2 factors determine AP conduction velocity:

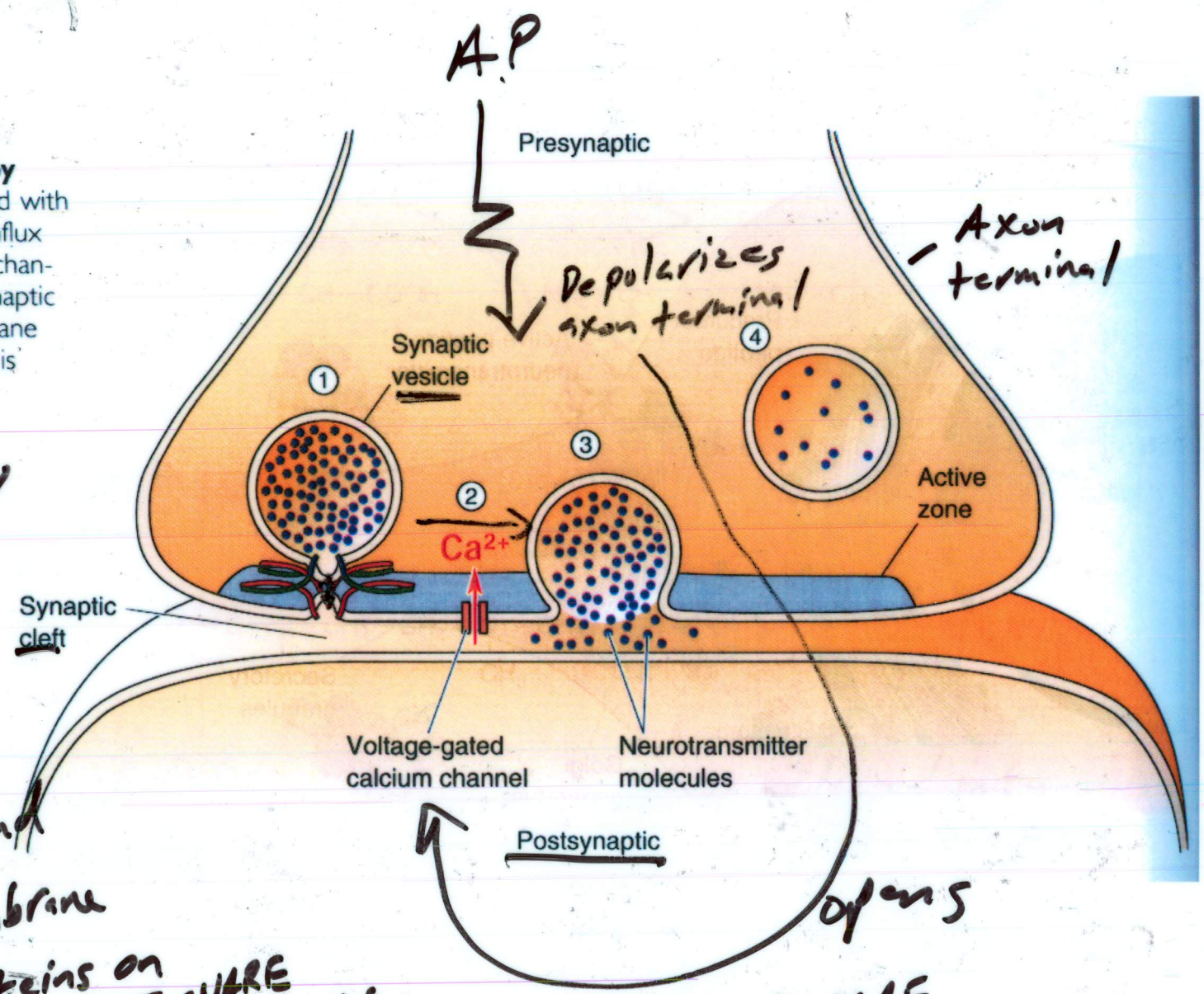
- Diameter of the axon
- Resistance to current leak outward across the axonal membrane

Vertebrates, maximize AP conduction velocity by wrapping segments of axon in myelin sheath.

Advantage of myelinating axon:

- Saltatory conduction
- minimizes amount of membrane that has to be depolarized during AP conduction.

FIGURE 5.11
The release of neurotransmitter by exocytosis. ① A synaptic vesicle loaded with neurotransmitter, in response to ② an influx of Ca^{2+} through voltage-gated calcium channels, ③ releases its contents into the synaptic cleft by the fusion of the vesicle membrane with the presynaptic membrane, and ④ is eventually recycled by the process of endocytosis.



$E_{Ca^{++}} = +123mV$

SNARE proteins expressed on the membrane of the synaptic vesicles and presynaptic membrane (V-SNARE proteins on synaptic vesicles + T-SNARE proteins on presynaptic membrane).

Ca^{++} binds to SNARE proteins exposing binding sites

- The amount of neurotransmitter released in a given period of time depends on the frequency of APs arriving at the axon terminal.

Higher freq. of APs → More neurotransmitter released.

Two types of responses can occur in the target cell depending on the receptor expressed on the post-synaptic membrane:

— Fast Synaptic Responses

— Slow Synaptic Responses

Fast Synaptic Responses

Mediated by receptors that are part of, or linked to, ion channels in the post-synaptic membrane.

The channel responds to the binding of neurotransmitter to the receptor.

"chemically-gated channels."

The opening of these channels allows ions to move across the membrane producing a post-synaptic potential (PSP)

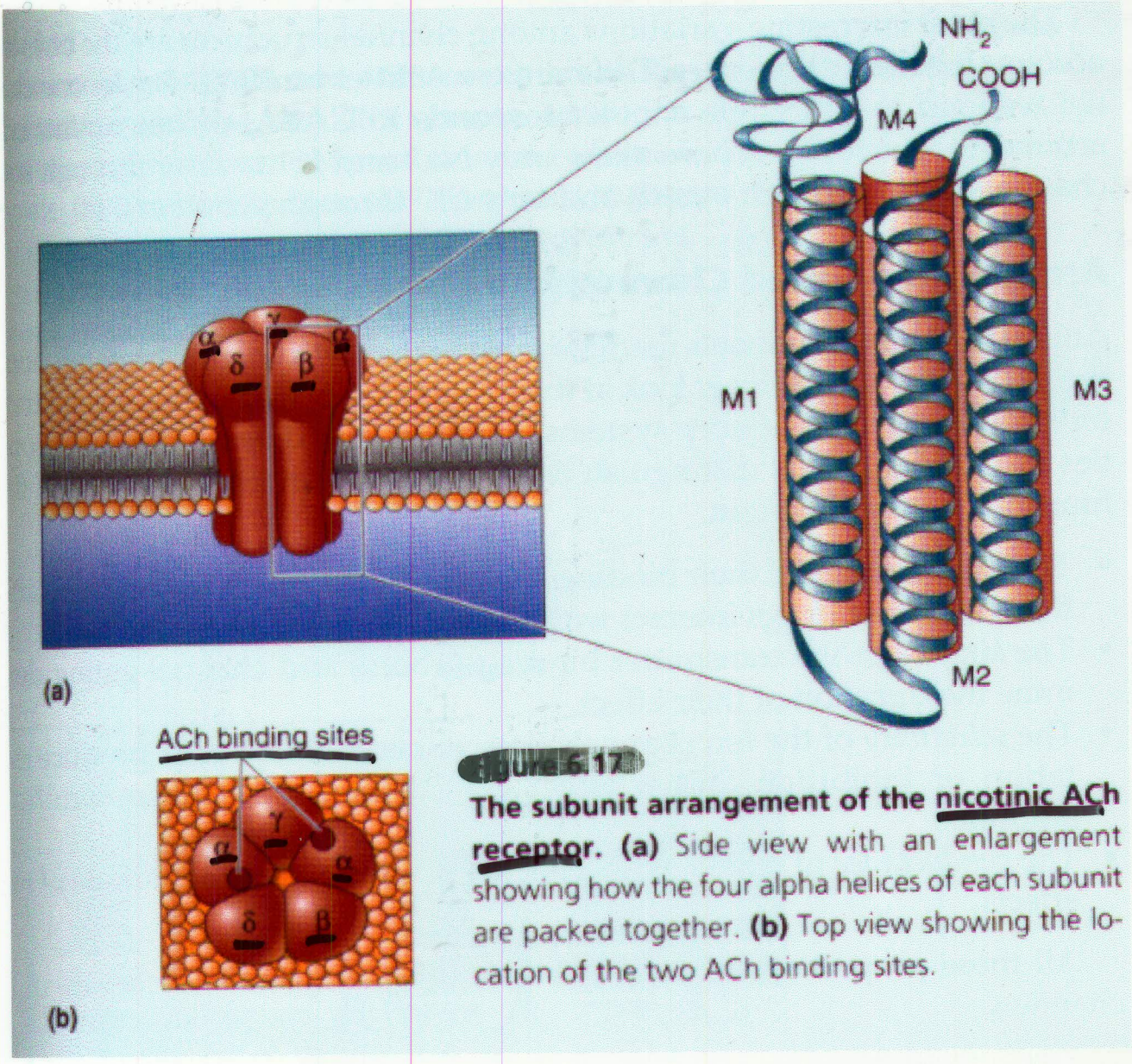


Figure 6.17

The subunit arrangement of the nicotinic ACh receptor. **(a)** Side view with an enlargement showing how the four alpha helices of each subunit are packed together. **(b)** Top view showing the location of the two ACh binding sites.

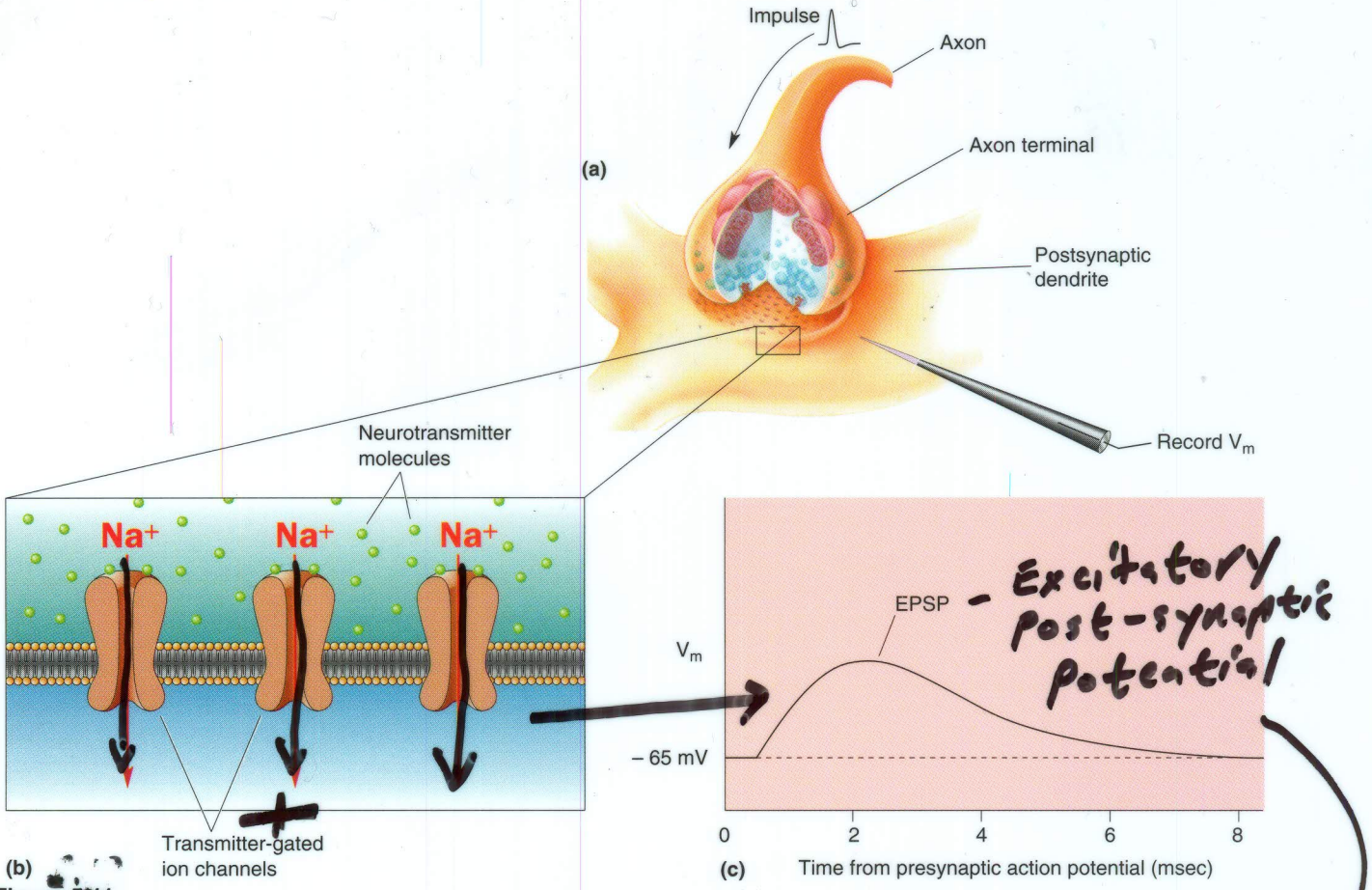


Figure 5.11
Generation of an EPSP. (a) An impulse arriving in the presynaptic terminal causes the release of neurotransmitter. **(b)** The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If Na^+ enters the postsynaptic cell through the open channels, the membrane will become depolarized. **(c)** The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the EPSP.

EPSP - Excitatory post-synaptic potential

Brings Vm closer to threshold for initiating an AP

Figure 5.11

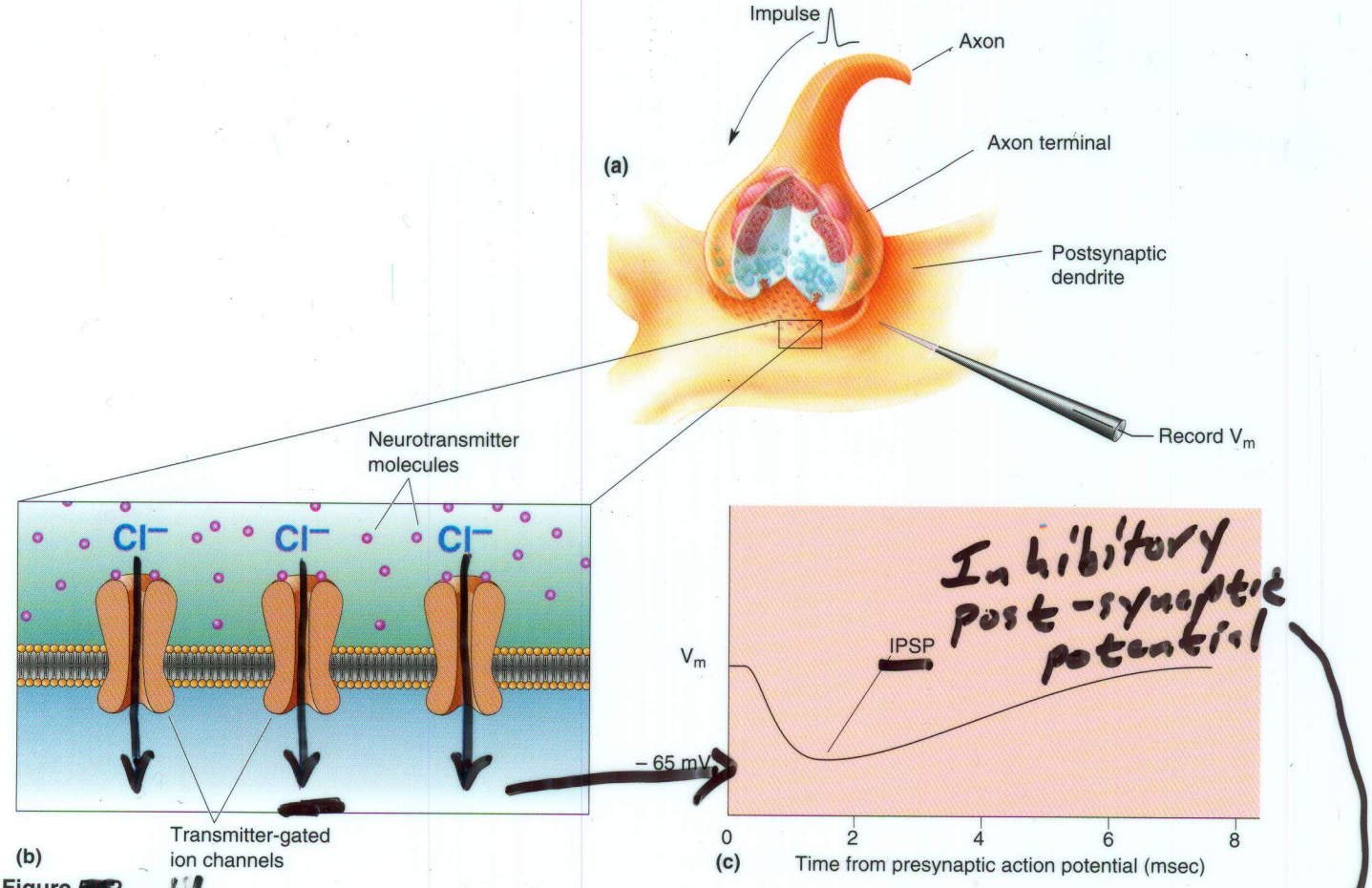


Figure 5.12
Generation of an IPSP. (a) An impulse arriving in the presynaptic terminal causes the release of neurotransmitter. **(b)** The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If Cl^- enters the postsynaptic cell through the open channels, the membrane will become hyperpolarized. **(c)** The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the IPSP.

- The amplitude of the PSP is determined by the # of ion channels that open in the post-synaptic membrane.

more channels open → more ions move across the membrane → greater the amplitude of the PSP

Recall, the # of channels that open is determined by amt of neurotransmitter released from axon terminal.

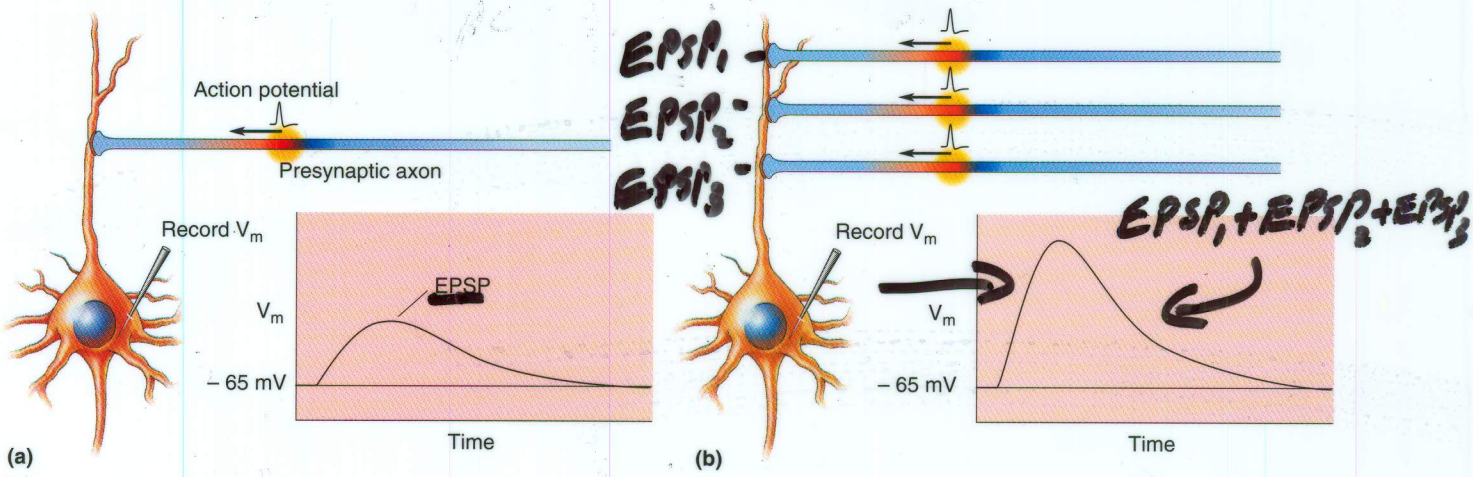
And the amount of neurotransmitter released depends on the freq. of APs arriving at the axon terminal.

Two types of summing of PSPs occur:

- Spatial summation
- Temporal summation

Summation is how neurons integrate inputs from other neurons.

Spatial summation



Temporal summation

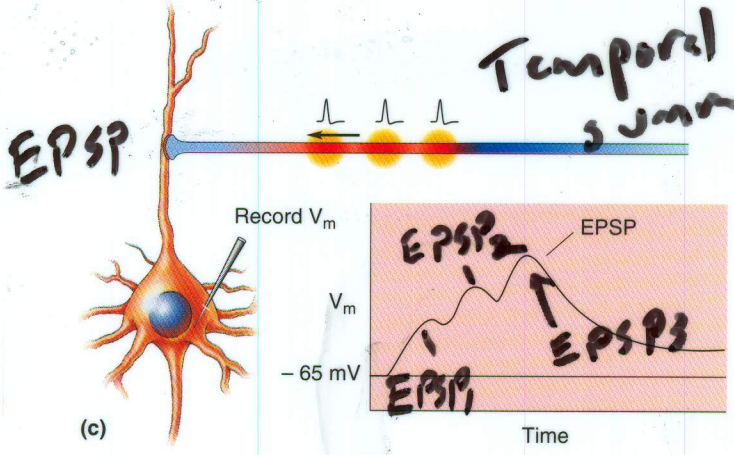


Figure
EPSP summation. (a) A presynaptic action potential triggers a small EPSP in a postsynaptic neuron. **(b)** Spatial summation of EPSPs: When two or more presynaptic inputs are active at the same time, their individual EPSPs sum. **(c)** Temporal summation of EPSPs: When the same presynaptic fiber fires action potentials in quick succession, the individual EPSPs sum.

mixing of IPSPs + EPSPs produces 1 of 3 results:

- IF EPSP > IPSP → EPSP − IPSP → smaller EPSP
- IF EPSP = IPSP → EPSP − IPSP → cancel each other
- IF EPSP < IPSP → EPSP − IPSP → smaller IPSP

Figure 5.15

Example of summation producing a response: muscle reflexes

muscle stretch receptors activated by stretch of the muscle.

Have axonal inputs to motor neurons of the muscle they are within.

Activation of the motor neuron requires activation of multiple receptors in the muscle → muscle contraction

PSPs spread passively through the cytosol diminishing in amplitude

Some dendrites have voltage gated Na^+ and voltage gated Ca^+ channels that help the PSP to spread, but are not abundant enough to conduct the PSP like the AP is conducted along the axon.

There is a correlation between the amplitude of the EPSP that enters the axon hillock and the freq. of APs initiated.

The greater the amplitude of the EPSP → the greater the freq. of APs initiated within the limits set by the absolute refractory period.

Highest possible freq. of APs is
1/msec due to the ARP

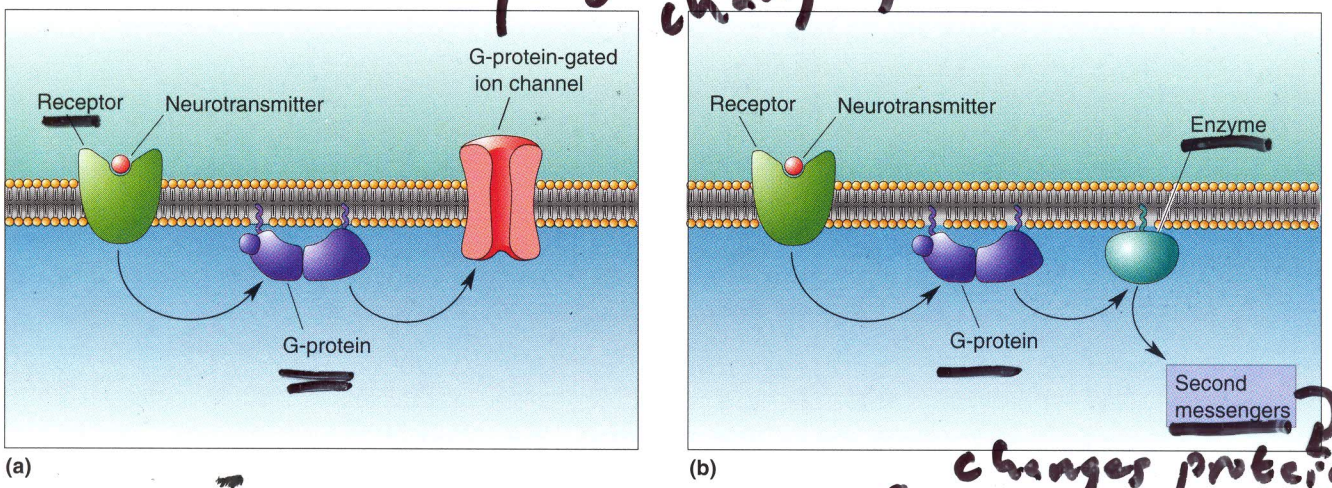
Info is coded in the nervous system
in terms of:

- Freq. of APs
- Amount of neurotransmitter
  released from axon terminal
- Amplitude of PSPs

Slow Synaptic Responses

Receptor consists of a single membrane spanning protein

Activation of G-protein can open or close ion channels changing Vm of the target cell



changes protein synthesis + metabolism

Figure 5.13
Transmitter actions at G-protein-coupled receptors. The binding of neurotransmitter to the receptor leads to activation of G-proteins. Activated G-proteins activate effector proteins, which may be **(a)** ion channels, or **(b)** enzymes that generate intracellular second messengers.

Binding of neurotransmitter to receptor activates the associated G-protein expressed on the inside of the post-synaptic membrane. The activation of the G protein results in one of two responses:

metabotropic receptors - change metabolism in the cell in response to binding of neurotransmitter

ionotropic receptors - change Vm by opening or closing ion channels

Figure 5.13

Table 6.1 The Neuropharmacology of Some Receptor Subtypes

NEUROTRANSMITTER	RECEPTOR SUBTYPE	AGONIST	ANTAGONIST
Acetylcholine (ACh)	Nicotinic receptor	Nicotine	Curare
	Muscarinic receptor	Muscarine	Atropine
Norepinephrine (NE)	α receptor	Phenylephrine	Phenoxybenzamine
	β receptor	Isoproterenol	Propranolol
Glutamate (Glu)	AMPA	AMPA	CNQX
	NMDA	NMDA	AP5
GABA	$GABA_A$	Muscimol	Bicuculline
	$GABA_B$	Baclofen	Phaclofen
ATP	P_{2X}	ATP	Suramin
	A type	Adenosine	Caffeine

Neurotransmitters

Criteria for being considered a neurotransmitter:

- It must be synthesized in a neuron and stored in the presynaptic neuron
- It must be released by the presynaptic neuron in response to depolarization.
- When applied to the post-synaptic neuron, the response must mimic the response produced by the release of the molecule from the presynaptic neuron.

4 main groups of neurotransmitters based on chemical structure:

— Acetyl Choline (ACh)

first neurotransmitter identified.

Neurons that use ACh are called Cholinergic neurons

— Neuropeptides — short chains of amino acids

Common examples: Substance P + Endorphins

used by neurons in pain pathways in the CNS

Neurons that use neuropeptides as neurotransmitters are called peptidergic neurons.

- Amino Acid neurotransmitters

Glycine - inhibitory neurotransmitter that opens Cl^- channels on target cells

Used by inhibitory neurons in spinal cord.

Gamma amino butyric acid (GABA)

also an inhibitory neurotransmitter that opens Cl^- channels on its target cells. Main inhibitory neurotransmitter in the brain

Glutamate - main excitatory neurotransmitter used in the CNS.
AMPA receptors - open Na^+/K^+ channels

NMDA receptors - open $Na^+/K^+/Ca^{++}$ channels.

Glycinergic neurons — use glycine

GABAergic neurons - use GABA

Glutaminergic neuron - use Glutamate

- Amine neurotransmitters

Derived from either tyrosine or tryptophan

Neurotransmitters derived from tyrosine are called catecholamines:

Epinephrine - neurons using this as their neurotransmitter are called adrenergic neurons

Norepinephrine — neurons using this are called noradrenergic

Dopamine – neurons using this are called dopaminergic neurons.

One neurotransmitter is derived from tryptophan → serotonin
5-Hydroxytryptamine (5-HT)

Neurons using 5-HT as their neurotransmitter are called serotonergic neurons.

"Unconventional" neurotransmitters
- Nitric oxide
- Carbon monoxide
- ATP

Dale's Principle — A neuron uses only one type of neurotransmitter

Characteristics of neurons using particular neurotransmitters.

Cholinergic neurons (neurons that use acetyl choline (ACh) as their neurotransmitter)

- They synthesize choline acetyl transferase (ChaT) for synthesis of ACh in the axon terminal.
- Their synaptic vesicles have ACh transporters that transport ACh into the synaptic vesicles.
- They synthesize acetyl choline esterase (AChE) that degrades ACh in the synaptic cleft.
- They have choline transporters in the presynaptic membrane that remove choline from the synaptic cleft after enzymatic degredation of ACh.

AChE
ACh → choline + Acetic acid

Peptidergic neurons (neurons that use a peptide or protein as their neurotransmitter)
Examples: Enkephalin, Endorphin, Substance P

- They have an abundance of rough endoplasmic reticulum in their soma for synthesis of their peptide neurotransmitter.
- They are synthesized as a precursor peptide that contains multiple copies of the neurotransmitter. The precursor peptide is subsequently sent to the Golgi apparatus where it is packaged with enzymes that cut the precursor peptide up into neurotransmitter peptides.
- The peptide neurotransmitter is packaged in secretory granules for storage and transport to the axon terminal.
- They synthesize peptidase enzymes that degrade the peptide neurotransmitter in the synaptic cleft.

Amino Acidergic neurons (neurons that use an amino acid as their neurotransmitter)

- Their cytosol has high than normal concentrations of the amino acid that is being used as the neurotransmitter.
- They have special amino acid transporters on their synaptic vesicles that concentrate the amino acid in their synaptic vesicles.
- They have special re-uptake transporters in the presynaptic membrane that remove the amino acid from the synaptic cleft.

Catecholaminergic neurons (neurons that use dopamine, epinephrine or norepinephrine as their neurotransmitter)

- They have the enzymes needed to convert the amino acid tyrosine into dopamine, norepinephrine, or epinephrine (see fig. 6.13)
- The synthesis of catecholaminerigic neurotransmitters occurs in the axon terminal.

- They have special re-uptake transporters that remove the catecholamine neurotransmitter from the synaptic cleft.
- They have special catecholamine transporters on their synaptic vesicles that transport catecholamines into their synaptic vesicles.
- They synthesize monoamine oxidase (MAO) for breaking down catecholamines.

Serotonergic neurons (neurons that use serotonin as their neurotransmitter)

- They use two enzymes, tryptophan hydroxylase and 5-HTP decarboxylase to convert the amino acid tryptophan into 5-HT (serotonin)(see fig. 6.14).
- They have re-uptake transporters on the presynaptic membrane that removes serotonin for the synaptic cleft.
- They have special serotonin transporters on their synaptic vesicles that transport serotonin into their synaptic vesicles.
- They synthesize monoamine oxidase for breaking down serotonin.

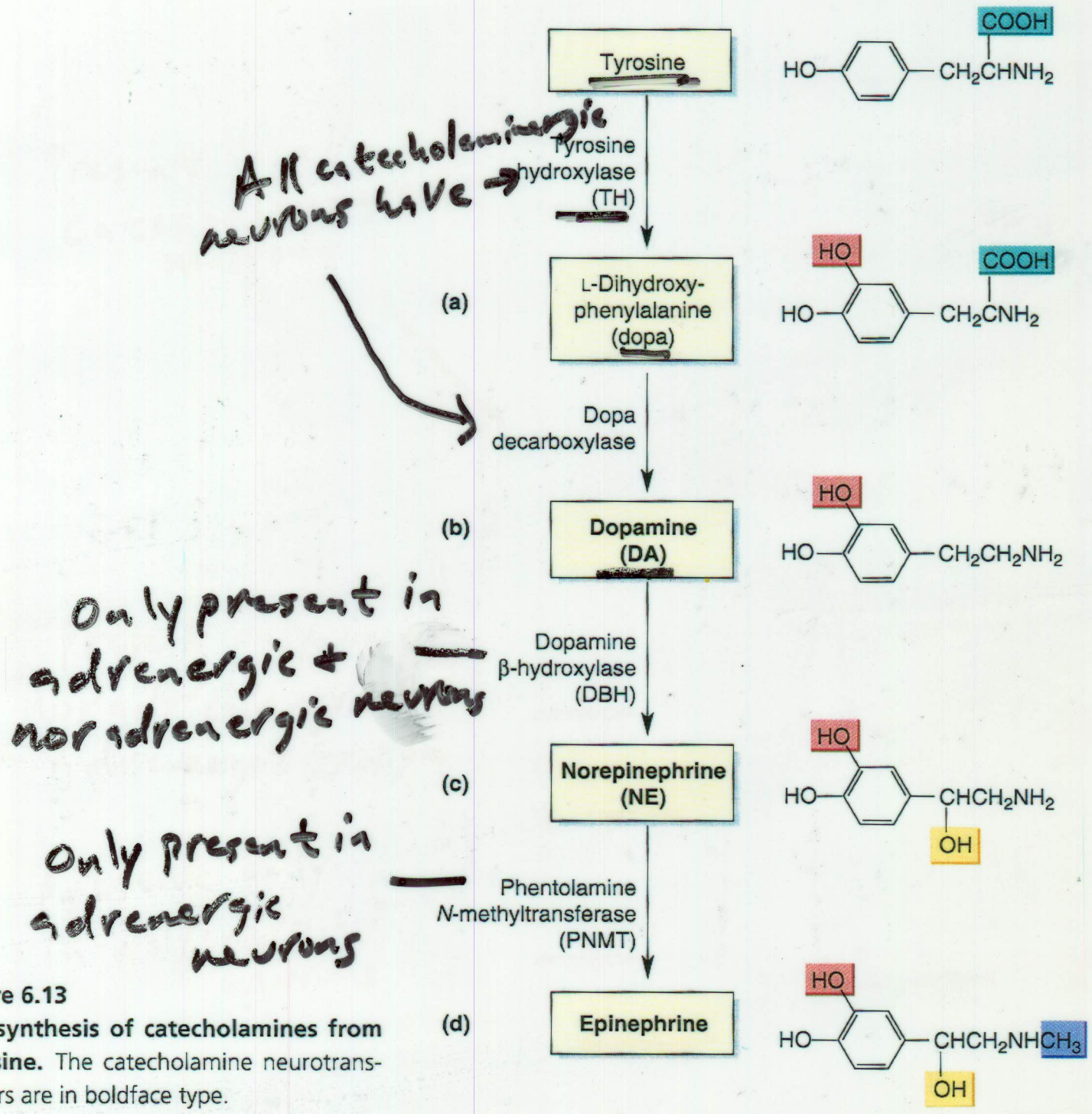


Figure 6.13
The synthesis of catecholamines from tyrosine. The catecholamine neurotransmitters are in boldface type.

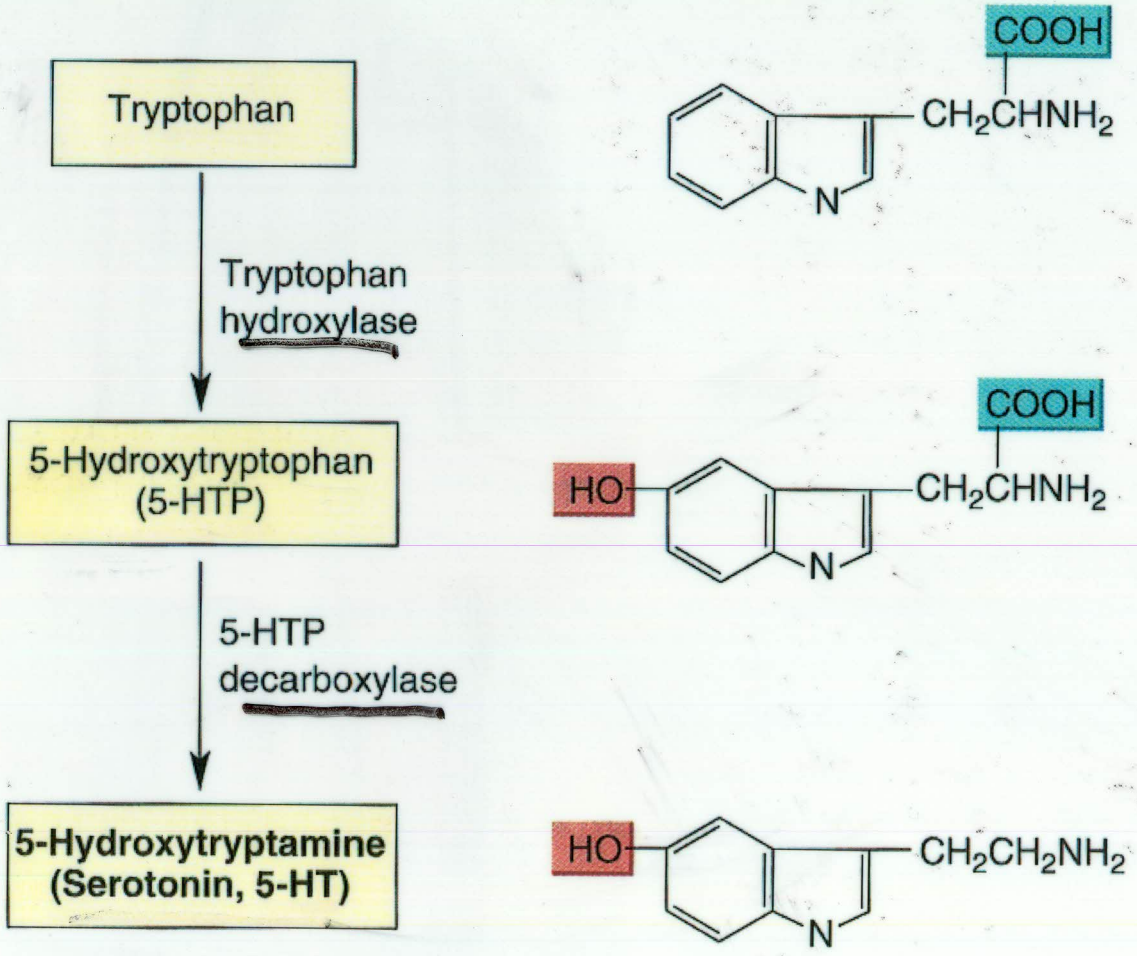


Figure 6.14
The synthesis of serotonin from tryptophan.