Synaptic Transmission

Postsynaptic Mechanisms

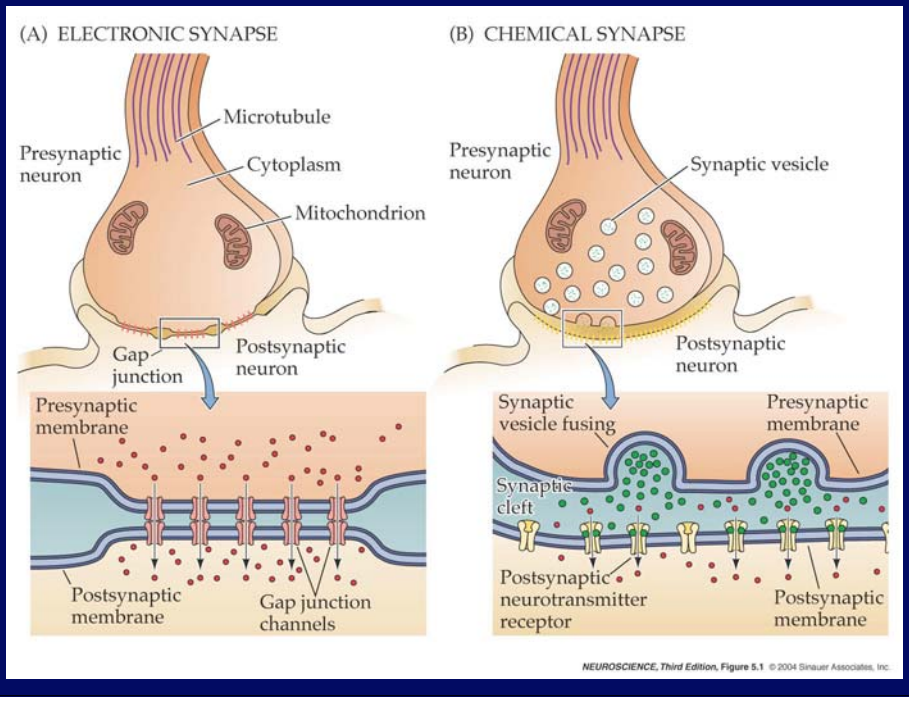
Part I

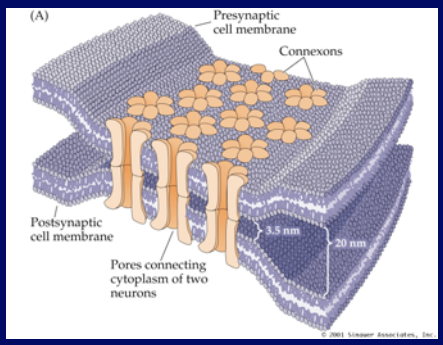
- Synapses
  electrical and chemical
- Neurotransmitters
  categories and life cycle
- Neurotransmitters
  examples and postsynaptic effects
- Pathology

Part II

- Neurotransmitter Receptors
  categories and examples
- Postsynaptic Potentials
  EPSP and IPSP

Electrical Neurotransmission	Chemical Neurotransmission
Direct contact between cells	No direct contact between cells
Fast	Comparatively slow
Two-directional	One-directional
Relatively simple effects	Often more complicated, receptor-dependent effects
Modulation possible	Can be modulated in many more ways





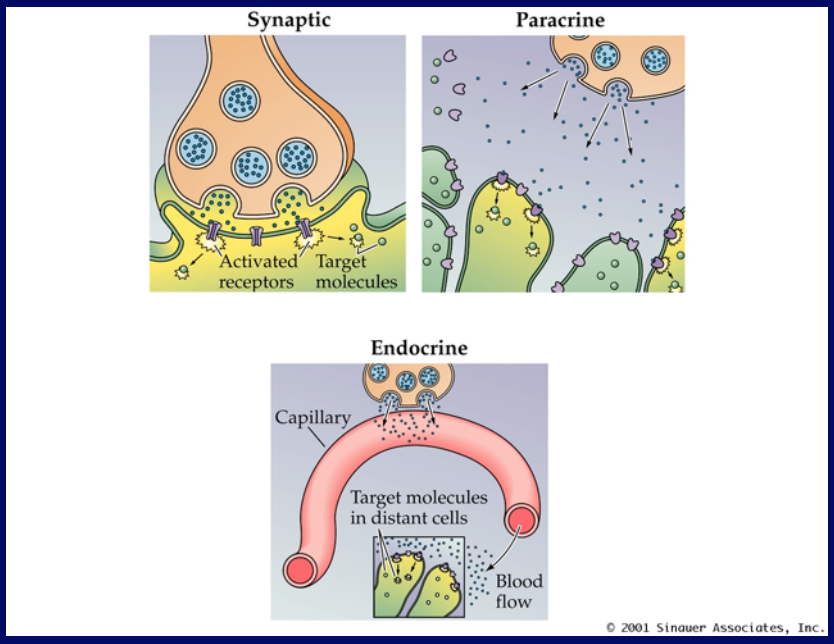
Electrical synapse

Gap junctions

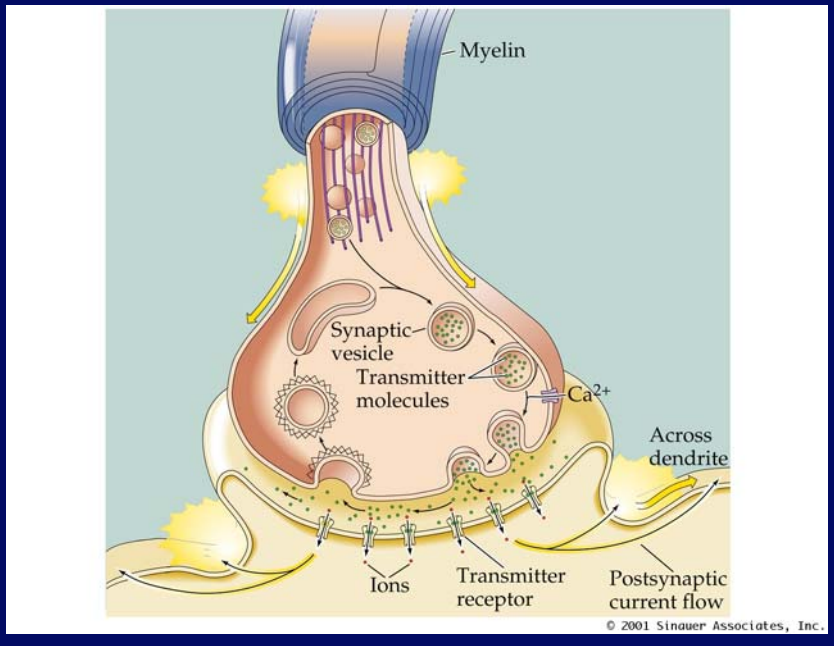
Hexameric structures made of subunits called connexons

Direct contact between cells – bidirectional transmission
Relatively uncommon in higher mammals

Chemical Signaling Mechanisms



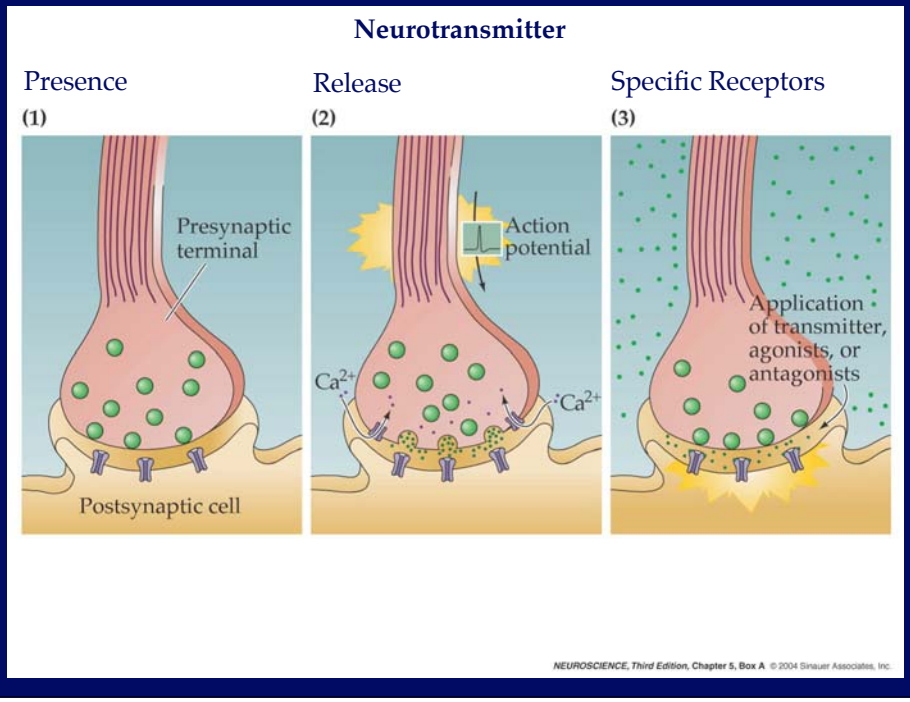
Chemical Neurotransmission



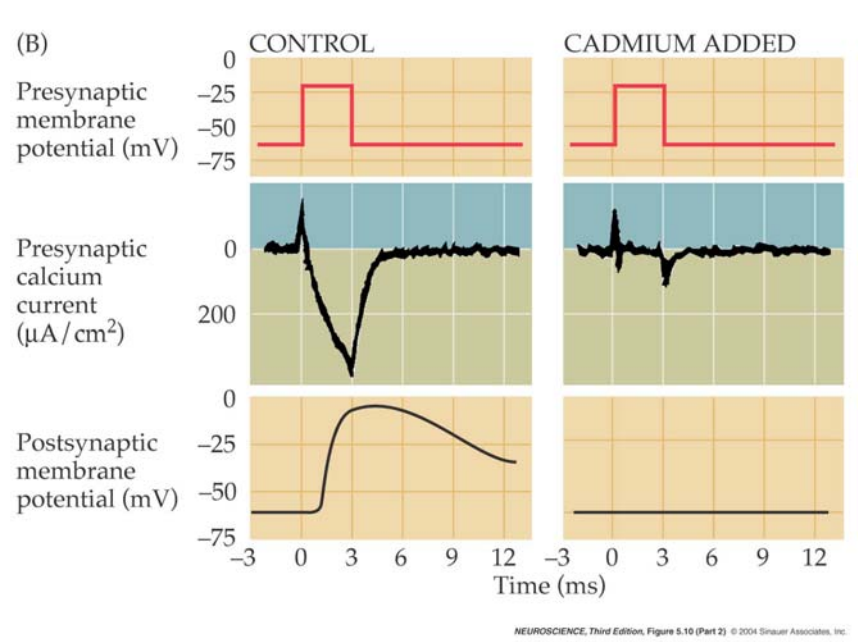
What happens on the presynaptic side?

1. Action potential depolarizes synaptic terminal
2. Calcium influx
3. Synaptic vesicles containing neurotransmitter fuse with the presynpatic membrane
4. Neurotransmitter is released into the synaptic cleft

Depending on the type of neurotransmitter and postsynaptic receptor a multitude of postsynaptic effects result…



Calcium-Dependent Transmitter Release



Neurotransmitters

Small-molecule Neurotransmitters

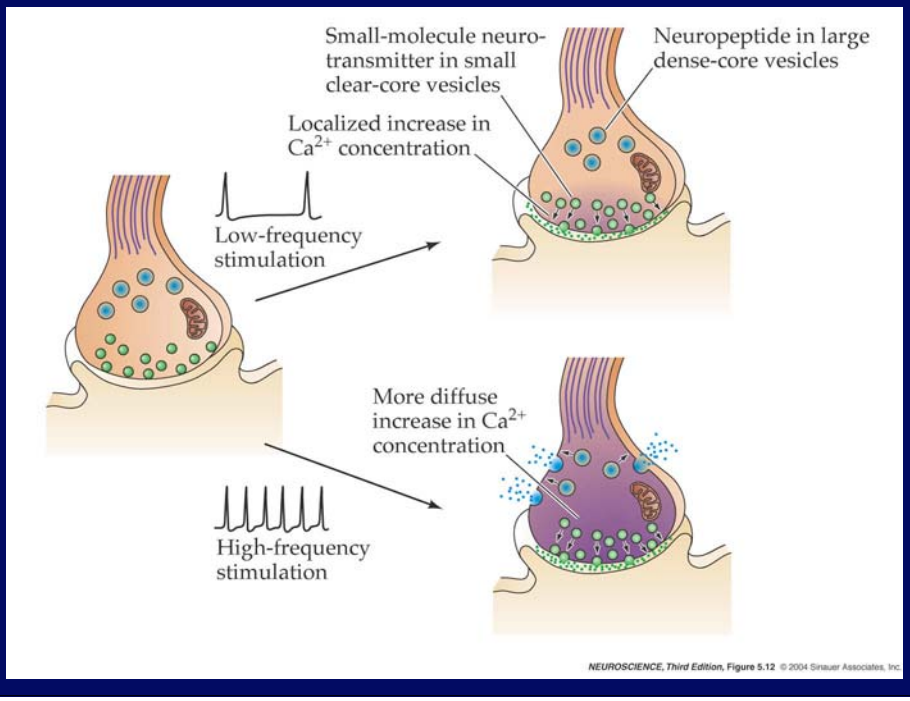
Small molecular size
1 amino acid, other type of molecule
Rapid synaptic actions

Biogenic amines
Sub-group of similar chemical properties

Neuropeptides

Large molecular size
3-36 amino acids
Slower, ongoing synaptic actions

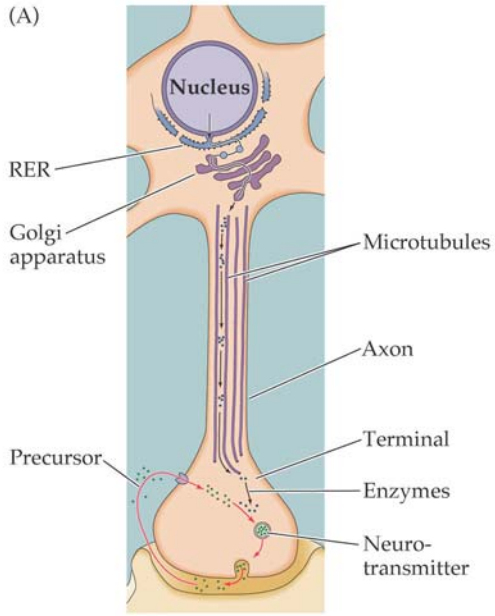
Neurons often release more than one type of neurotransmitter



Neurotransmitter Life Cycle

- Synthesis
- Packaging
- Release
- Removal

Small-Molecule Neurotransmitters



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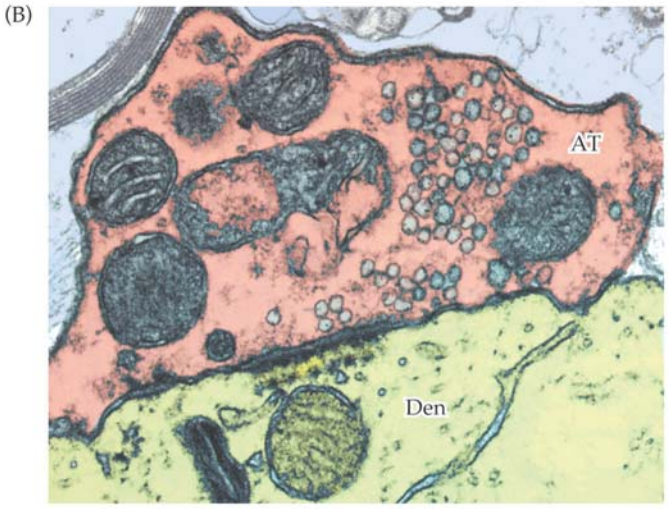
Small-Molecule Neurotransmitters



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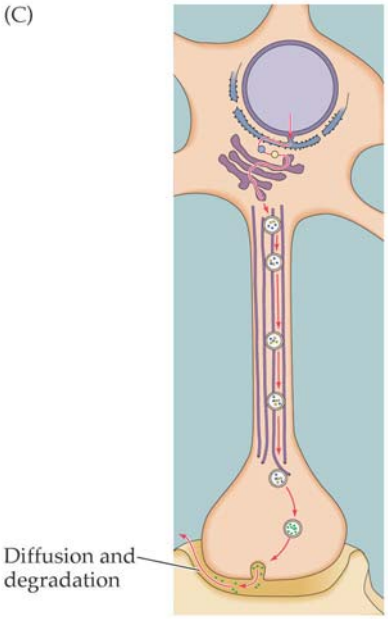
Neuropeptides



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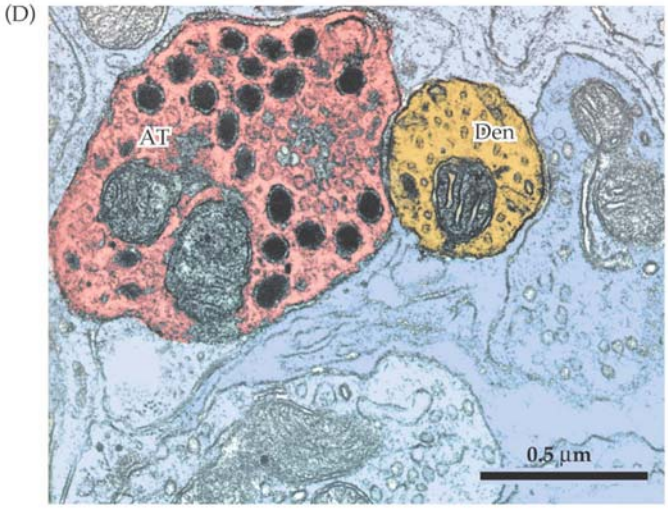
Neuropeptides



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SMALL-MOLECULE NEUROTRANSMITTERS

Acetylcholine $(CH_3)_3\overset{+}{N}-CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$

AMINO ACIDS

Glutamate $H_3\overset{+}{N}-\underset{\underset{CH_2-CH_2-COOH}{|}}{\overset{H}{\overset{|}{C}}}-COO^-$

Aspartate $H_3\overset{+}{N}-\underset{\underset{CH_2-COOH}{|}}{\overset{H}{\overset{|}{C}}}-COO^-$

GABA $H_3\overset{+}{N}-CH_2-CH_2-CH_2-COO^-$

Glycine $H_3\overset{+}{N}-\underset{\underset{H}{|}}{\overset{H}{\overset{|}{C}}}-COO^-$

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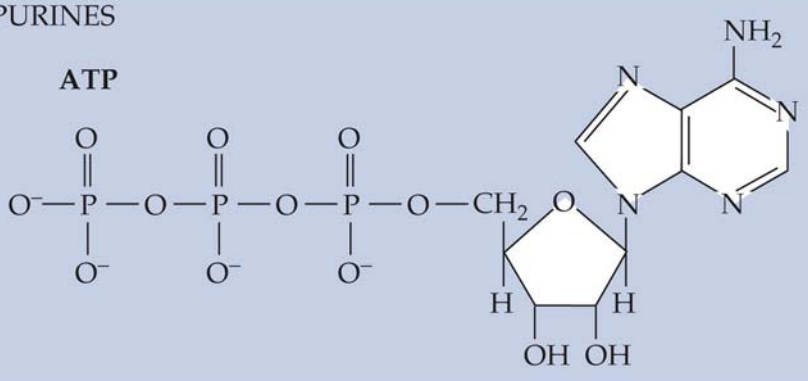
SMALL-MOLECULE NEUROTRANSMITTERS

PURINES

ATP



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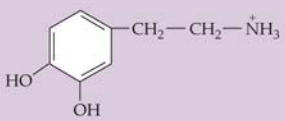
SMALL-MOLECULE NEUROTRANSMITTERS

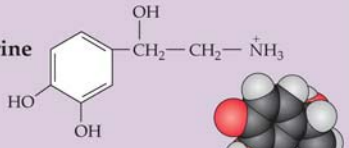
BIOGENIC AMINES

CATECHOLAMINES

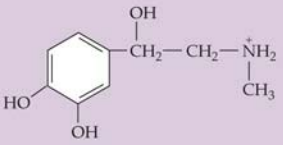
Dopamine



Norepinephrine



Epinephrine



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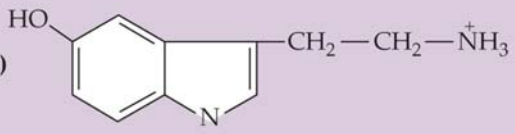
SMALL-MOLECULE NEUROTRANSMITTERS

BIOGENIC AMINES

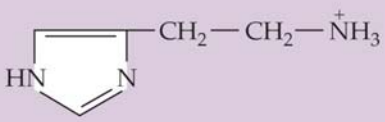
INDOLEAMINE

Serotonin (5-HT)



IMIDAZOLEAMINE

Histamine



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PEPTIDE NEUROTRANSMITTERS

Example: **Methionine enkephalin** (Tyr–Gly–Gly–Phe–Met)

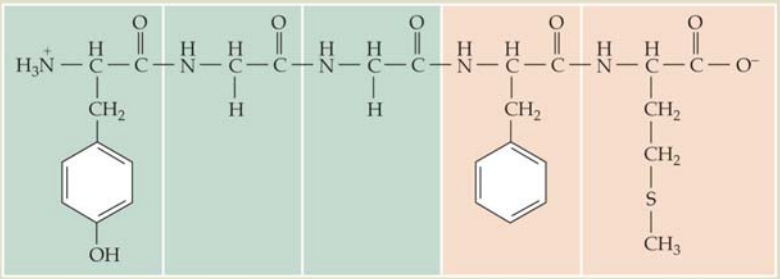

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TABLE 6.1
Functional Features of the Major Neurotransmitters *(Part 1)*

Neurotransmitter	*Postsynaptic effect*[a]	*Precursor(s)*	*Rate-limiting step in synthesis*	*Removal mechanism*	*Type of vesicle*
ACh	Excitatory	Choline + acetyl CoA	CAT	AChEase	Small, clear
Glutamate	Excitatory	Glutamine	Glutaminase	Transporters	Small, clear
GABA	Inhibitory	Glutamate	GAD	Transporters	Small, clear
Glycine	Inhibitory	Serine	Phosphoserine	Transporters	Small, clear
Catecholamines (epinephrine, norepinephrine, dopamine)	Excitatory	Tyrosine	Tyrosine hydroxylase	Transporters, MAO, COMT	Small dense-core, or large irregular dense-core

[a]The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 7).

NEUROSCIENCE, Third Edition, Table 6.1 (Part 1) © 2004 Sinauer Associates, Inc.

TABLE 6.1
Functional Features of the Major Neurotransmitters *(Part 2)*

Neurotransmitter	*Postsynaptic effect*[a]	*Precursor(s)*	*Rate-limiting step in synthesis*	*Removal mechanism*	*Type of vesicle*
Serotonin (5-HT)	Excitatory	Tryptophan	Tryptophan hydroxylase	Transporters, MAO	Large, dense-core
Histamine	Excitatory	Histidine	Histidine decarboxylase	Transporters	Large, dense-core
ATP	Excitatory	ADP	Mitochondrial oxidative phosphorylation; glycolysis	Hydrolysis to AMP and adenosine	Small, clear
Neuropeptides	Excitatory and inhibitory	Amino acids (protein synthesis)	Synthesis and transport	Proteases	Large, dense-core
Endocannabinoids	Inhibits inhibition	Membrane lipids	Enzymatic modification of lipids	Hydrolasis by FAAH	None
Nitric oxide	Excitatory and inhibitory	Arginine	Nitric oxide synthase	Spontaneous oxidation	None

[a]The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 7).

Prolonged excitatory neurotransmission mediated by glutamate can destroy neurons.

↓

Excitotoxicity

Under normal conditions the glutamate concentration in the synaptic cleft reaches approx. 1mM. But only for a few milliseconds.

During brain injury excessive amounts of glutamate can be released and/or re-uptake mechanisms inhibited.
Example: stroke

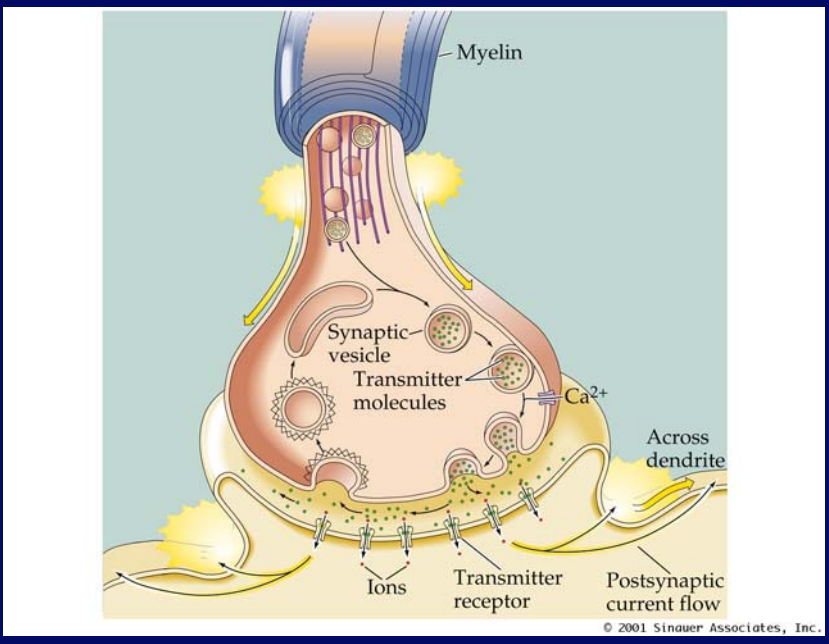
Drug-induced imbalance of neurotransmitter release, response and/or re-uptake

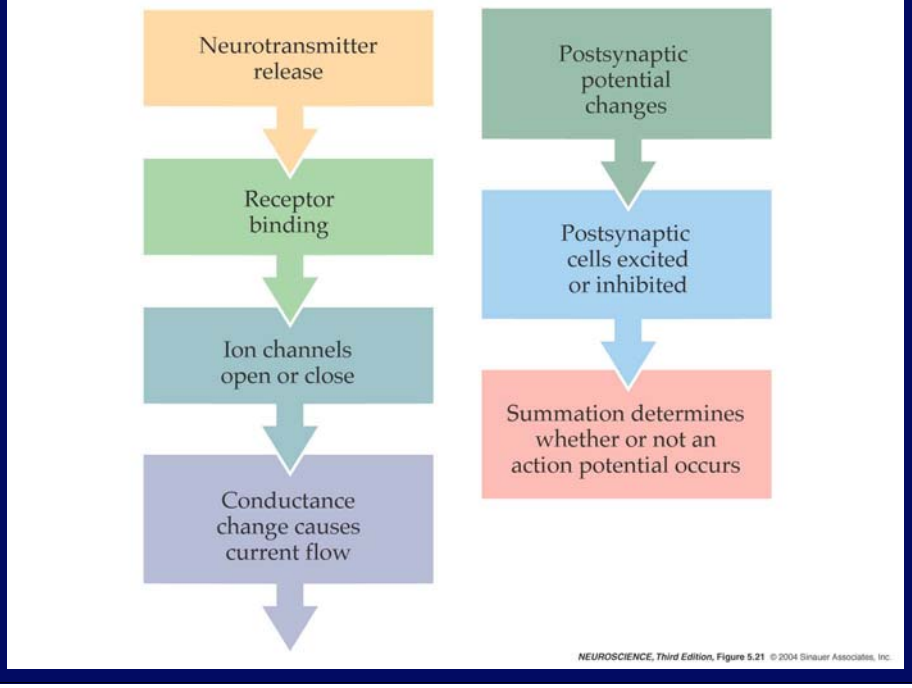
↓

Addiction

Example: cocaine effects based on increased dopamine levels in brain regions involved in motivation and emotional reinforcement

Chemical Neurotransmission





Postsynaptic Neurotransmitter Receptors
(protein molecules)

Ionotropic Receptors
Linked directly to ion channels

2 functional domains combined in one molecular entity:
Extracellular transmitter binding site
Membrane-spanning ion channel

Multimers of 4 or 5 protein subunits, each contributing to the channel pore

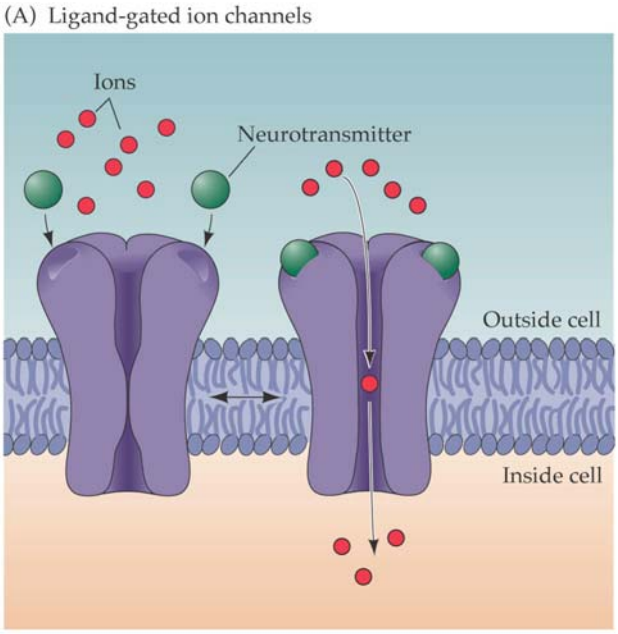
Metabotropic Receptors
Receptors don't contain ion channels

Channels affected by intermediated molecules (G-Proteins)

Monomeric proteins with extracellular transmitter binding site and intracellular G-Protein binding site

Neurotransmitter binds, G-Protein activates, dissociates from receptor, interacts with ion channel or other effector proteins

Ionotropic Receptors



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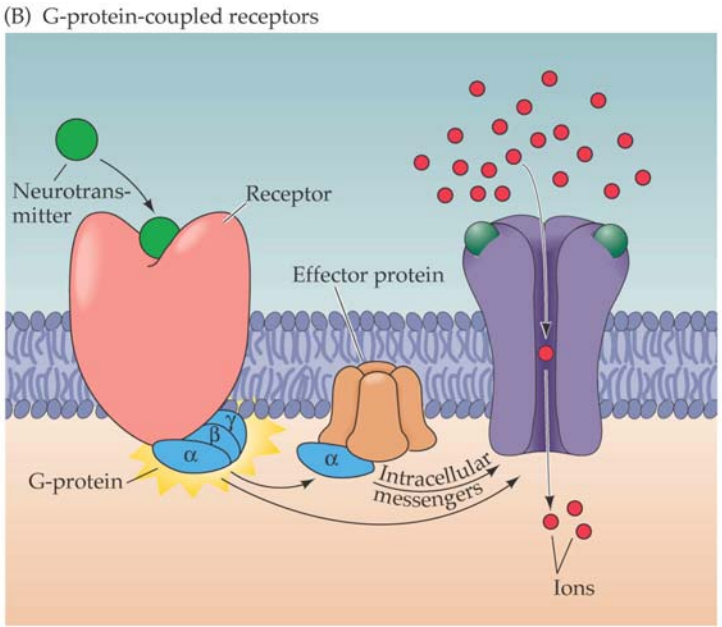
Metabotropic Receptors



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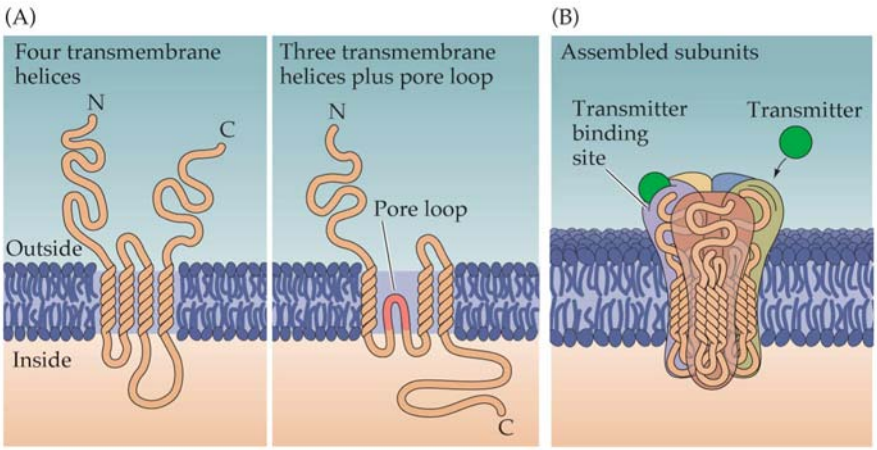
Ionotropic Receptors



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Ionotropic Receptors

(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits	Glu R1	NR1	Glu R5	α_{1-7}	α1	α_{2-9}	5-HT_3	P_{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	α2	β_{1-4}		P_{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	α3	γ		P_{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P_{2X4}
		NR2D	KA2	ε	β			P_{2X5}
				ρ_{1-3}				P_{2X6}
								P_{2X7}

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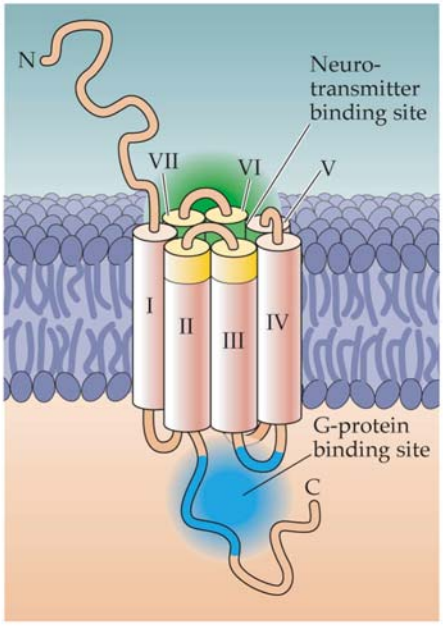
Metabotropic Receptors

(A)



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Metabotropic Receptors

(B)

Receptor class	Glutamate	$GABA_B$	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	$GABA_B$ R1	$D1_A$	α1	H1	5-HT 1	A type	M1
	mGlu R1	$GABA_B$ R2	$D1_B$	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

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Activation of Postsynaptic Receptors Results in PSPs

Ionotropic Receptors

Mediate rapid postsynaptic effects

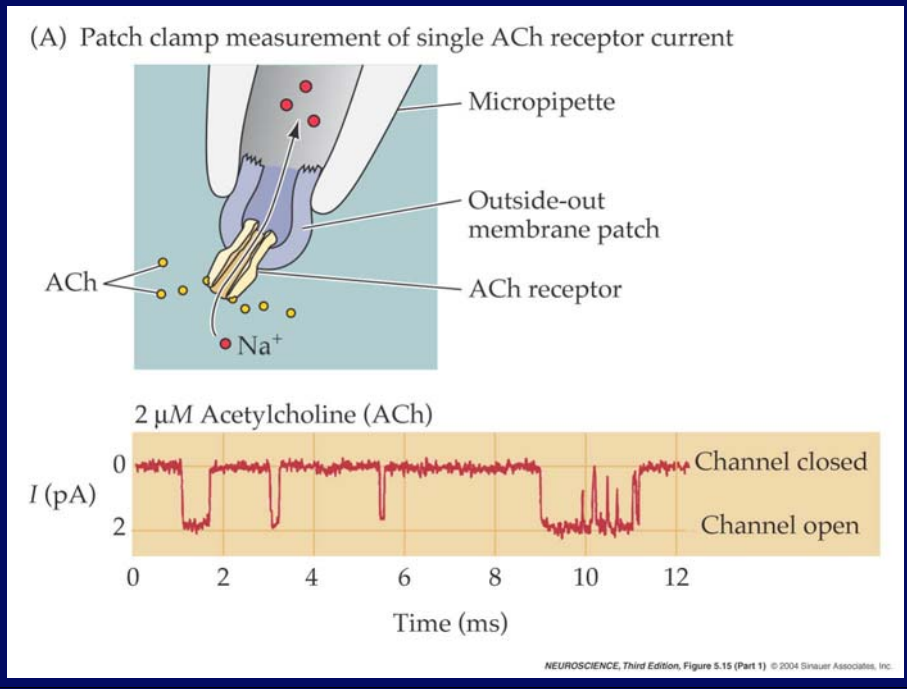
Arise 1-2 ms after AP reaches presynaptic terminal

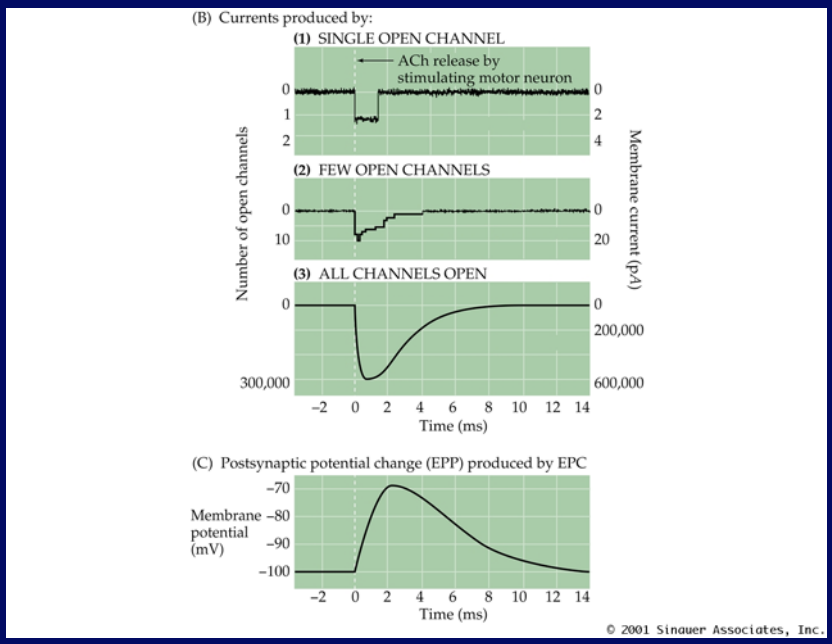
Last a few tens of ms

Metabotropic Receptors

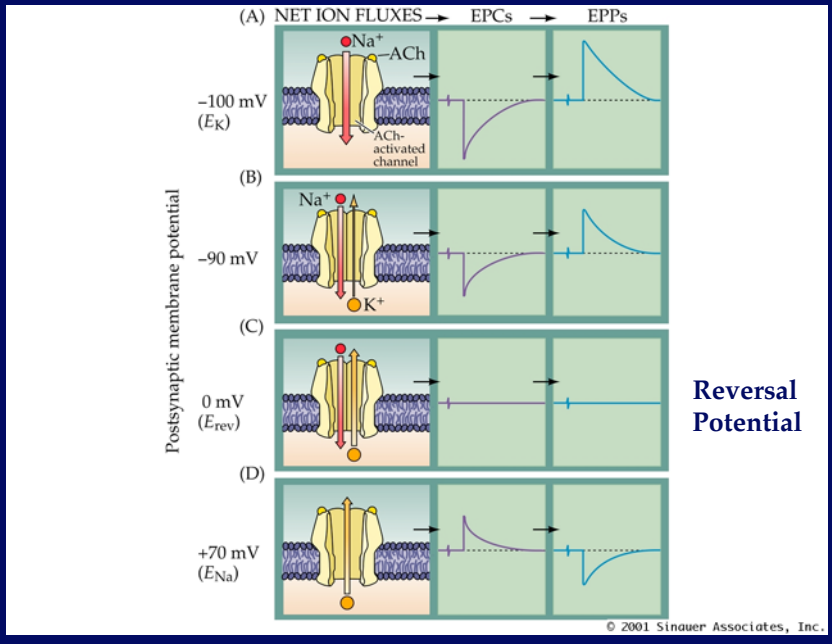
Mediates slower responses

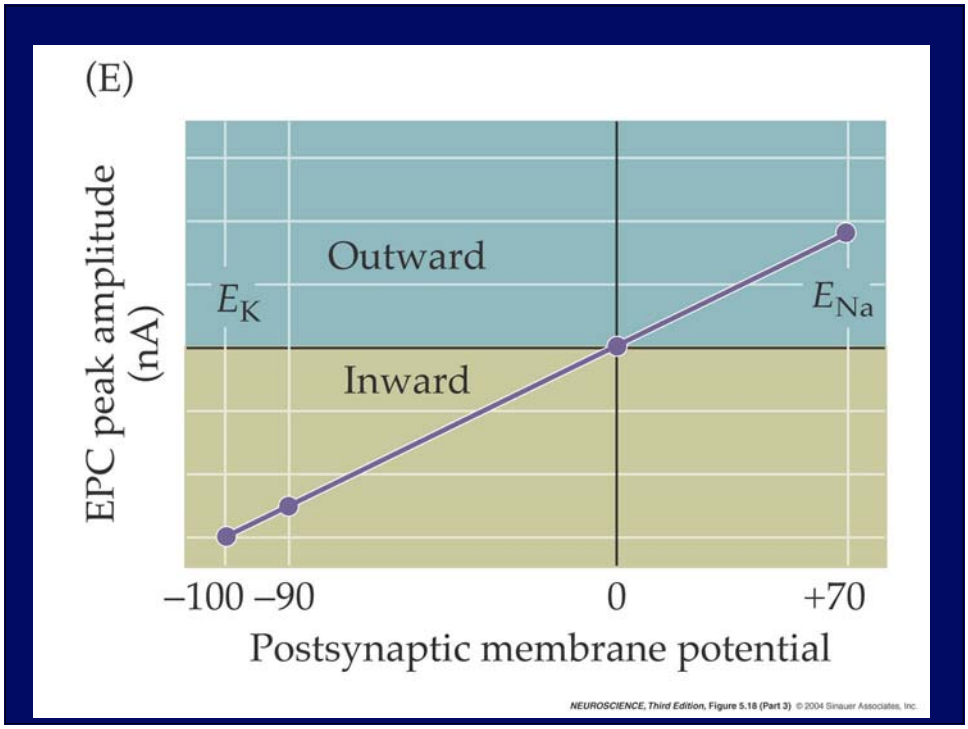
Hundreds of ms to minutes or longer

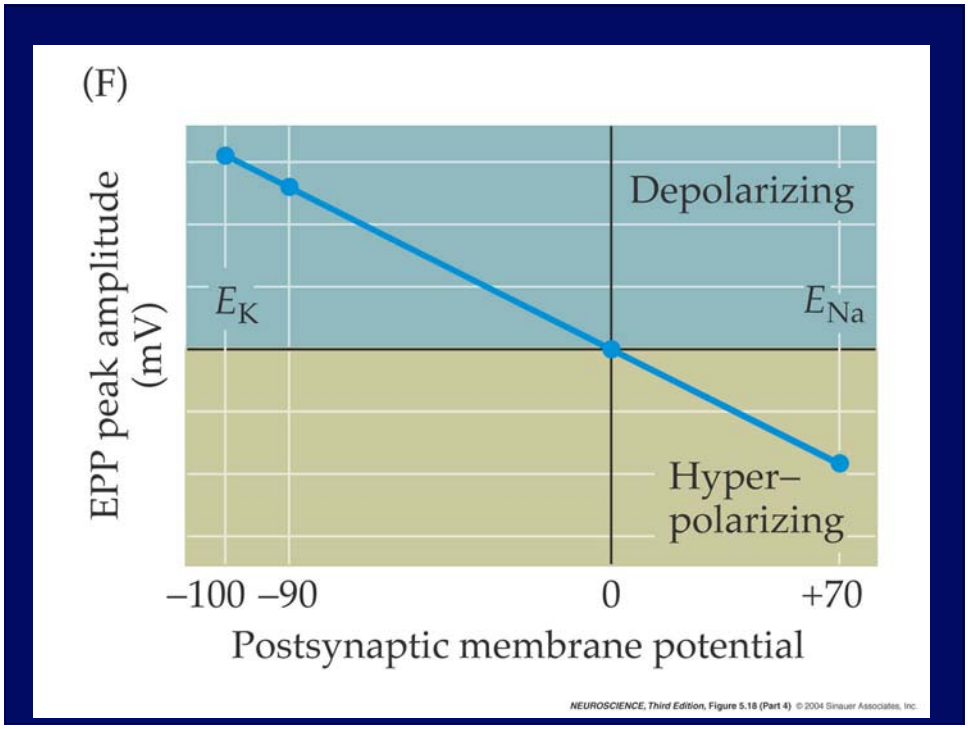




Postsynaptic potential determines relative ion fluxes




(E)
EPC peak amplitude (nA)
Outward
Inward
E_K
E_{Na}
–100 –90
0
+70
Postsynaptic membrane potential
NEUROSCIENCE, Third Edition, Figure 5.18 (Part 3) © 2004 Sinauer Associates, Inc.


(F)
EPP peak amplitude (mV)
Depolarizing
Hyper–
polarizing
E_K
E_{Na}
–100 –90
0
+70
Postsynaptic membrane potential
NEUROSCIENCE, Third Edition, Figure 5.18 (Part 4) © 2004 Sinauer Associates, Inc.

Excitatory and Inhibitory Postsynaptic Potentials

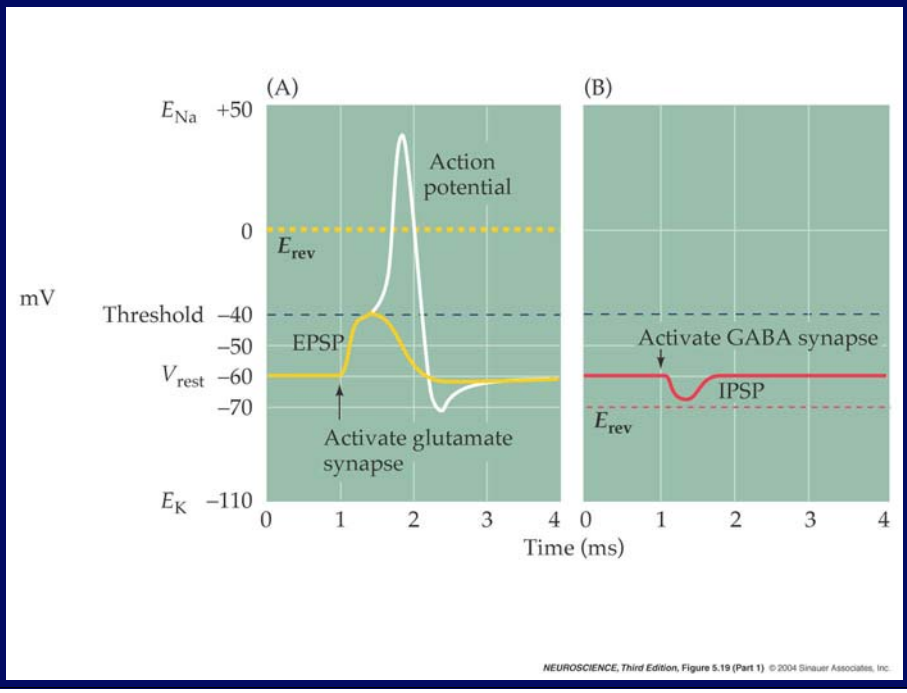
EPSPs

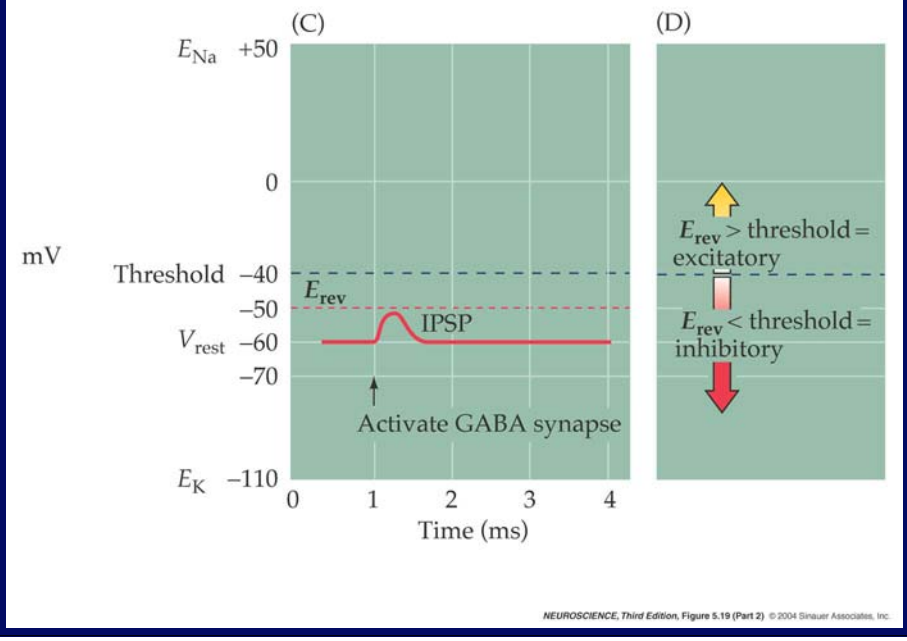
Depolarize postsynaptic cell and increase probability of AP generation

IPSPs

Hyperpolarize postsynaptic cell and decrease probability of AP generation

The relationship of reversal and threshold potential determines if a PSP is excitatory or inhibitory.





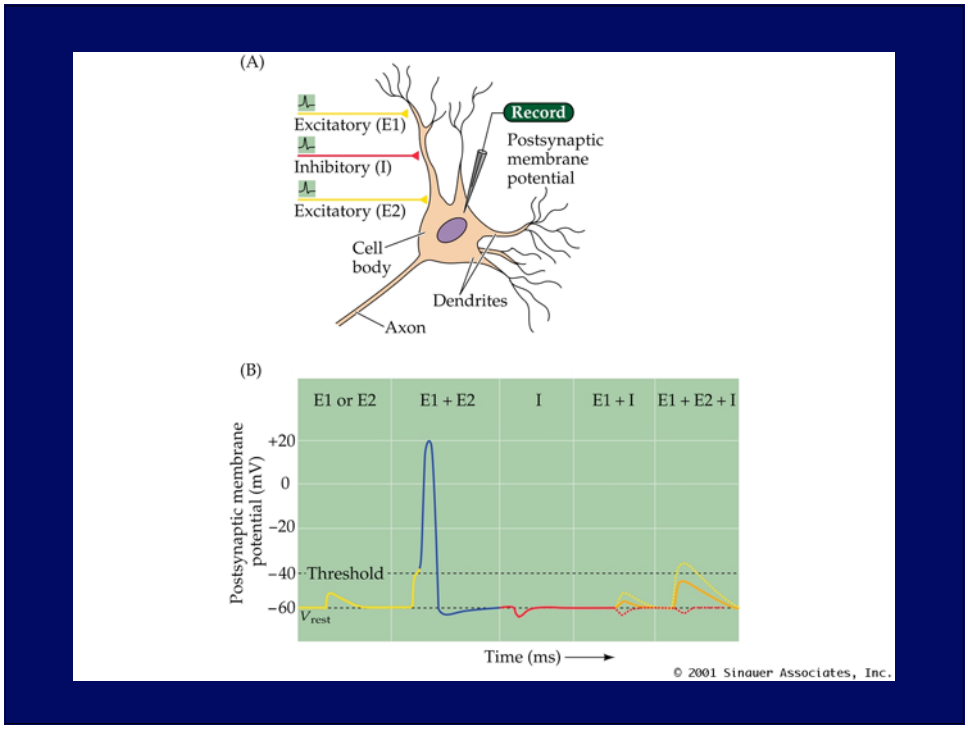
Summation of Postsynaptic Potentials

PSPs resulting from the activity of single synapses are almost always well below the threshold potential.

But neurons are commonly innervated by thousands of synapses. Therefore summation of PSPs in space and time occurs.

Summation allows the neuron to integrate all the electrical information provided by all the excitatory and inhibitory synapses innervating it.

The balance between excitation and inhibition therefore determines AP generation.


(A)
Excitatory (E1)
Inhibitory (I)
Excitatory (E2)
Record
Postsynaptic membrane potential
Cell body
Dendrites
Axon
(B)
E1 or E2
E1 + E2
I
E1 + I
E1 + E2 + I
Postsynaptic membrane potential (mV)
+20
0
−20
−40
−60
Threshold
V_{rest}
Time (ms)
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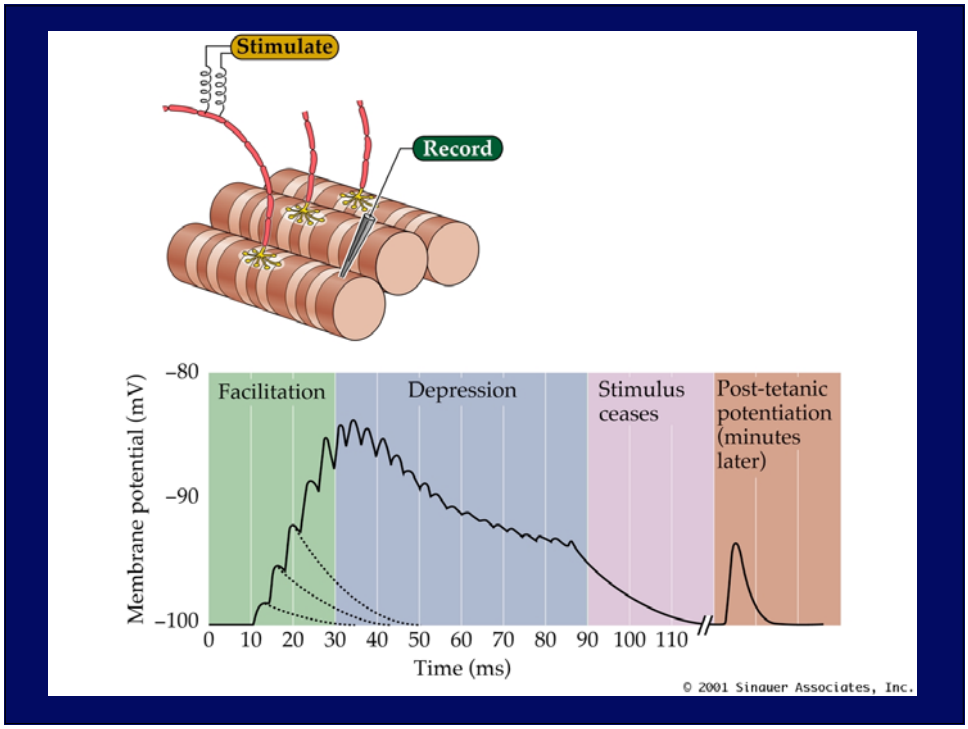
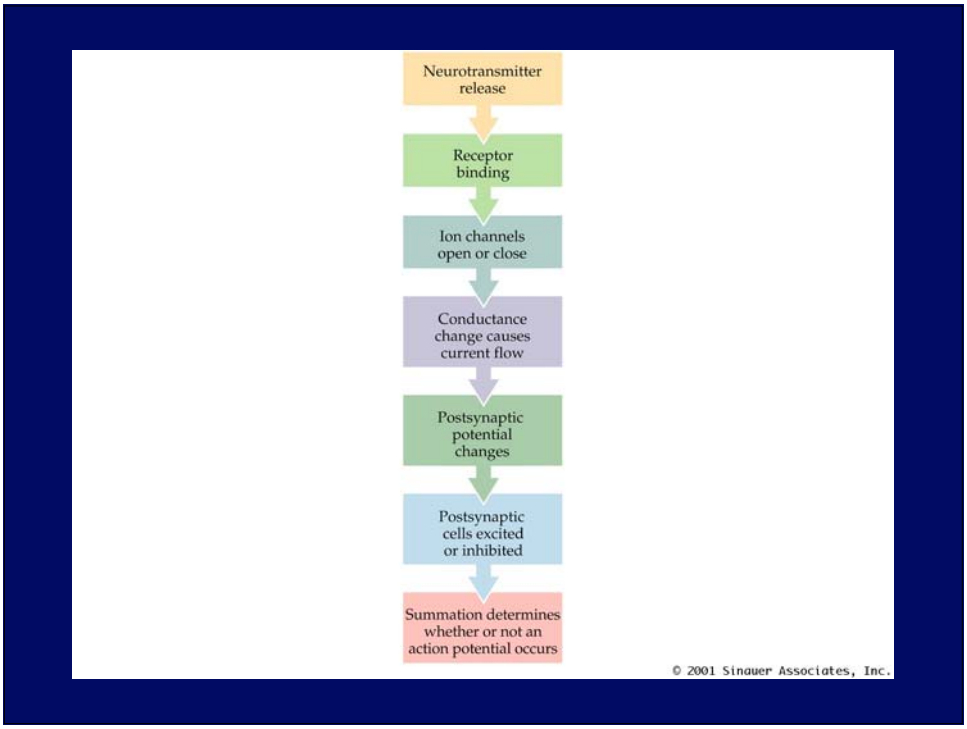

Stimulate
Record
Membrane potential (mV)
−80
−90
−100
Facilitation
Depression
Stimulus ceases
Post-tetanic potentiation (minutes later)
0 10 20 30 40 50 60 70 80 90 100 110
Time (ms)
© 2001 Sinauer Associates, Inc.


Neurotransmitter release
Receptor binding
Ion channels open or close
Conductance change causes current flow
Postsynaptic potential changes
Postsynaptic cells excited or inhibited
Summation determines whether or not an action potential occurs
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