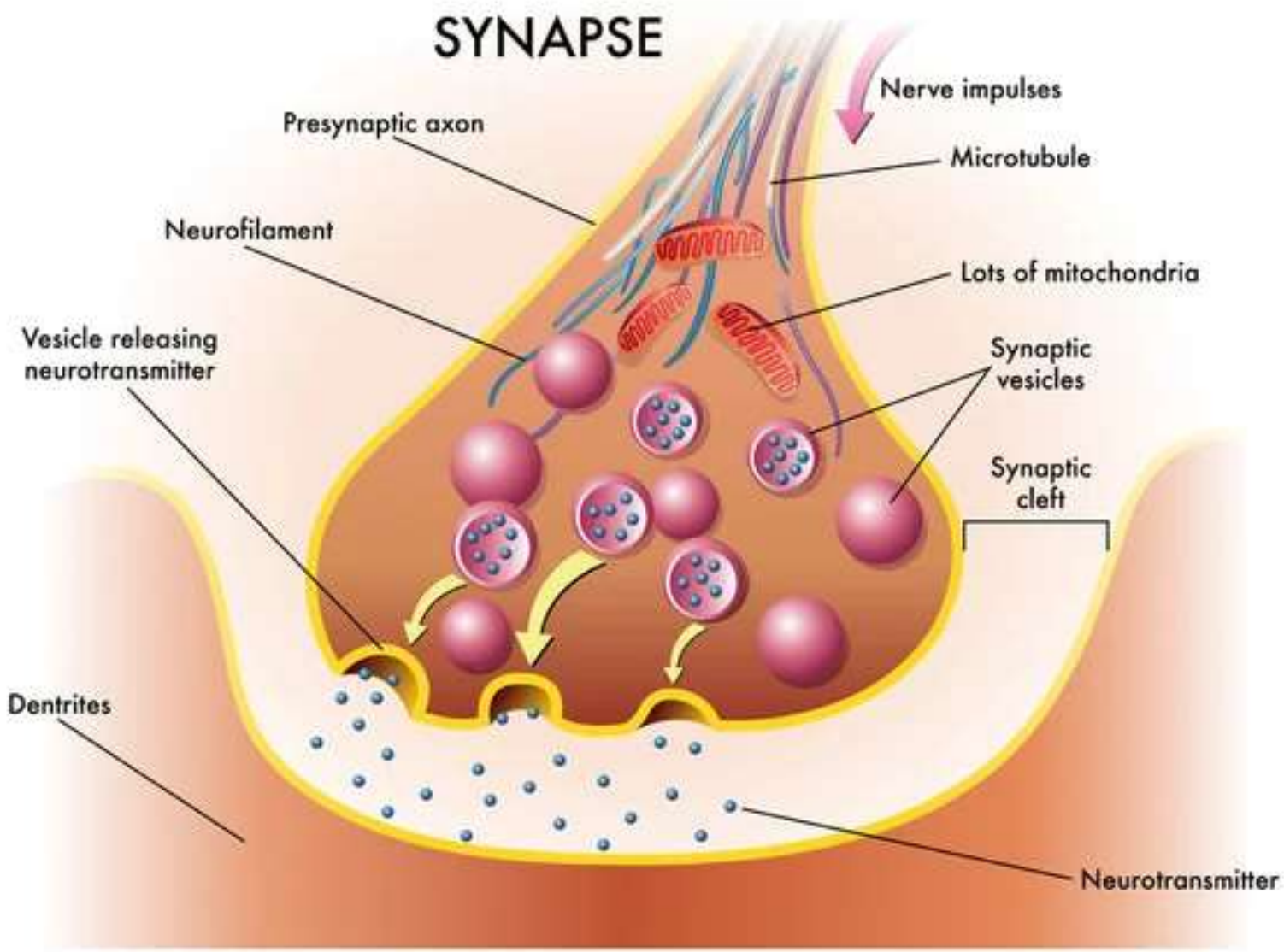
Synaptic transmission

- There are 2 types of synapses: electric and chemical.
- At electric synapses, the plasma membranes of the pre- and postsynaptic cells are joined by gap junctions
- These allow the local currents resulting from arriving AP's to flow directly across the junction through the connecting channels in either direction from one neuron to the neuron on the other side of the junction, depolarizing the membrane to threshold thus initiating an AP in the 2^{nd}.
- Electric synapses rare in the mammalian nervous system and mostly found in cardiac and smooth muscles
- Most common are chemical synapses


SYNAPSE
Nerve impulses
Presynaptic axon
Microtubule
Neurofilament
Lots of mitochondria
Vesicle releasing neurotransmitter
Synaptic vesicles
Synaptic cleft
Dentrites
Neurotransmitter

Synapses

FUNCTIONS OF SYNAPSE

Main function of the synapse is to transmit the impulses, i.e. action potential from one neuron to another.

However, some of the synapses inhibit these Impulses hence impulses are not transmitted to the postsynaptic neuron.

On the basis of functions, synapses are divided into two types:

1. Excitatory synapses, which transmit the impulses (excitatory function)
2. Inhibitory synapses, which inhibit the transmission of impulses (inhibitory function).

EXCITATORY FUNCTION

- Excitatory Postsynaptic Potential
- Excitatory postsynaptic potential (EPSP) is the non-propagated electrical potential that develops during the process of synaptic transmission.
- When the action potential reaches the presynaptic axon terminal, the Voltage gated calcium channels at the presynaptic membrane are opened

- .The calcium ions enter the axon terminal from ECF
- Calcium ions cause the release of neurotransmitter substance from the vesicles by means of exocytosis.
- Neurotransmitter, which is excitatory in function (excitatory neurotransmitter) passes through presynaptic membrane and synaptic cleft and reaches the postsynaptic membrane

CONT…

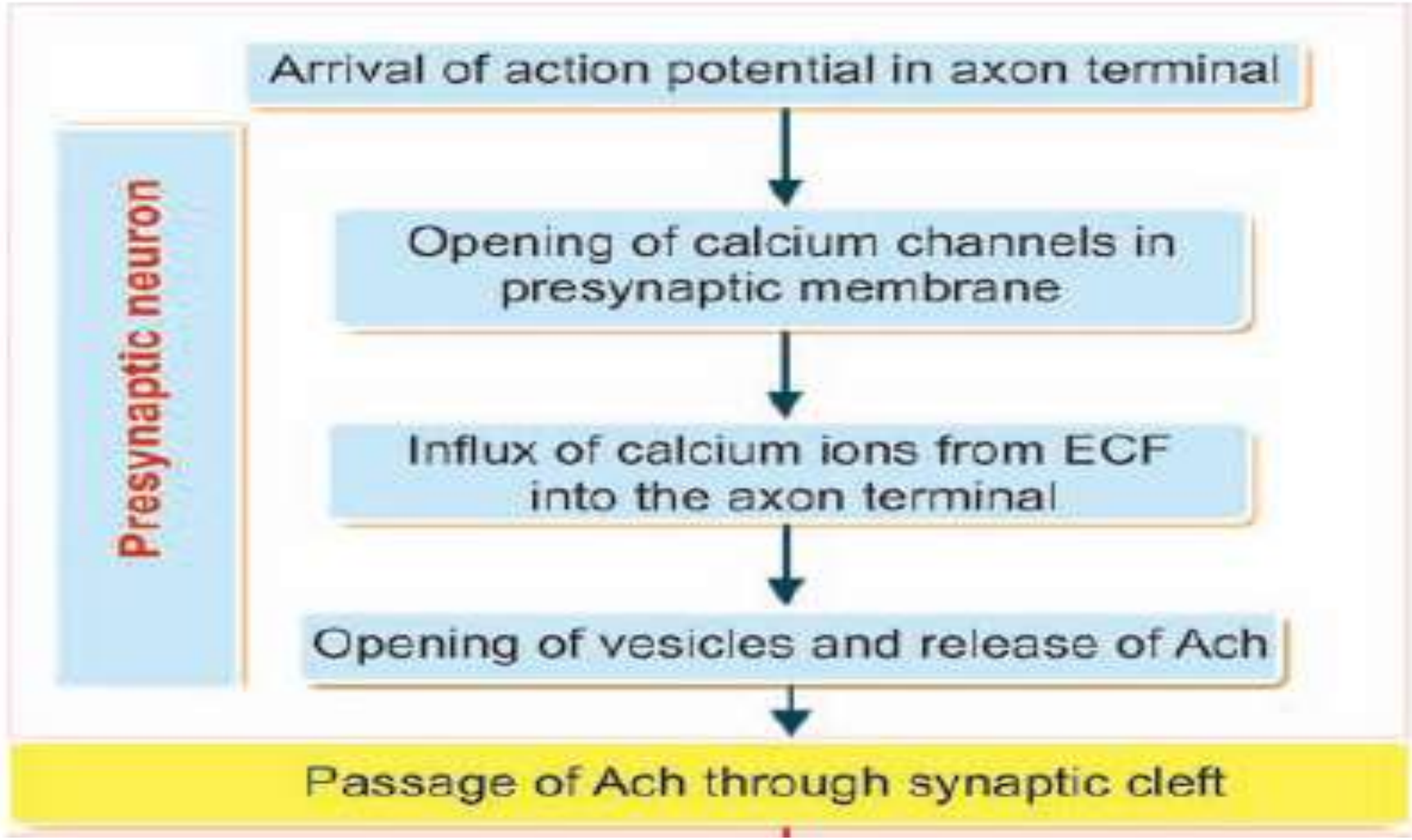
- .The neurotransmitter binds with receptor protein present in postsynaptic membrane to form neurotransmitter-receptor complex.
- Neurotransmitter receptor complex causes production of a non-propagated EPSP.
- Common excitatory neurotransmitter in a synapse is acetylcholine.

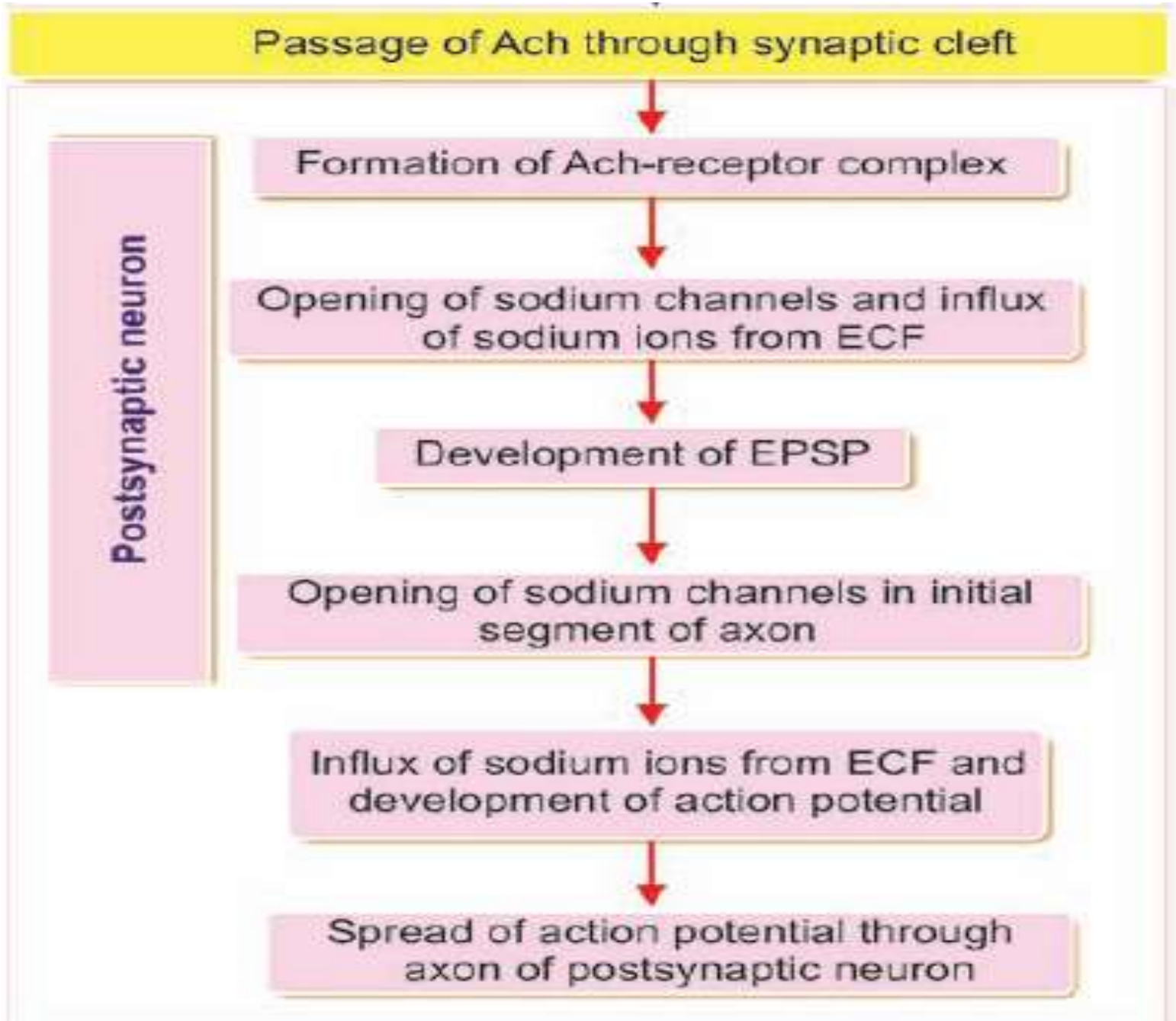
Mechanism of Development of EPSP

- Neurotransmitter-receptor complex causes opening of ligand gated Na+ channels.
- The Na+ ions from ECF enter the cell body of postsynaptic neuron.
- As the sodium ions are positively charged, RMP inside the cell body is altered and mild depolarization develops.
- This type of mild depolarization is called EPSP.
- It is a local potential (response) in the synapse.

Mechanism of Development of EPSP

Neurotransmitter-receptor complex causes opening of ligand-gated **sodium channels**. Now, the **sodium ions**




Passage of Ach through synaptic cleft
Postsynaptic neuron
Formation of Ach-receptor complex
Opening of sodium channels and influx of sodium ions from ECF
Development of EPSP
Opening of sodium channels in initial segment of axon
Influx of sodium ions from ECF and development of action potential
Spread of action potential through axon of postsynaptic neuron

Properties of EPSP

- EPSP is confined only to the synapse.
- It is a graded potential similar to receptor potential.
- EPSP has two properties:
- 1. It is non propagated
- 2. It does not obey all or none law

Significance of EPSP

- EPSP is not transmitted into the axon of postsynaptic neuron.
- However, it causes development of action potential in the axon.
- When EPSP strong enough, causes the opening of voltage gated sodium channels in the initial segment of axon.
- Due to the entrance of sodium ions, the depolarization occurs in the initial segment of axon and thus, the AP develops.
- From here, the AP spreads to other segment of the axon.

Inhibitory Function

Postsynaptic or Direct Inhibition

- Postsynaptic inhibition is the type of synaptic inhibition that occurs due to the release of an inhibitory neurotransmitter from presynaptic terminal instead of an excitatory neurotransmitter substance.
- Also called direct inhibition.
- Inhibitory neurotransmitters are gamma aminobutyric acid (GABA), dopamine and glycine.

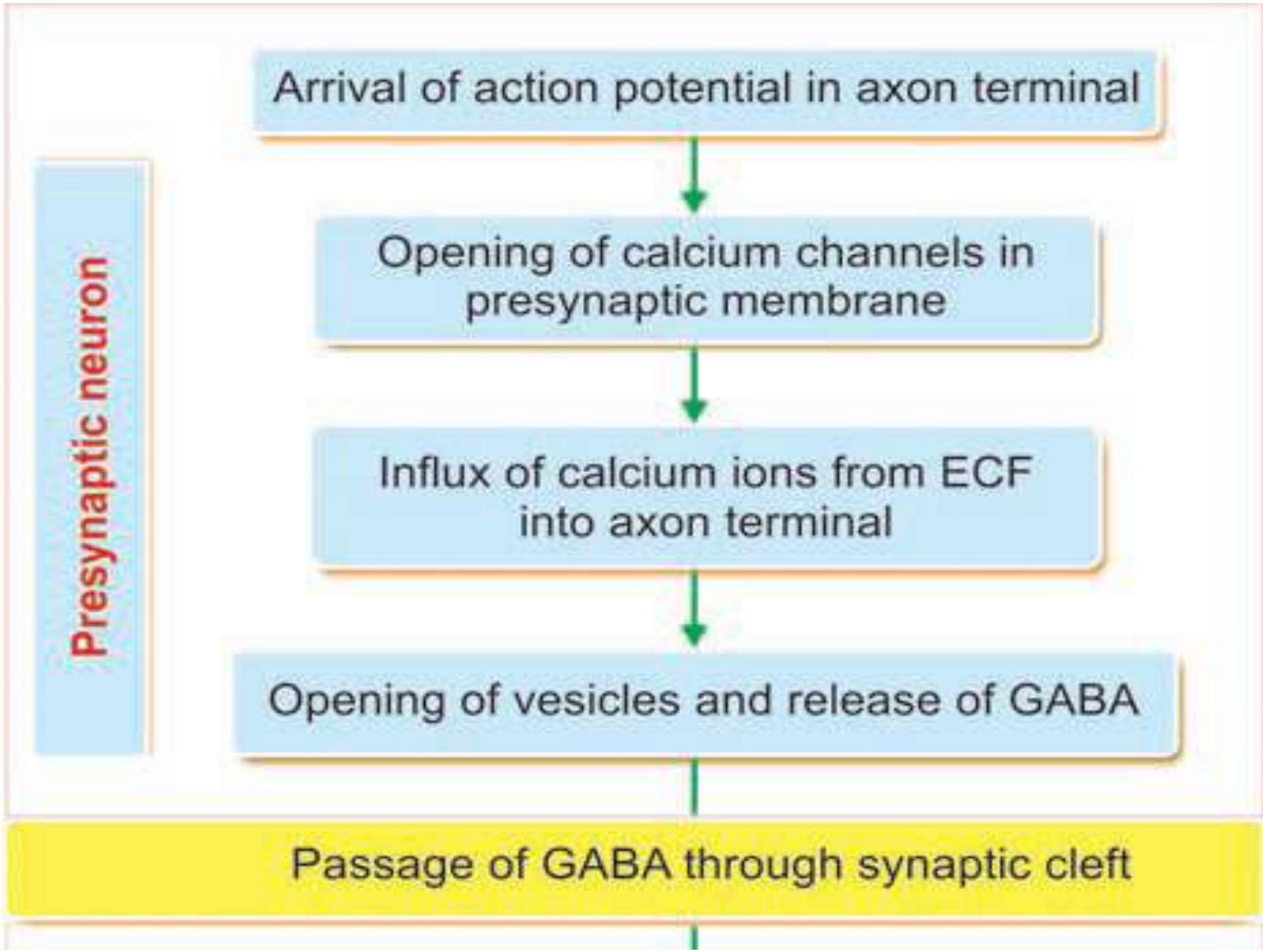
Action of GABA

Development of inhibitory postsynaptic potential

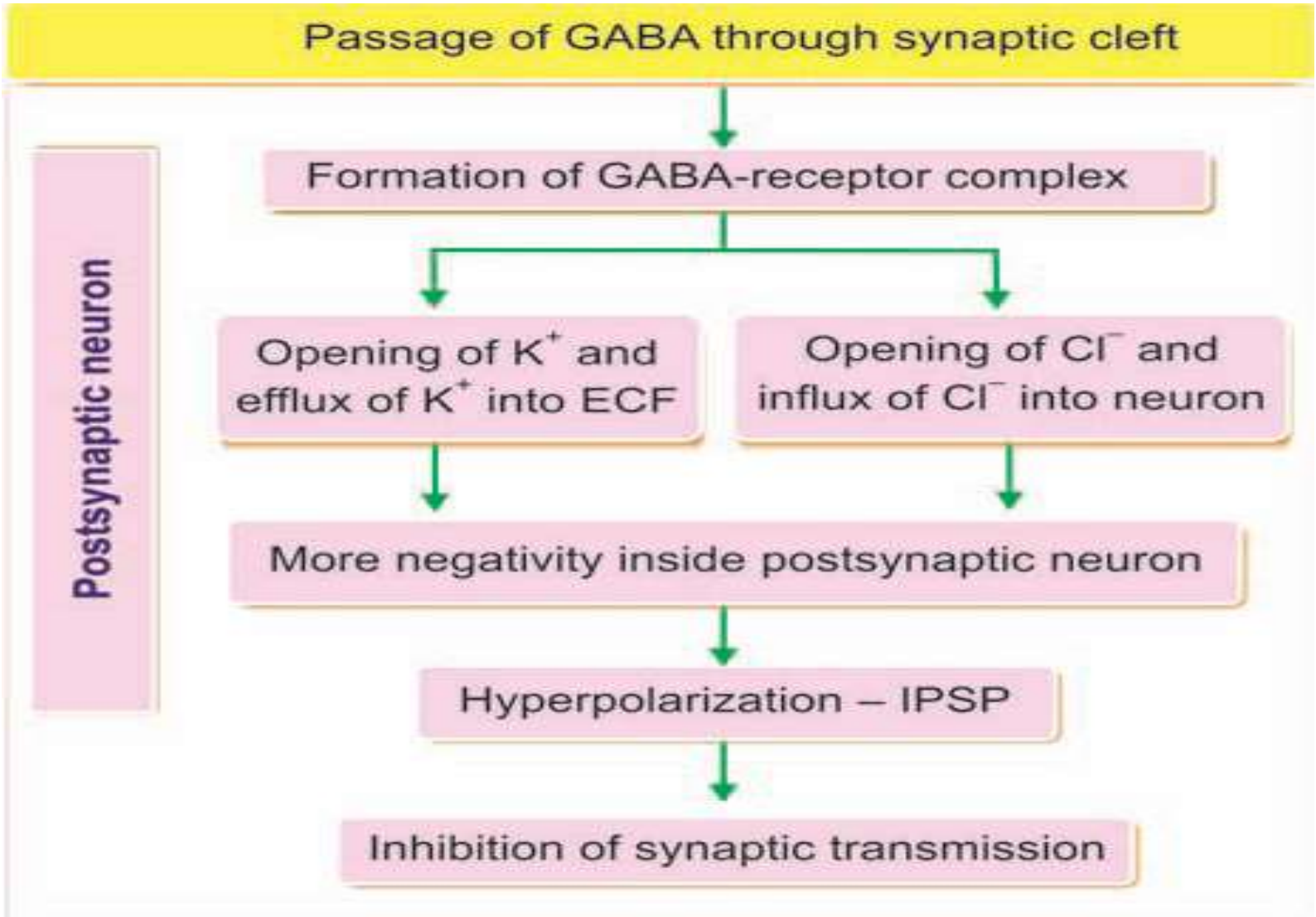
- Inhibitory postsynaptic potential (IPSP) is the electrical potential in the form of hyperpolarization that develops during postsynaptic inhibition.
- Inhibitory neurotransmitter substance acts on postsynaptic membrane by binding with receptor.
- Transmitter receptor complex opens the ligand gated potassium channels instead of sodium channels.

CONT…

- The K+ ions, which are available in plenty in the cell body of postsynaptic neuron move to ECF.
- Simultaneously, chloride channels also open and chloride ions (which are more in ECF) move inside the cell body of postsynaptic neuron.
- The exit of potassium ions and influx of chloride ions cause more negativity inside, leading to hyperpolarization.
- Hyperpolarized state of the synapse inhibits synaptic transmission


Presynaptic neuron
Arrival of action potential in axon terminal
Opening of calcium channels in presynaptic membrane
Influx of calcium ions from ECF into axon terminal
Opening of vesicles and release of GABA
Passage of GABA through synaptic cleft

CONT…


Passage of GABA through synaptic cleft
Postsynaptic neuron
Formation of GABA-receptor complex
Opening of K^+ and efflux of K^+ into ECF
Opening of Cl^- and influx of Cl^- into neuron
More negativity inside postsynaptic neuron
Hyperpolarization – IPSP
Inhibition of synaptic transmission

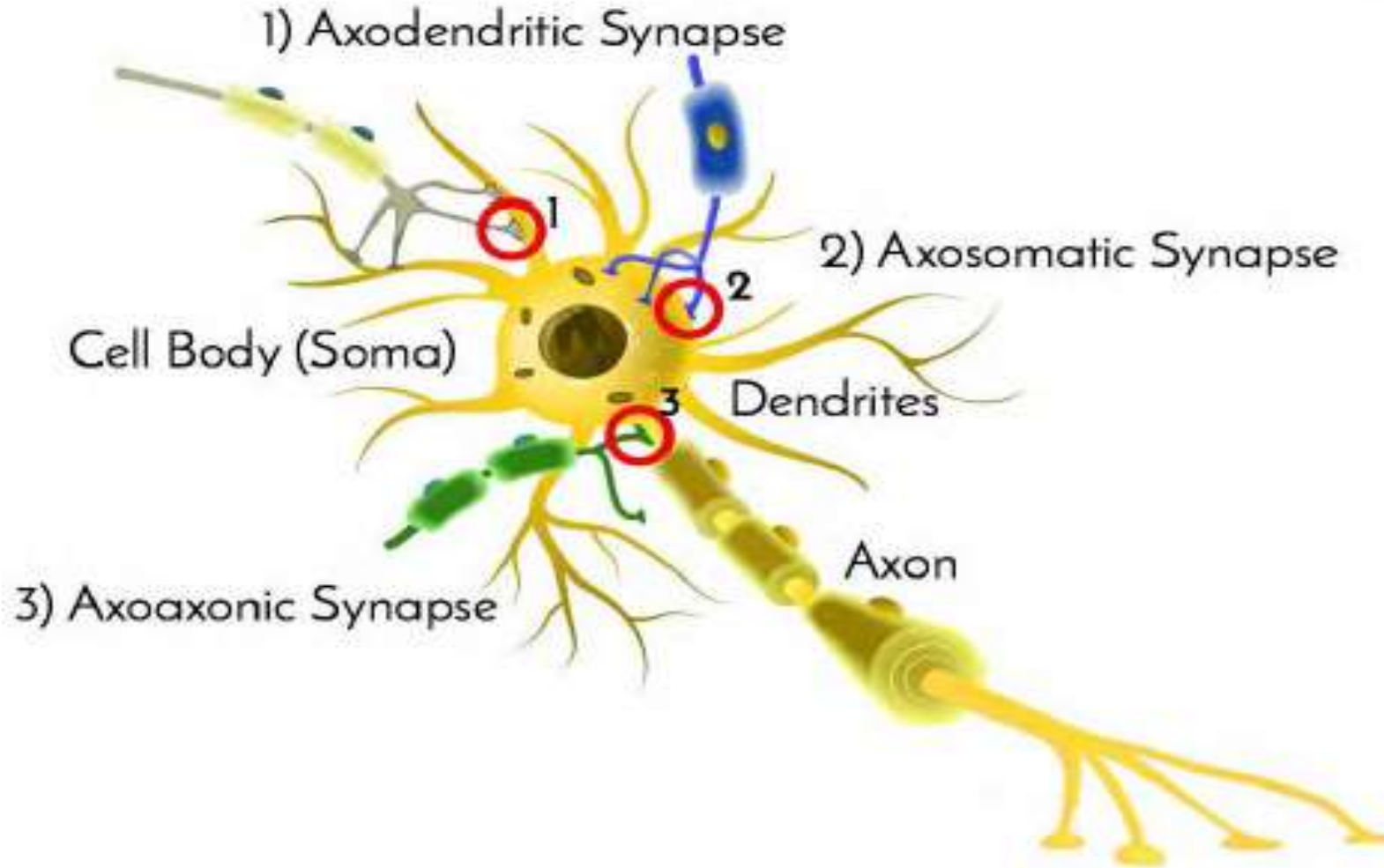
Refractory period

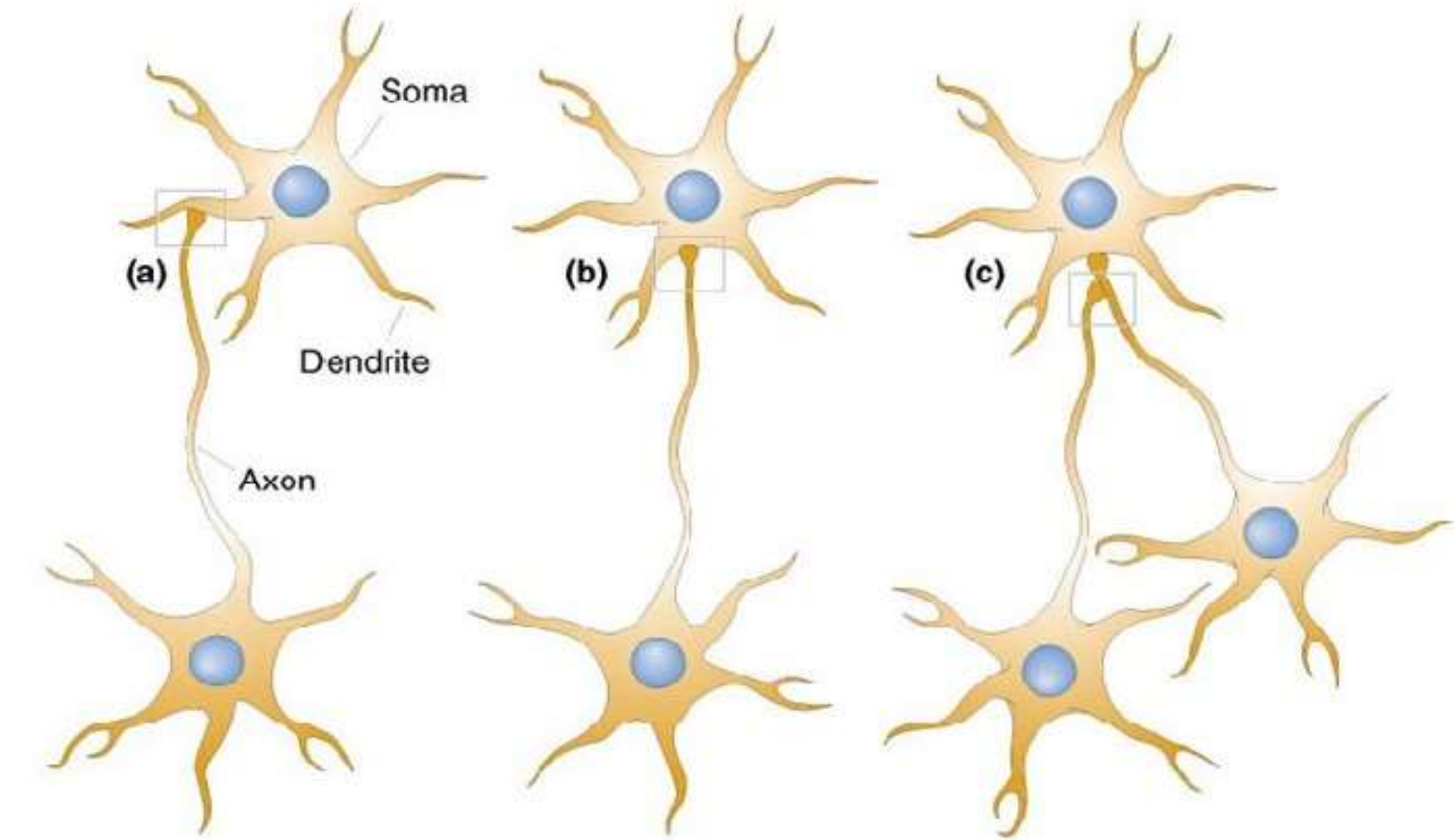
- During the AP, a 2nd stimulus, no matter how strong, will not produce a second AP
- The membrane is said to be in its absolute refractory period.
- Occurs since the voltage-gated Na channels enter a closed, inactive state at the peak of the AP
- Membrane must repolarize before the Na channel can be open.
- After absolute refractory period, there is an interval during which a second action potential can be produced, but only if the stimulus strength is considerably greater than usual.
- Is the relative refractory period, and lasts 10 to 15 ms or longer in neurons
- Occurs during hyperpolarization.

- If a depolarization exceeds the increased threshold or outlasts the relative refractory period, additional action potentials will be fired.
- The refractory periods limit the number of AP’s that can be produced by an excitable membrane in a given period of time.
- Also increase reliability of neural signaling because they help limit extra impulses.
- Most nerve cells respond at frequencies of up to 100 AP’s per sec

Presynaptic or Indirect Inhibition:

- Presynaptic inhibition occurs due to the failure of presynaptic axon terminal to release sufficient quantity of excitatory neurotransmitter substance.
- It is also called indirect inhibition.
- Presynaptic inhibition is mediated by axoaxonal synapses.
- Prominent in spinal cord and regulates propagation of information to higher centers in brain.


1) Axodendritic Synapse
1
2) Axosomatic Synapse
2
Cell Body (Soma)
3
Dendrites
Axon
3) Axoaxonic Synapse



Axodendritic Axosomatic Axoaxonic

CONT…

- Normally, during synaptic transmission, action potential reaching the presynaptic neuron causes development of EPSP’s in the postsynaptic neuron.
- But, in spinal cord, a modulatory neuron called presynaptic inhibitory neuron forms an axoaxonic synapse with the presynaptic neuron
- This inhibitory neuron inhibits the presynaptic neuron and decreases the magnitude of action potential in presynaptic neuron.

- The smaller action potential reduces calcium influx.
- This in turn decreases the quantity of neurotransmitter released by presynaptic neuron.
- The magnitude of EPSP in postsynaptic neuron is decreased resulting in synaptic inhibition

Spatial summation

- Excitation of a single presynaptic terminal on the surface of a neuron almost never excites the neuron
- Because single terminal causes EPSP of only about 0.5 – 1mv instead of the 20 – 30 required to reach threshold
- Many synapses usually stimulated at same time and this effects summate to reach threshold

Temporal summation

- Each time a presynaptic terminal fires, the released transmitter substance opens the membrane channels for at most a millisecond or so.
- This changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed.
- A second opening of the same channels can increase the postsynaptic potential to a still greater level

- The more rapid the rate of stimulation, the greater the postsynaptic potential becomes.
- Thus, successive discharges from a single presynaptic terminal, if they occur rapidly enough, can add to one another; that is, they can “summate.”
- This is temporal summation

Fatigue of Synaptic Transmission

- When excitatory synapses are repetitively stimulated at a rapid rate, no. of discharges by postsynaptic neuron very high at first, but rate becomes progressively less in succeeding milliseconds or seconds.
- This is fatigue
- Important as in case of epileptic seizures where fatigue subdues the seizures finally
- Is protective mechanism against excess neuronal activity

- Mainly due to exhaustion of transmitter substance pre-synaptically
- Could also be due to:
- (1) progressive inactivation of many of the postsynaptic membrane receptors
- (2) slow development of abnormal concentrations of ions inside the postsynaptic neuronal cell.

Effect of Acidosis or Alkalosis

- PH affects neuronal transmission highly
- Alkalosis increases excitability highly
- PH of 7.8 – 8 often causes seizures
- Acidosis decreases excitability
- In very severe diabetic patients, coma will develop

Effect of Hypoxia

- Neuronal excitability highly dependent on an adequate oxygen supply.
- Cessation of oxygen for only a few seconds can cause complete in-excitability of some neurons.
- Observed when the brain’s blood flow is temporarily interrupted, because within 3 to 7 seconds the person becomes unconscious

Effect of Drugs

- Many drugs increase or decrease the excitability of neurons
- Caffeine, theophylline, and theobromine, found in coffee, tea, and cocoa respectively, all increase neuronal excitability mostly by decreasing threshold
- Most anesthetics increase threshold for excitation thus decreasing synaptic transmission at many points in the nervous system

Synaptic delay

- During transmission of a neuronal signal from a presynaptic neuron to a postsynaptic neuron, a certain amount of time is consumed in the process of
- (1) discharge of the transmitter substance by the presynaptic
- terminal,
- (2) diffusion of the transmitter to the postsynaptic neuronal membrane,
- (3) action of the transmitter on the membrane receptor,

- (4) action of the receptor to increase the membrane permeability, and
- (5) inward diffusion of sodium to raise the excitatory postsynaptic potential to a high enough level to elicit an action potential.
- The minimal period of time required for all these events to take place, even when large numbers of excitatory synapses are stimulated simultaneously, is about 0.5 millisecond.
- This is synaptic delay.

NEUROTROPHINS

- For trophic support of neurons
- Some proteins, referred to as neurotrophins, have been found to be necessary for survival and growth of neurons
- Some are products of the muscles or other structures that the neurons innervate whereas others are produced by astrocytes.
- They bind to receptors at the endings of a neuron,, are then internalized and then transported by retrograde transport to the neuronal cell body
- Here cause production of proteins associated with neuronal development, growth, and survival.

- Other neurotrophins are produced in neurons and transported anterogradely to the nerve ending, where they maintain the integrity of the postsynaptic neuron.
- The neurons have receptors for the neutrophils for the uptake into neuron
- One of the most important is the **Nerve Growth Factor**

Nerve growth factor

- It is a protein growth factor necessary for the growth and maintenance of sympathetic neurons and some sensory neurons.
- Made up of two α, two β, and two γ subunits.
- It is picked up by neurons in the extracerebral organs they innervate
- Transported in retrograde fashion from the endings of the neurons to their cell bodies.

- NGF also present in the brain
- Appears to be responsible for the growth and maintenance of cholinergic neurons in the basal forebrain and striatum.
- Injection of antiserum against NGF in newborn animals leads to near total destruction of the sympathetic ganglia
- there is evidence that the maintenance of neurons by NGF is due to a reduction in apoptosis (programmed cell death)

- Others include Brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), NT-4/5 which again help in reduction of apoptosis among other effects
- Schwann cells and astrocytes produce ciliary neurotrophic factor (CNTF).
- It promotes the survival of damaged and embryonic spinal cord neurons
- May prove to be of value in treating human diseases in which motor neurons degenerate

Chemical transmission at synapse

- Nerve endings have been called biological transducers that convert electrical energy into chemical energy.
- This conversion process involves

i. The synthesis of the transmitter agents,

ii. The storage of neurotransmiter in synaptic vesicles, and

iii. The release of NT by the nerve impulses into the synaptic cleft.

iv. The NT acting on appropriate receptors on postsynaptic membrane

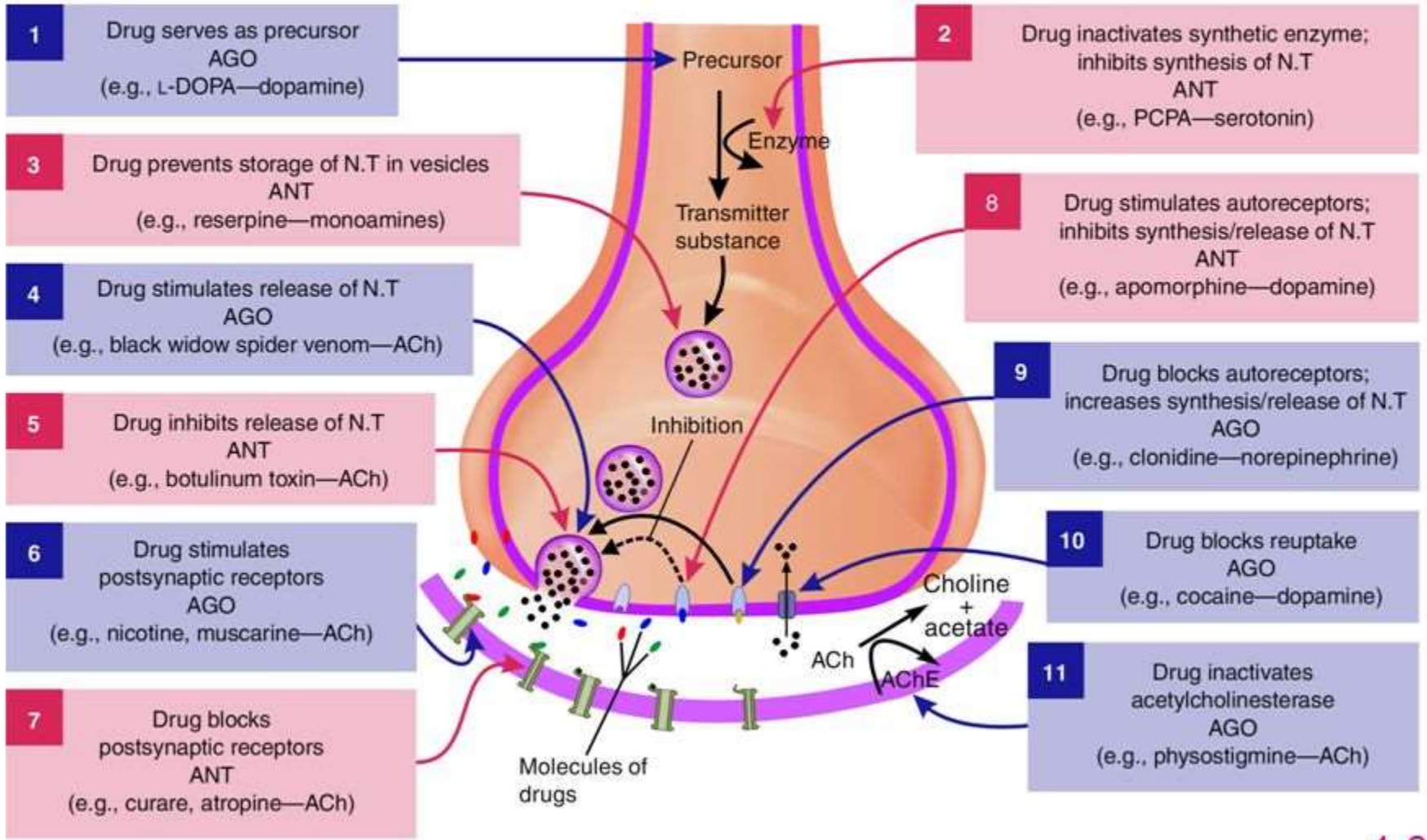
v. Rapid removal of the NT the synaptic cleft.

- All these processes, plus the postreceptor events in the postsynaptic neuron, are regulated by many physiologic factors and can be altered by drugs.
- Therefore, interventions can be done to alter nerve function in any one of the steps involved in synaptic transmission as we will find out later

- A great majority of drugs that act on the nervous system do so by altering synaptic mechanisms and thus synaptic effectiveness.
- All the synaptic mechanisms in earlier slide are vulnerable.
- Long-term effects of drugs are sometimes difficult to predict because the imbalances produced by the initial drug action are soon counteracted by feedback mechanisms that normally regulate the processes.
- EG: If a drug interferes with the action of a NT by inhibiting its synthesis, the neurons may respond by increasing the rate of precursor transport into the axon terminals to maximize the use of any enzyme that is available.

- Drugs that bind to a receptor and produce a response similar to the normal activation of that receptor are called agonists, and drugs that bind to the receptor but are unable to activate it are antagonists.
- By occupying the receptors, antagonists prevent binding of the normal neurotransmitter when it is released at the synapse.
- Specific agonists and antagonists can affect receptors on both pre- and postsynaptic membranes.
- Diseases can also affect synaptic mechanisms.

Drug Action on Synaptic Transmission



Antagonist drugs are in red, Agonists are in blue

Neurotransmiters

- Acetylcholine Acetylcholine (ACh) is synthesized from choline and acetyl coenzyme A in the cytoplasm of synaptic terminals and stored in synaptic vesicles.
- After release, activates receptors on the postsynaptic membrane
- Inactivated (metabolized) by the enzyme acetylcholinesterase located on the pre- and postsynaptic membranes
- Choline released during inactivation taken up into presynaptic axon for synthesis of new ACh.
- The ACh concentration at the receptors is also reduced by simple diffusion away from the site

- Found in both peripheral and CNS
- Receptors in brain are important in cognitive functions.
- Some play major role in attention, learning, and memory by reinforcing the ability to detect and respond to meaningful stimuli.
- Degeneration of this neurons common in people with Alzheimer’s disease, a brain disease that is usually age-related and is the most common cause of declining intellectual function in late life, affecting 10 to 15 percent of people over age 65, and 50 percent of people over age 85.

- Because of the degeneration of cholinergic neurons, this disease is associated with a decreased amount of ACh in certain areas of the brain and even the loss of the postsynaptic neurons that would have responded to it.
- These defects and those in other neurotransmitter systems that are affected in this disease are related to the declining language and perceptual abilities, confusion, and memory loss that characterize Alzheimer’s victims.
- The exact causes of this degeneration are unknown

Biogenic Amines

- Are neurotransmitters that are synthesized from amino acids and contain an amino group (R–NH2).
- Most common are dopamine, norepinephrine, serotonin, and histamine and epinephrine
- Catecholamines
- Dopamine, norepinephrine (NE), and epinephrine referred to as catecholamines.
- Formed from amino acid tyrosine and share the same basic synthetic pathway
- Synthesis and release from the presynaptic terminals strongly modulated by autoreceptors on the presynaptic terminals.

- After activation of the receptors on the postsynaptic cell, the NT is decreased by
- Active transport into the presynaptic axon terminal.
- Metabolism by enzymes at terminal mostly by monoamine oxidase and Catechol –o- methyl transferase
- Monoamine oxidase inhibitors, which increase the brain extracellular concentration of the catecholamine neurotransmitters, are used in the treatment of diseases such as depression
- In the CNS play essential roles in states of consciousness, mood, motivation, directed attention, movement, blood-pressure regulation among others

Serotonin

- Produced from amino acid tryptophan
- Its effects generally have a slow onset, indicating that it works as a neuromodulator.
- Serotonin releasing neurons innervate virtually every structure in the brain and spinal cord and operate via at least 16 different receptor types.
- In general, it has an excitatory effect on pathways that are involved in the control of muscles, and an inhibitory effect on pathways that mediate sensations.

- The activity of serotonergic neurons is lowest or absent during sleep and highest during states of alert wakefulness.
- In addition to their contributions to motor activity and sleep also involved in
- Regulation of food intake (depresses appetite),
- Reproductive behavior (activation reduces sexual behavior), and
- Emotional states such as mood and anxiety (low levels associated with emotional disorders).

Amino Acid Neurotransmitters

- Several amino acids function as neurotransmitters.
- Are by far the most prevalent neurotransmitters in CNS
- EXCITATORY AMINO ACID NT's
- Glutamate and aspartate, serve as neurotransmitters at most of excitatory synapses in the CNS
- In fact, most excitatory synapses in the brain release glutamate.
- The excitatory amino acids function in learning, memory, and neural development.
- Also implicated in epilepsy, Alzheimer's and Parkinson's diseases, and the neural damage that follows strokes, brain trauma, and other conditions of low oxygen availability

- INHIBITORY Amino Acid NT’s
- GABA (gamma-aminobutyric acid) and Glycine are the major inhibitory neurotransmitters in the CNS
- Drugs such as Valium that reduce anxiety, guard against seizures, and induce sleep enhance the action of GABA.