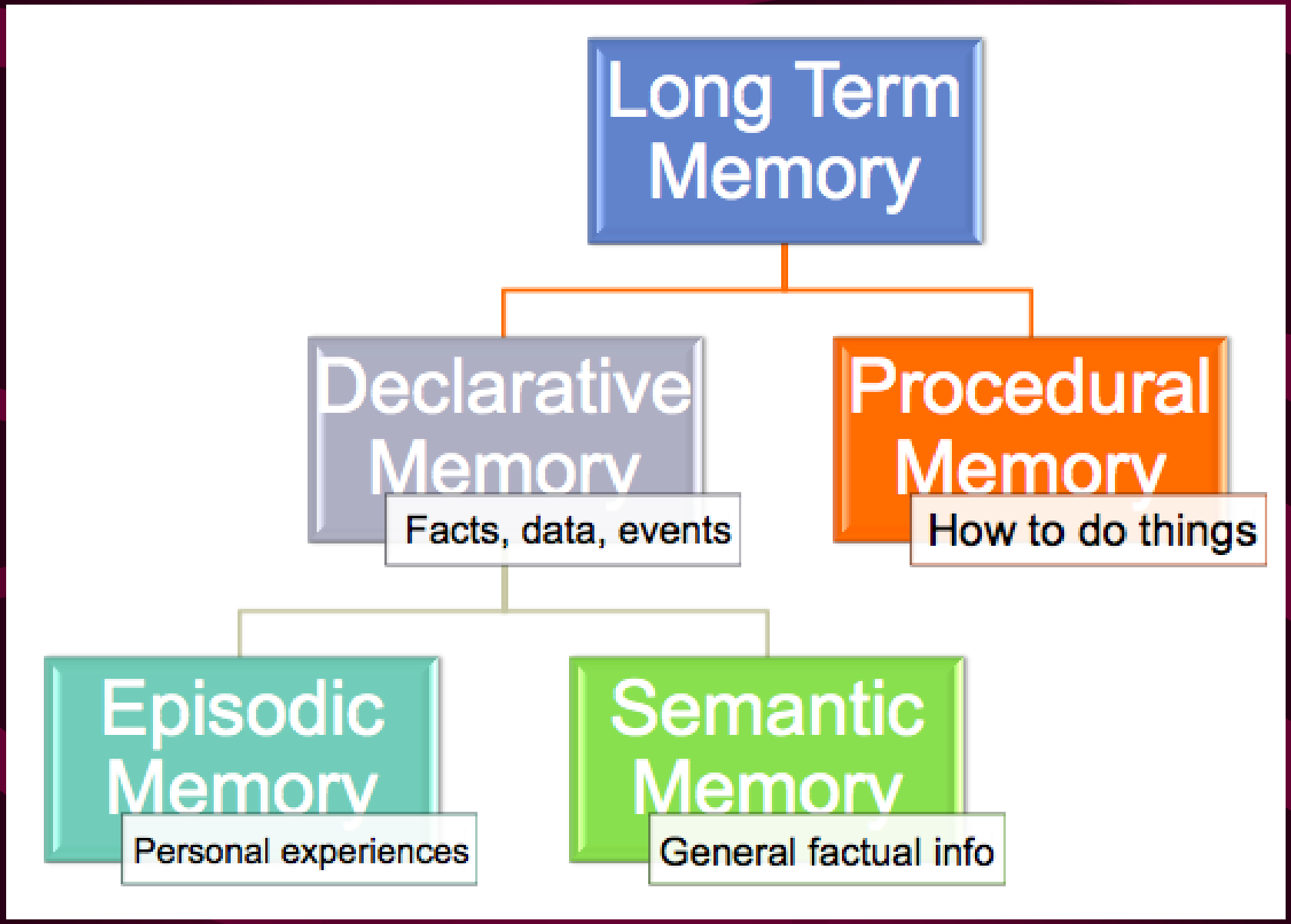


Figure 15.15 The cholinergic diffuse modulatory systems arising from the basal forebrain and brain stem. The medial septal nuclei and basal nucleus of Meynert project widely upon the cerebral cortex, including the hippocampus. The pontomesencephalotegmental complex projects to the thalamus and parts of the forebrain.


Memory
Long-Term Memory
Short-Term Memory
Explicit or declarative Memory: WHAT
Procedural or nondeclarative Memory: HOW
knowledge of facts, events and concepts
knowing how to perform and respond to the world
kinesthetic -we remember by doing
Episodic & autobiographical
Semantic
skills
conditioned responses
memory of an event (episodes)
Declarative: knowledge of concepts & facts
sensorimotor, perceptual, cognitive skills: sports, driving a car
social and emotional responses: images, events, trauma

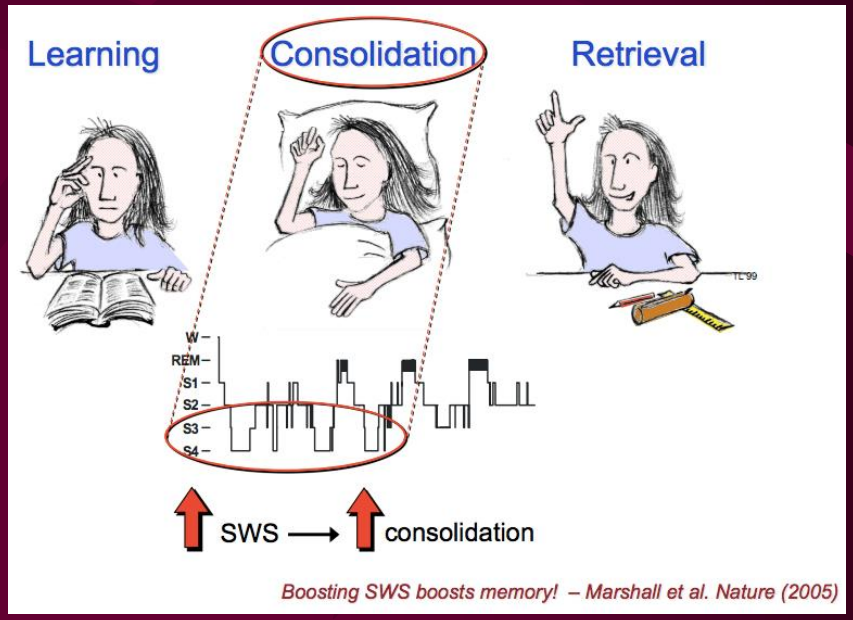
Short Term Memory (working memory)

- Short term memory is typified by one's memory of 7 to 10 numerals in a phone number for a few sec to a few min
- As long as the person continues to think about the numbers (facts)
- Short- Term Memory is dependent on the region of the frontal and parietal lobes


Long Term Memory
Declarative Memory
Facts, data, events
Procedural Memory
How to do things
Episodic Memory
Personal experiences
Semantic Memory
General factual info

Consolidation of Memory

- The more the information is repeated or used, the more likely it is to be retained in log-term memory (which is why, for example, studying helps people to perform better on test)
- This proces of consolidation, the stabilizing of a memory trace after its initial acquisition, is treated in more detail in a separate section

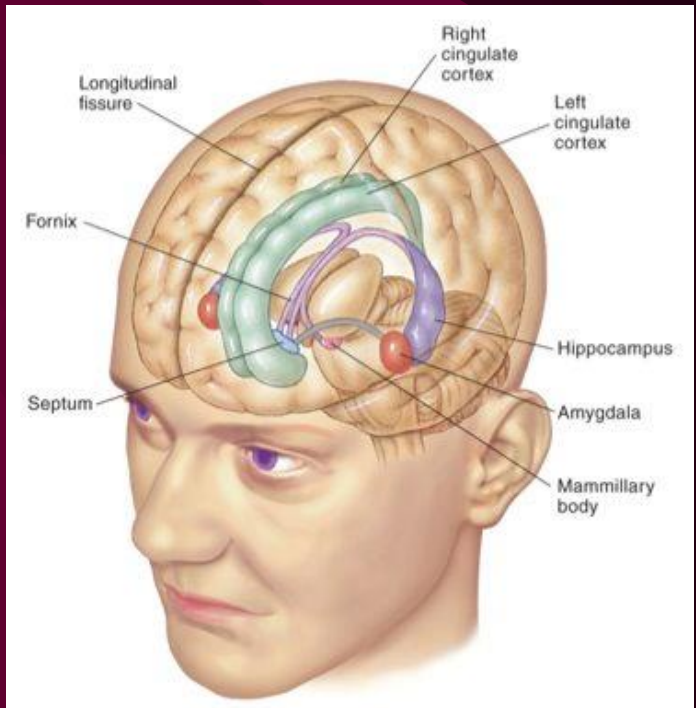


Consolidation of Memory

- For short-term memory to be converted into long-term memory that can recalled weeks, years later, it must becme consolidated that is, the short-term memor if activated repeatedly will initiate chemical, physical, and anatomical changes in the synapses that are responsible for the long time type of memory
- This proces requires 5 to 10

minutes for minimal consolidation

and 1 hour for or more for strong consolidation

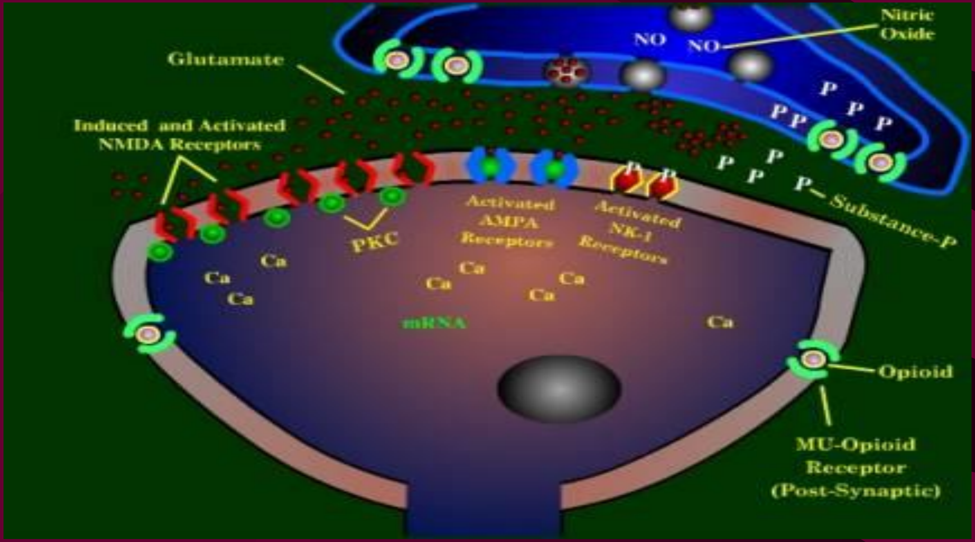


Molecular Mechanism of Memory

- Mechanism: Release of serotonin
- Serotonin acts on its receptors and activation of adenyl cyclase, formation of cAMP
- cAMP activates protein kinase – phosphorilation – K channels – blockage of K conductance
- Lack of K conductance causes greatly prolonged action potential
- Prolonged action potential causes prolonged activation of Ca channels and facilitating synaptic transmission

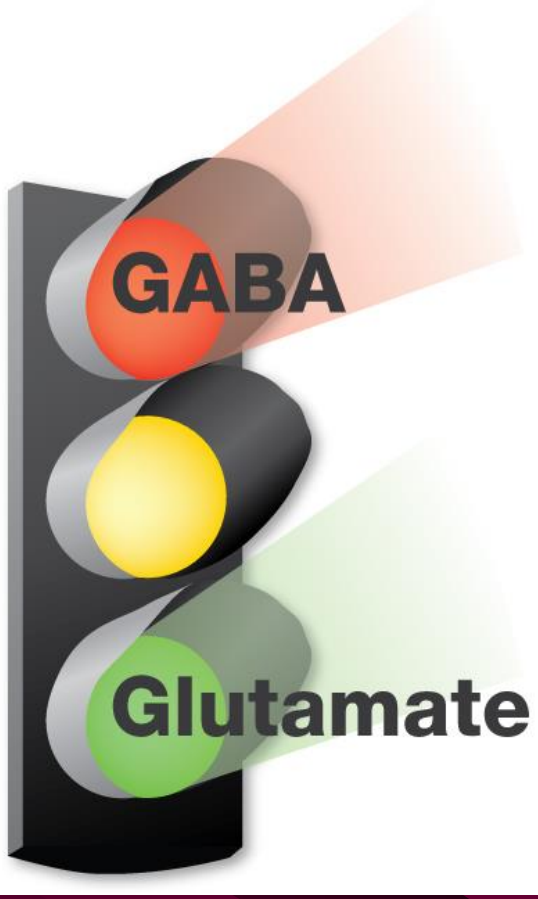
NMDA receptor

- associated with synaptic learning/memory
- binds glutamate
- ionic channels associated with the NMDA receptor are both ligand and voltage gated



- in order to open it needs to be both depolarized and in the presence of glutamate and Ca++ will influx and cause the cellular machinery to manufacture more AMPA glutamate receptors that require only glutamate to cause depolarization

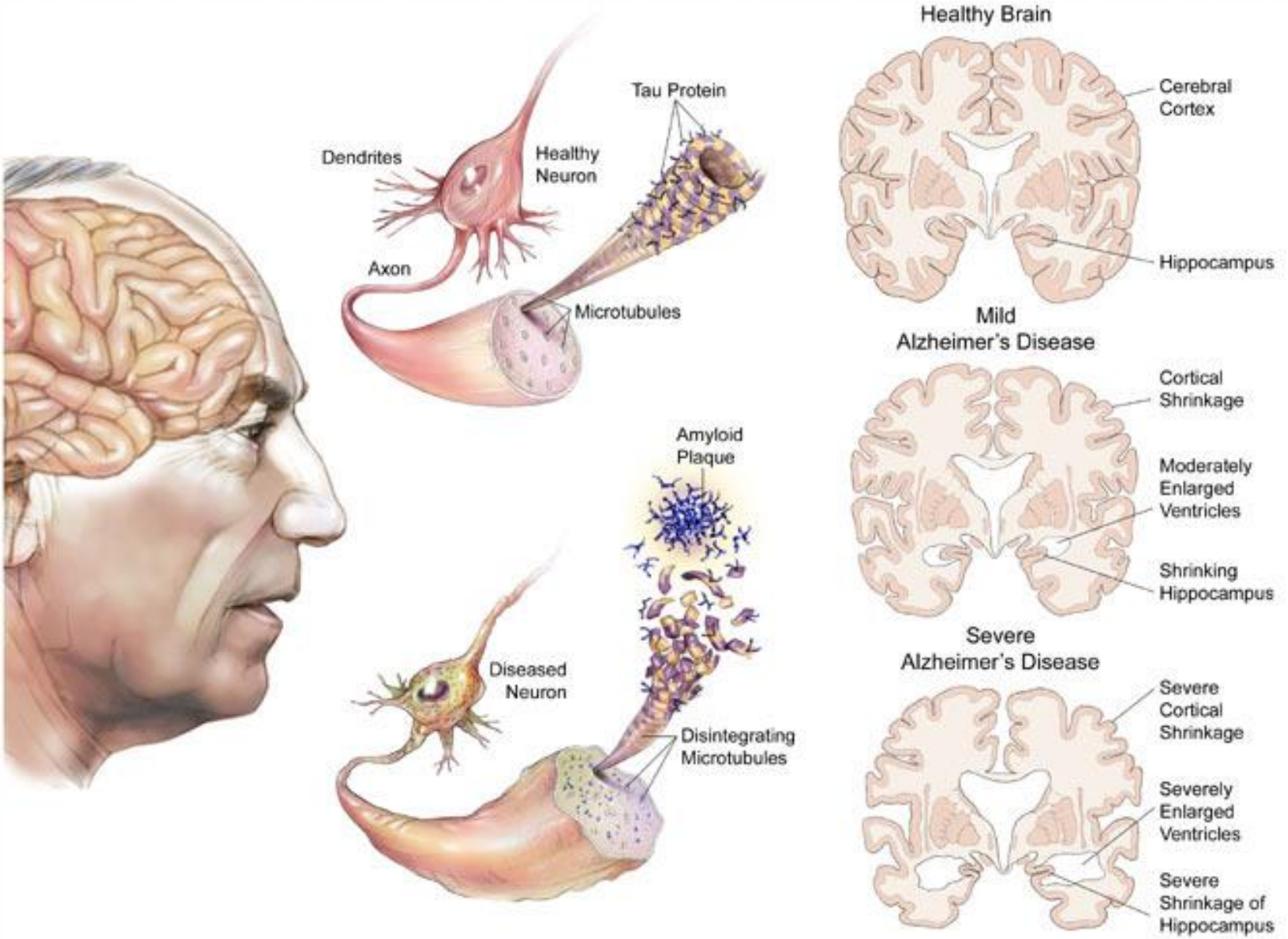
Glutamate



- the amino acid glutamate is the main excitatory transmitter in the brain and spinal cord
- it has been calculated that it is the transmitter responsible for 75% of the excitatory transmissionin the brain
- however, excessive levels of glutamate occur in response to ischemia, anoxia, hypoglycemia, or trauma
- Glutamate and some of its synthetic congeners are unique in that when they act on neuronal cell bodies, they can produce so much Ca2+ influx that neurons die

Alzheimer's Disease…

- Alzheimer's disease (AD) may begin before the age of 50.
- One of its first symptoms is memory loss.
- The AD patient may become moody, confused, paranoid, combative or hallucinatory.
- AD affects about 11% of the U.S. population over the age of 65; the incidence rises to 47% by age 85.
- No single test can detect Alzheimer's.
- In the intercellular spaces there are ***senile plaques*** consisting of aggregations of cells, altered nerve fibers and a core of b-amyloid protein.
- AD is marked by degeneration of cholinergic neurons and a deficiency of ACh.


Tau Protein
Dendrites
Healthy Neuron
Axon
Microtubules
Amyloid Plaque
Diseased Neuron
Disintegrating Microtubules
Healthy Brain
Cerebral Cortex
Hippocampus
Mild Alzheimer's Disease
Cortical Shrinkage
Moderately Enlarged Ventricles
Shrinking Hippocampus
Severe Alzheimer's Disease
Severe Cortical Shrinkage
Severely Enlarged Ventricles
Severe Shrinkage of Hippocampus

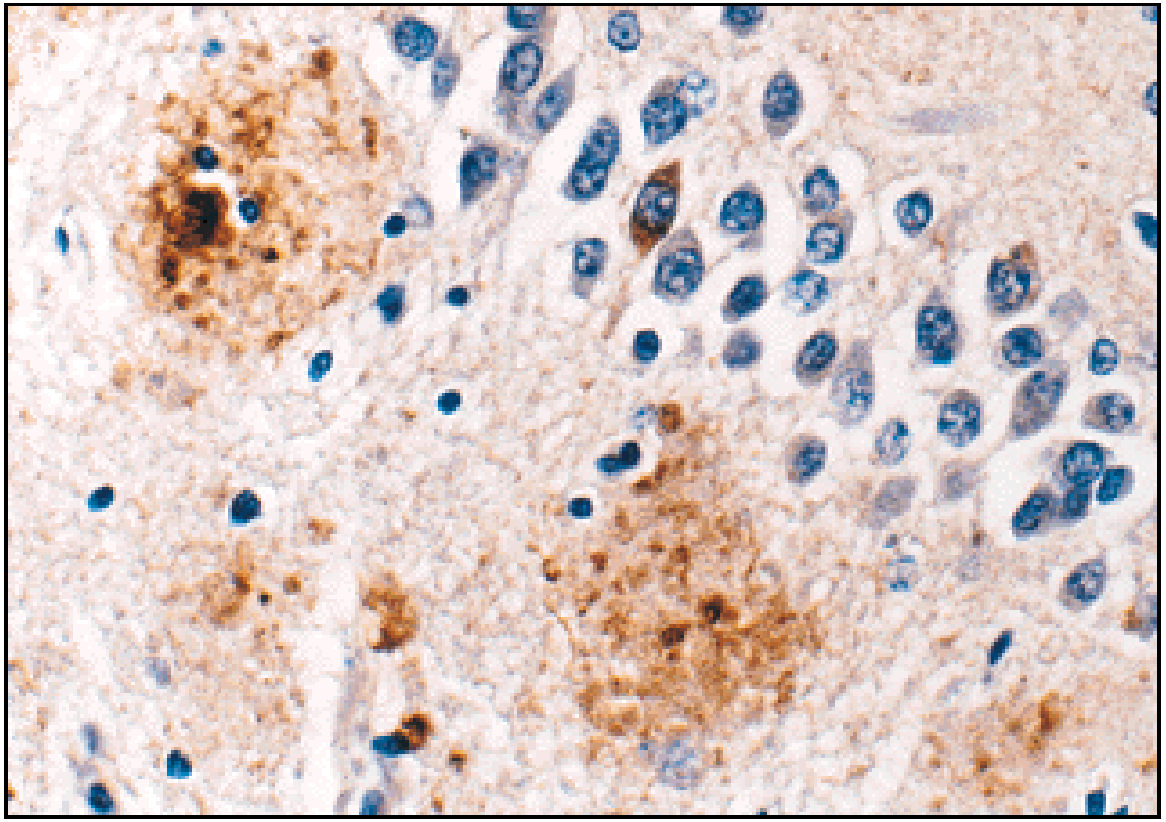
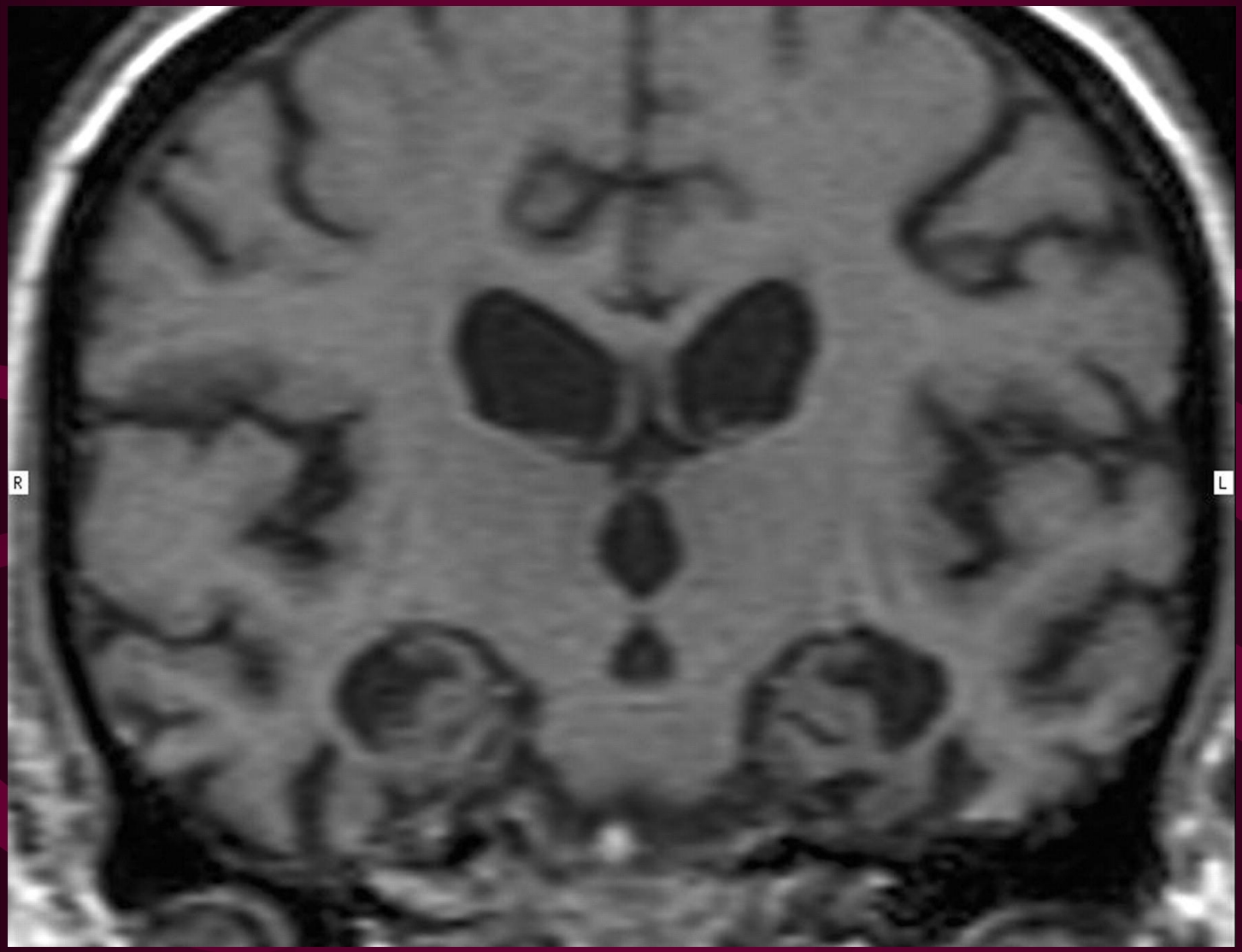


Figure 1. Amyloid plaques and neurofibrillary tangles at specified densities in sectioned brain tissue constitute the neuropathologic criteria confirming Alzheimer's disease. Here both plaques and tangles appear in the hippocampal dentate gyrus of an Alzheimer patient. The plaques (stained reddish brown) are extracellular lesions best known for their content of the amyloid peptide Aβ. More than 30 other proteins have also been found. The tangles (stained blue) are intraneuronal bundles of paired helical filaments consisting perhaps entirely of protein tau, which normally stabilizes the cell's microtubules. The plaques may occur in the absence of dementia, while the tangles are seen in illnesses other than Alzheimer's disease. Moreover, the neuropathology is known—indeed, definitive of Alzheimer's disease—only after the patient's death, often long after the onset of dementia. In consequence, the relation between the pathology and the actual mechanism of the disease remains unclear. (Micrograph courtesy Christine Hulette, Duke University)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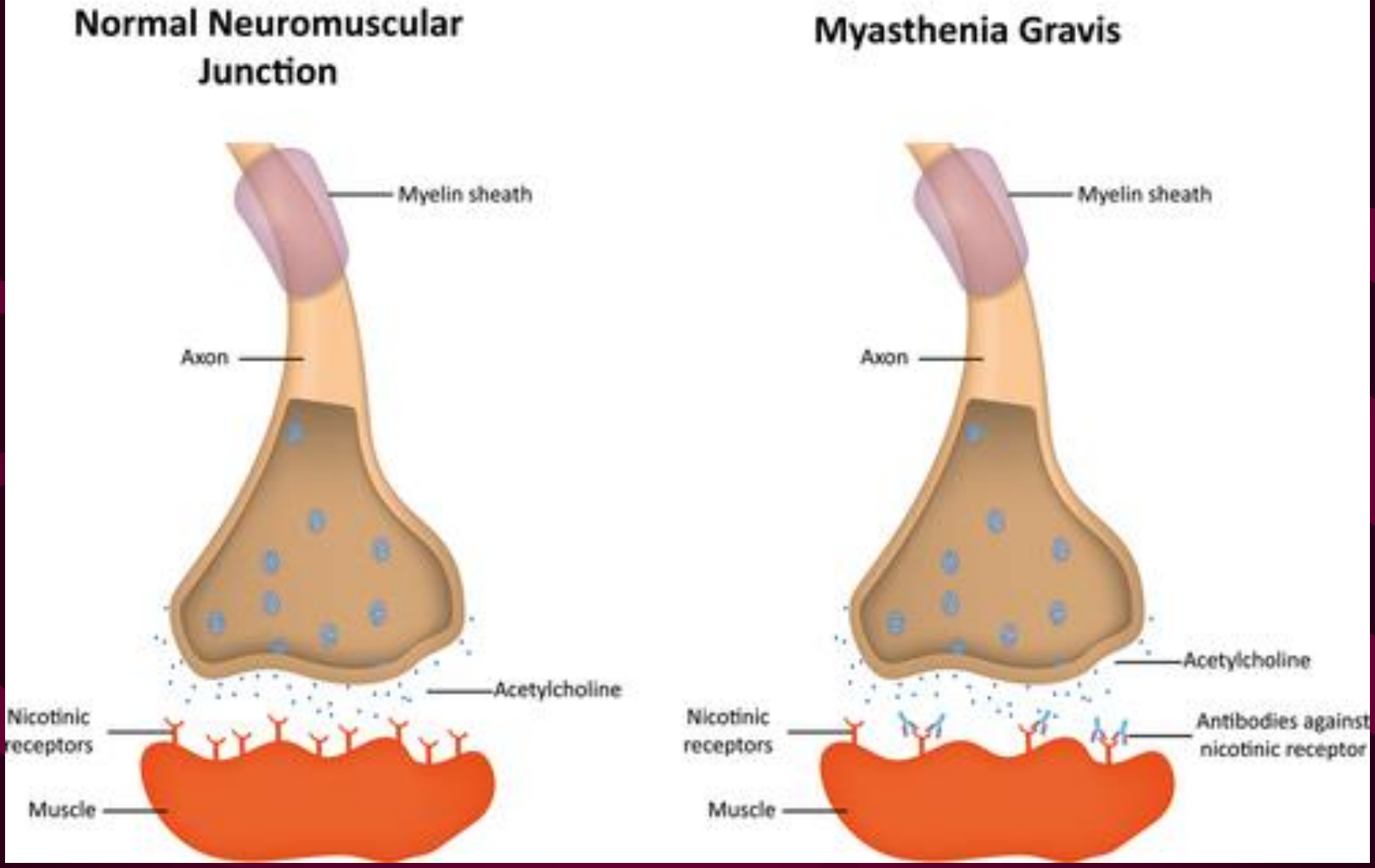
Alzheimer's Disease – treatment

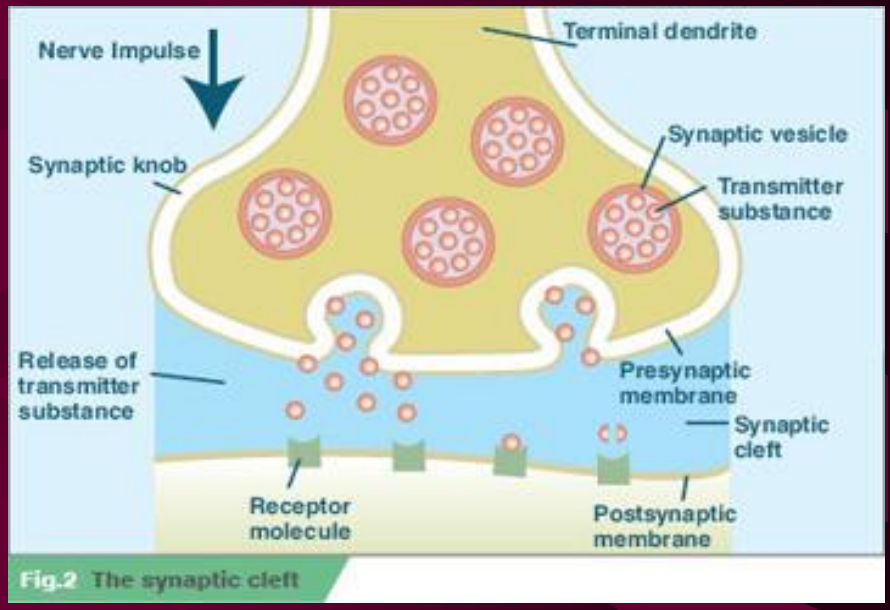
- Cholinesterase inhibitors – donepezil (Aricept), galantamine (Rozadyne), rivastigmine (Exelon).
- NMDA antagonists – memantine
- Psychosocial interventions
- Occupational and lifestyle therapies

Myasthenia Gravis



Myasthenia Gravis

- a chronic Autoimmune Disease
- affects the Neuromuscular junction
- postsynaptic acetylcholine receptors on muscle cells plasma membrane are no longer recognized as 'self' and elicit the generation of auto antibodies.



Pathology

- IgG antibody is produced against the acetylcholine receptors and fixes to receptor sites, blocking the binding of acetylcholine.
- Diminished transmission and lack of muscular depolarization results.

Myasthenia Gravis-symptoms

- Muscle weakness caused by myasthenia gravis worsens as the affected muscle is used repeatedly

- In more than half the people who develop myasthenia gravis, their first signs and symptoms involve eye problems, such as:

-drooping of one or both eyelids (ptosis).

-double vision (diplopia), which may be horizontal or vertical, and improves or resolves when one eye is closed.

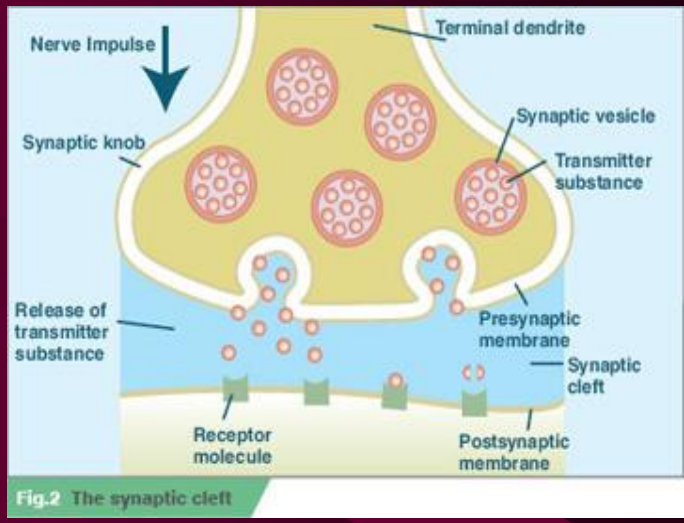


Fig.2 The synaptic cleft

- In about 15 percent of people with myasthenia gravis, the first symptoms involve face and throat muscles.
- Myasthenia gravis can cause weakness in your neck, arms and legs, but this usually happens along with muscle weakness in other parts of your body, such as your eyes, face or throat.

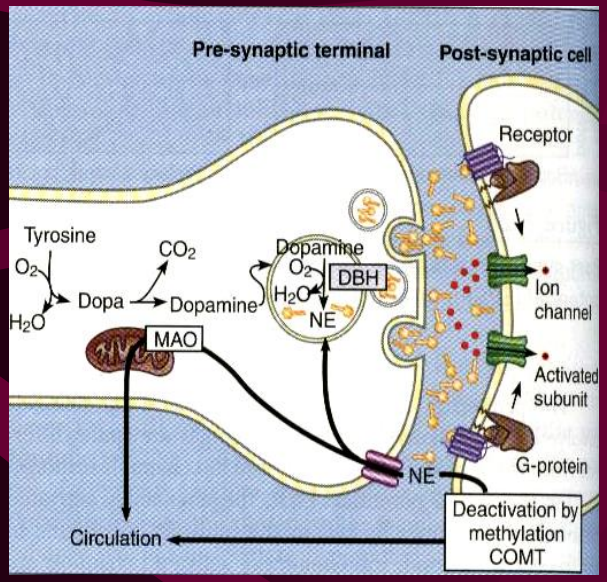
Treatment

- **Medication**
  - Cholinesterase inhibitors
    - These include neostigmine and pyridostigmine
    - Helps improve neuromuscular transmission and increase muscle strength
  - Immunosuppressive drugs
    - These include prednisone, cyclosporine, and azathioprine
    - Improves muscle strength by suppressing the production of abnormal antibodies
  - Corticosteroids
    - Inhibits the immune system
    - Limits antibody production.

Treatment

- **Plasmapheresis**
  - remove abnormal antibodies from the blood
  - Used for more serious conditions.
  - Benefits last around a few weeks
- **High-dose of Intravenous Immune Globulin (IVIG)**
  - Modifies immune system temporarily
  - Provides the body with normal antibodies from donated blood
  - Less risk of side effects
  - Benefits last 1-2 months and takes a couple weeks to start working

Norepinephrine metabolism



-NE may be recycled back into vesicles for later release (80%)

-NE they may be degraded by the enzymes: monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT)

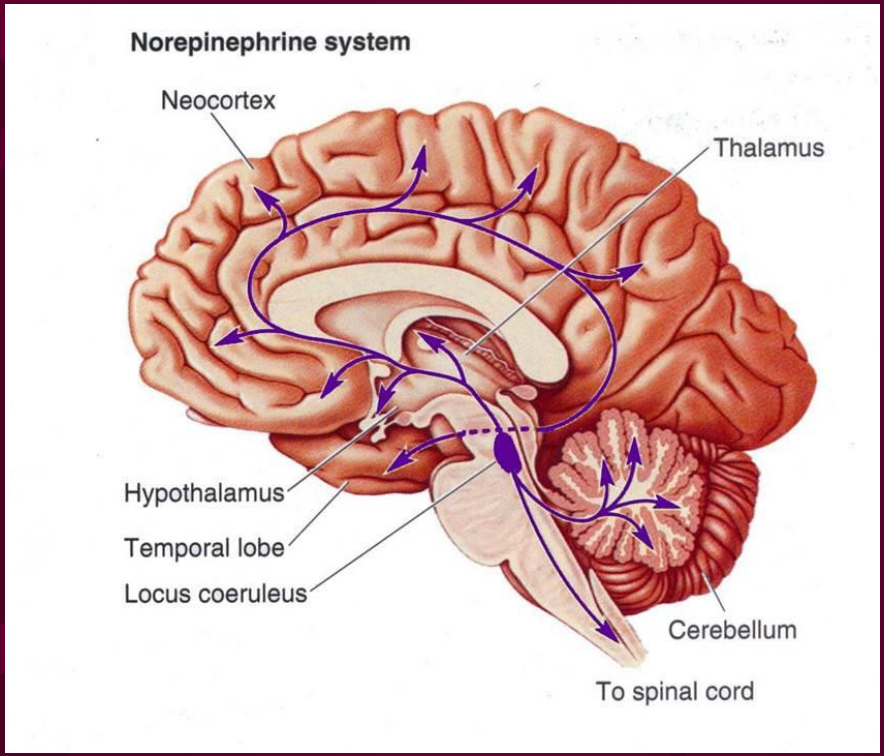
-NE may travel to the blood

Norepinephrine

Function: attention, arousal, sleep-wake cycles,learning, memory, anxiety, pain and mood

Neurons originate: locus coeruleus of the pons

Neurons terminate: cerebral cortex, thalamus, hypothalamus, olfactory bulb, cerebellum, midbrain, spinal cord



Amphetamine

- Block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.
  - Clinical use:
- 1. Narcolepsy.
- 2. Attention-deficit hyperactivity disorder

Table 1-2. Agents Affecting Neuromuscular Transmission

Example	Action	Effect on Neuromuscular Transmission
Botulinus toxin	Blocks release of ACh from presynaptic terminals	Total blockade
Curare	Competes with ACh for receptors on motor end plate	Decreases size of EPP; maximal doses produce paralysis of respiratory muscles and death
Neostigmine	Anticholinesterase	Prolongs and enhances action of ACh at muscle end plate
Hemicholinium	Blocks reuptake of choline into presynaptic terminal	Depletes ACh stores from presynaptic terminal

ACh = acetylcholine; EPP = end plate potential.

Cocaine:Neurotransmitter Actions of Cocaine

- Potentiates synaptic action due to actively blocking the reuptake of DA, NE & serotonin
- Exerts inhibitory effect on postsynaptic dopamine receptors
- Blocks the presynaptic transporter protein for DA
- Increases levels of DA at the synaptic cleft, creating a euphoric sensation
- Serotonin binding provides additional reinforcement

Cocaine in high doses blocks sodium ion channels in neuron membranes blocking conduction or action potentials. This is the basis of the local anesthetic action of cocaine.

The first local anesthetic was cocaine and by convention local anesthetic names usually end in "caine". E.g. procaine which is now widely used as a local anesthetic.