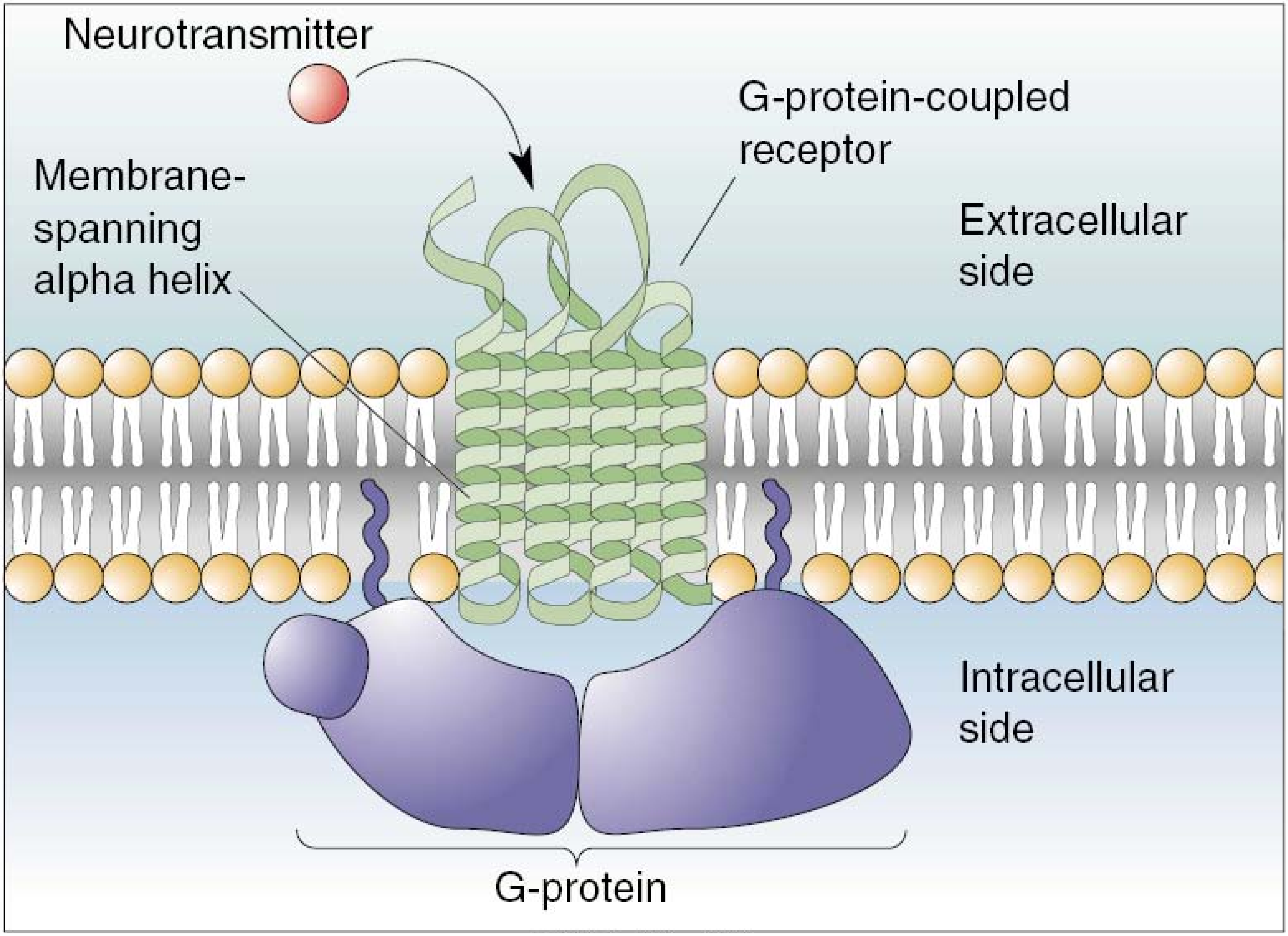
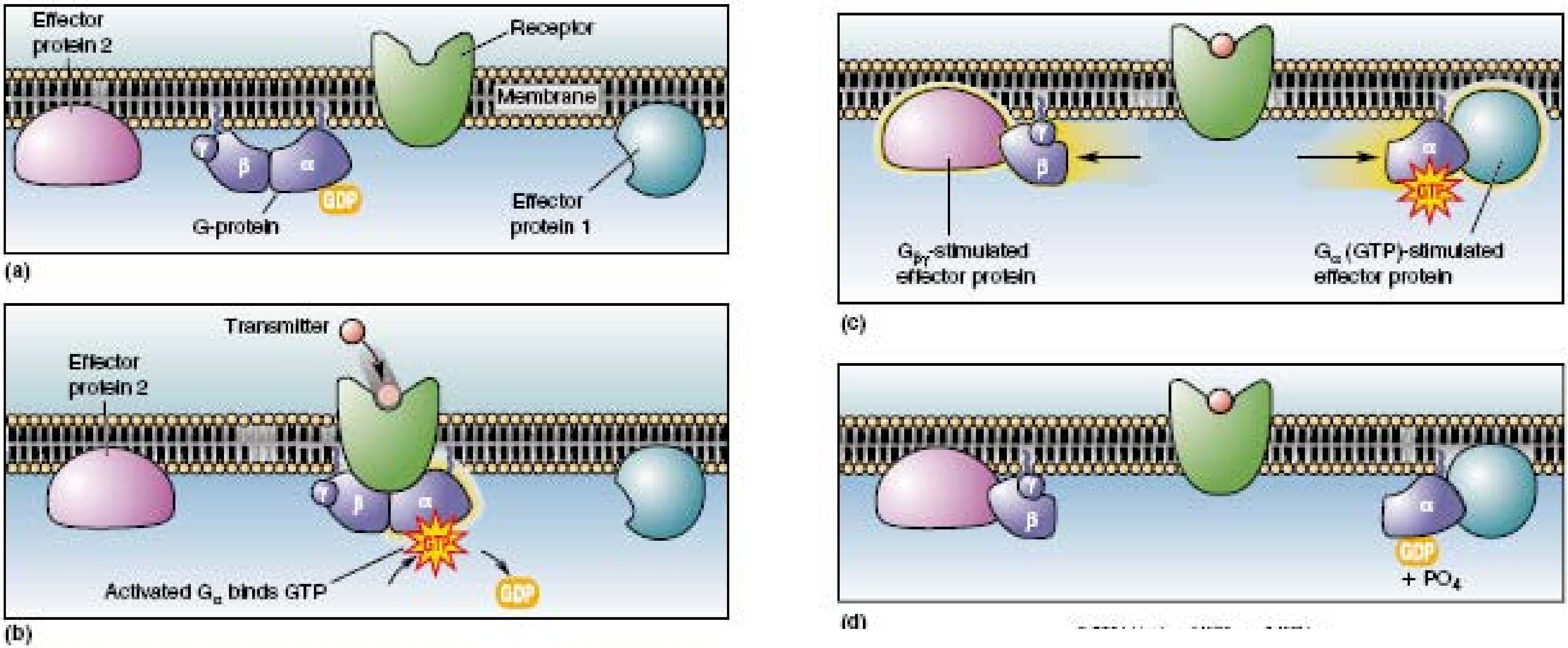
9.01 Introduction to Neuroscience
Fall 2007

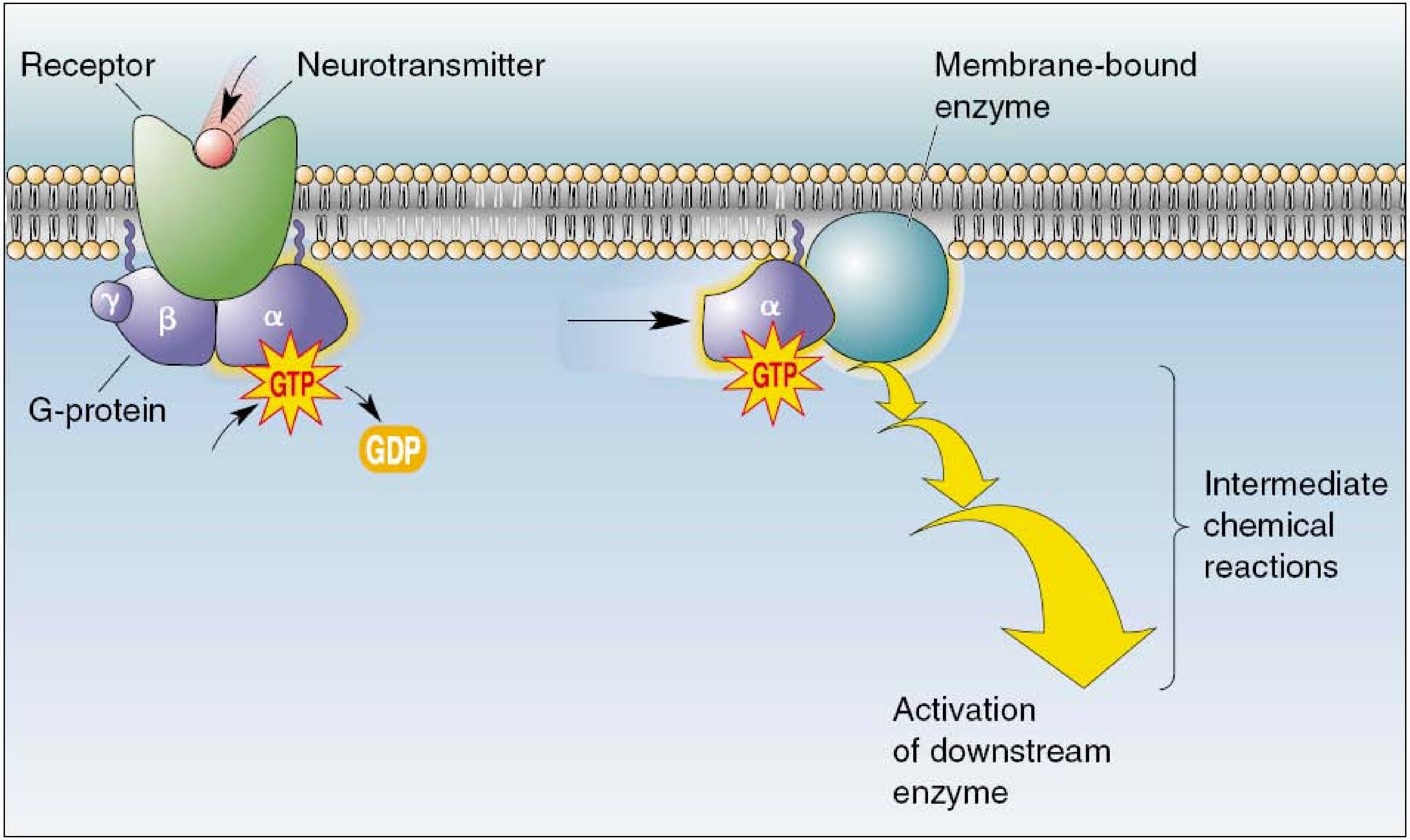
G-protein-coupled receptors



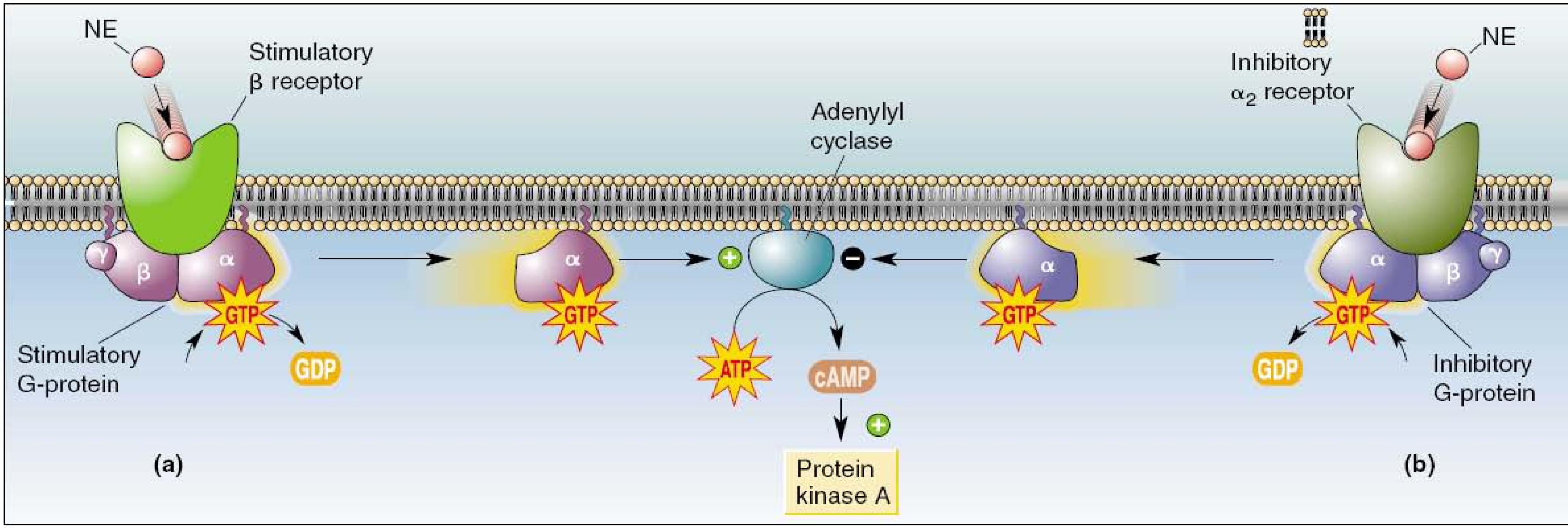
G-protein mode of operation



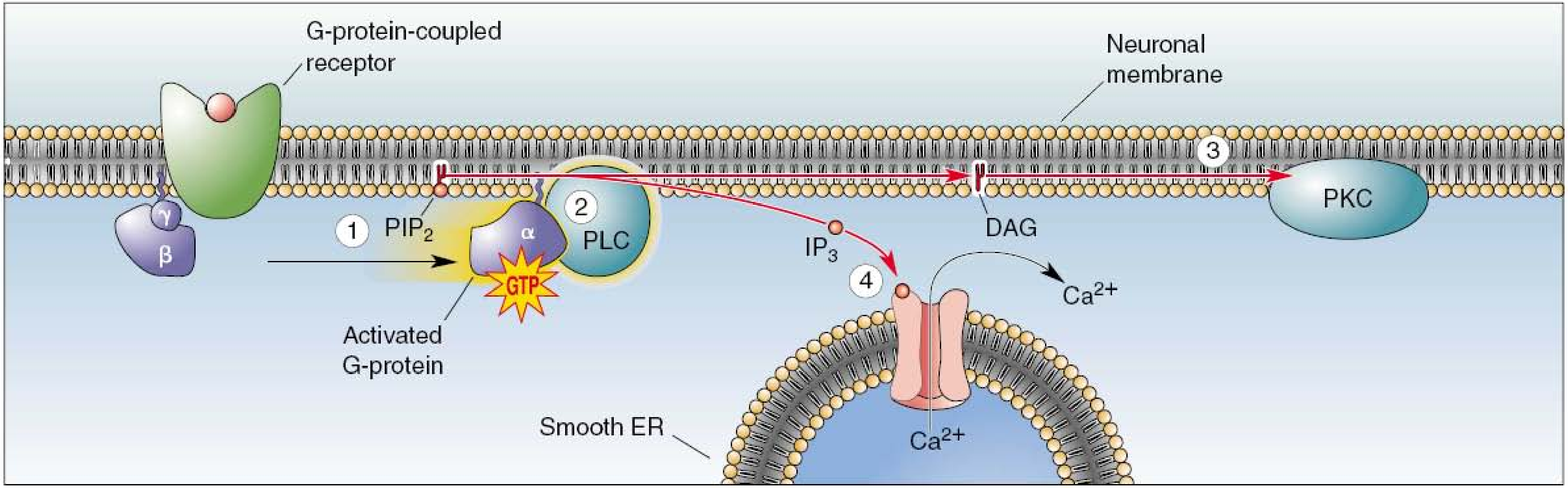
Second messenger cascades



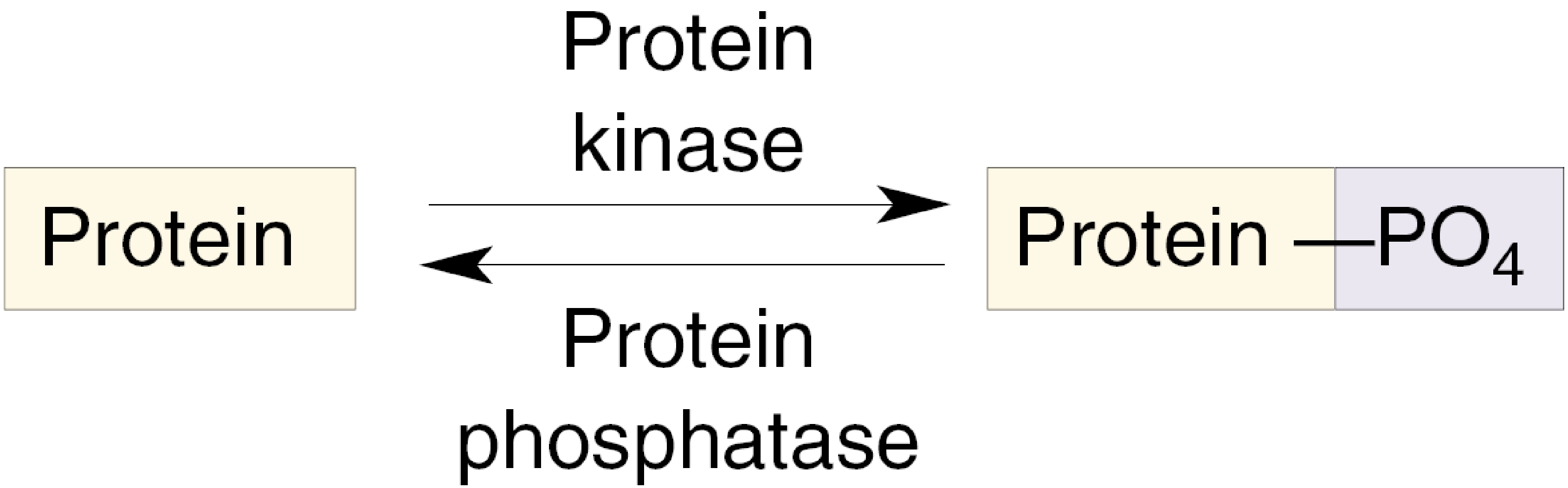
Adenylyl cyclase signalling



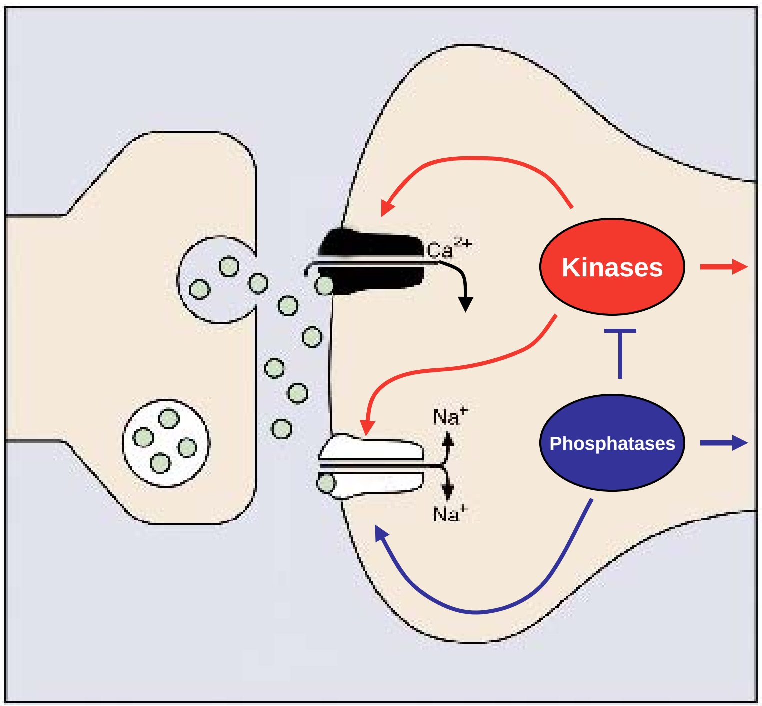
PIP_2 signalling

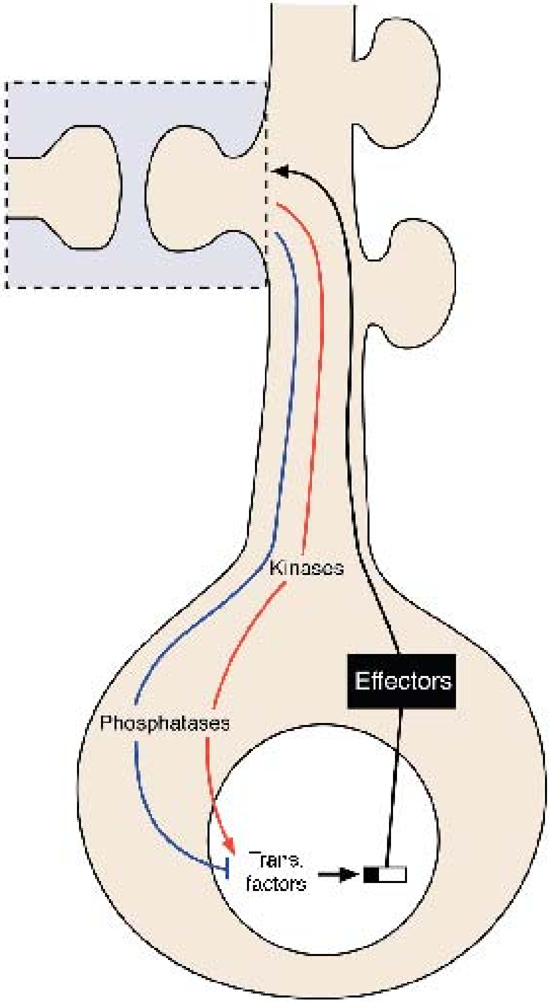


The balance of protein phosphorylation states



Molecular components synaptic modification?





Timecourse of post-synaptic potentials

1) Gap junctions – 3nm distance – instantaneous transmission

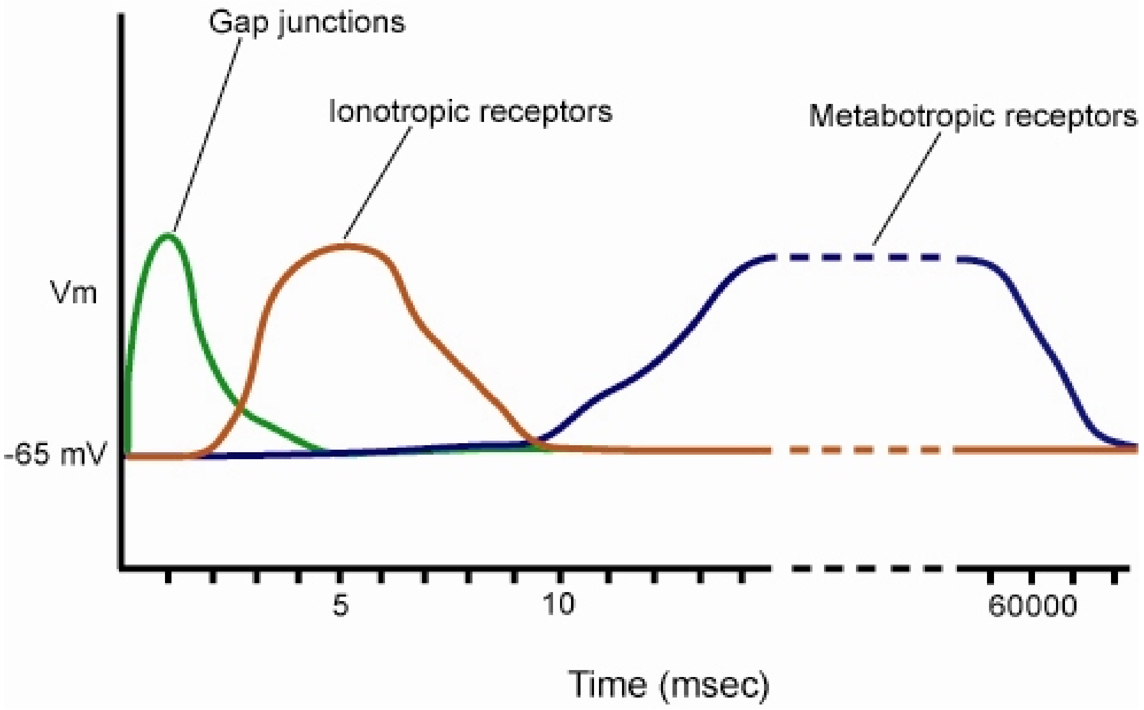
2) Chemical synapses – 20-50nm synaptic cleft:

a) Ionotropic receptors - milliseconds

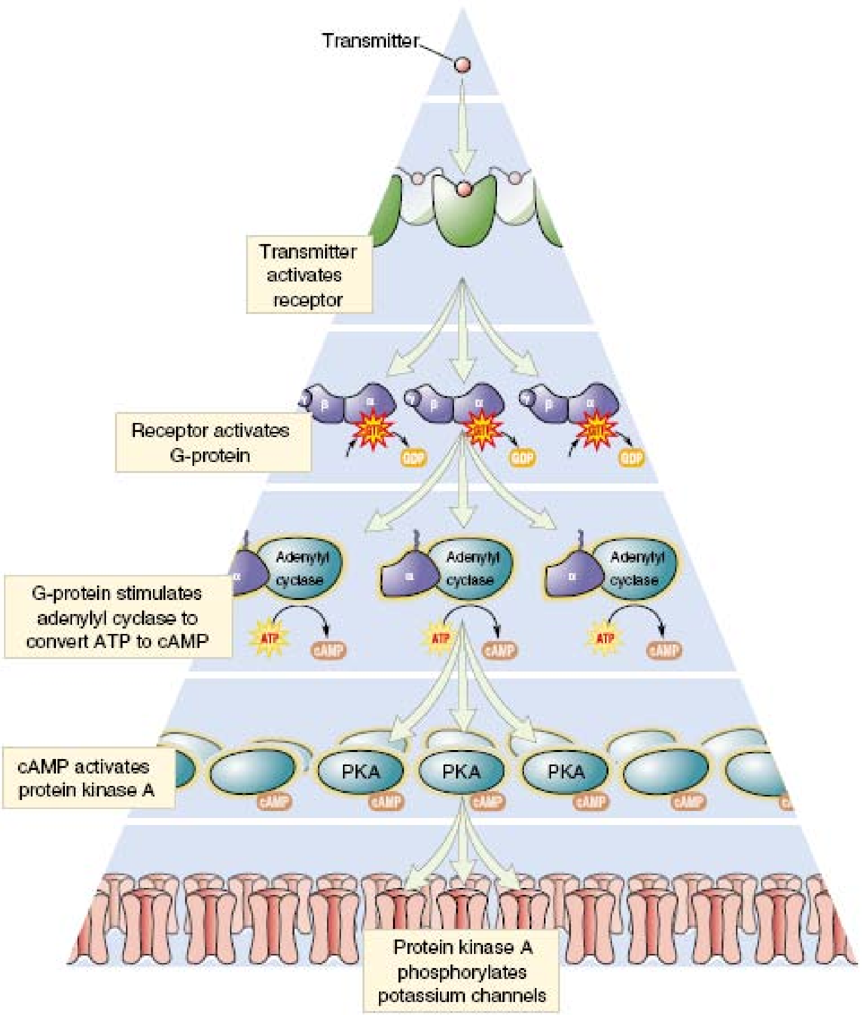
b) G-protein-coupled with ion channel – tens of milliseconds

c) G-protein coupled with second messengers - hundreds of milliseconds

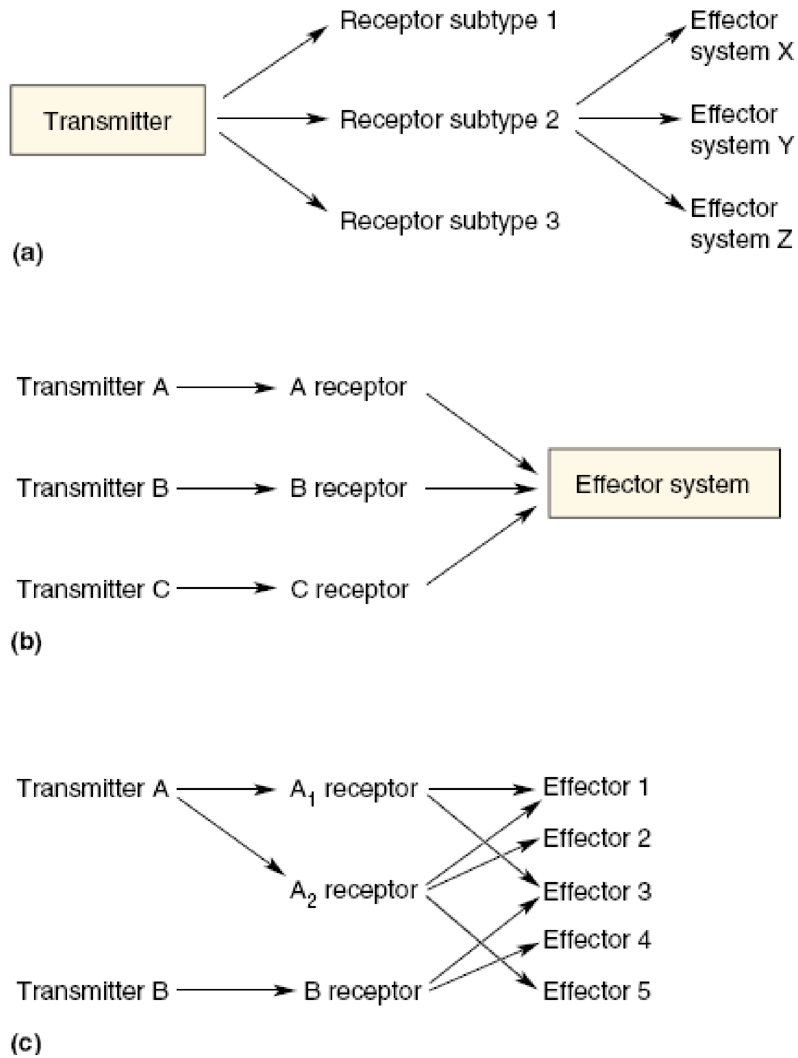
Latency to offset for second messenger effects can be in the range of minutes



Amplification of signal by second messenger systems



Divergence/convergence in neurotransmitter systems



Summary of G-protein-dependent signalling

1. G-proteins are dependent on guanosine triphosphate binding for activation

2. Ionotropic receptors mediate fast chemical transmission while G-protein coupled (metabotropic) receptor action is slower

3. G-protein coupled (metabotropic) receptors act via a panoply of intracellular mechanisms to mediate different timecourses of responses – direct ion channel opening, opening of internal calcium stores, activation of protein kinases A and C.

4. G-protein signalling allows for the amplification of neurotransmitter action

5. G-protein signalling also enables divergence and convergence of responses to neurotransmitters

List of major ionotropic vs. G-protein-coupled receptors

Ligand:	Ionotropic receptors:	G-protein-coupled receptors:
Glutamate	AMPA, NMDA, Kainate	mGluR
GABA	$GABA_A$, $GABA_C$	$GABA_B$
Glycine	GlyR	
Acetylcholine	nAchR	mAchR
Serotonin	5-HT_3	5-$HT_{1,2,4-7}$
Norepinephrine		αNE, βNE
Dopamine		D1-like, D2-like

Amino acid neurotransmitters

Glutamate

$$\begin{array}{l} COOH \\ | \\ NH_3CHCH_2CH_2COOH \end{array}$$

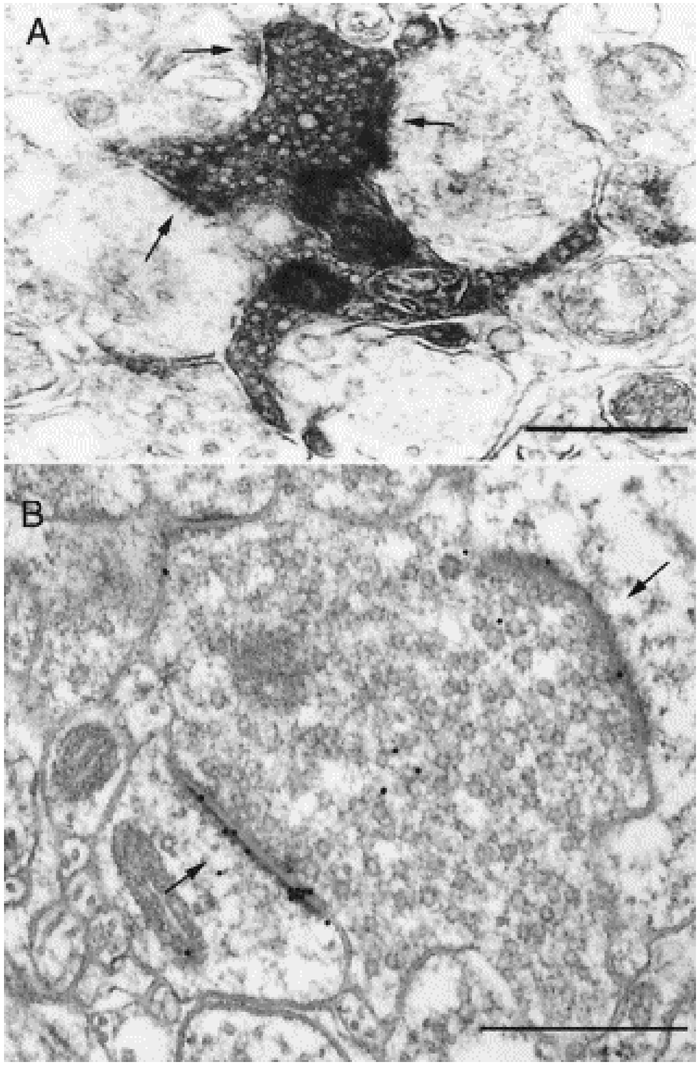
Glycine

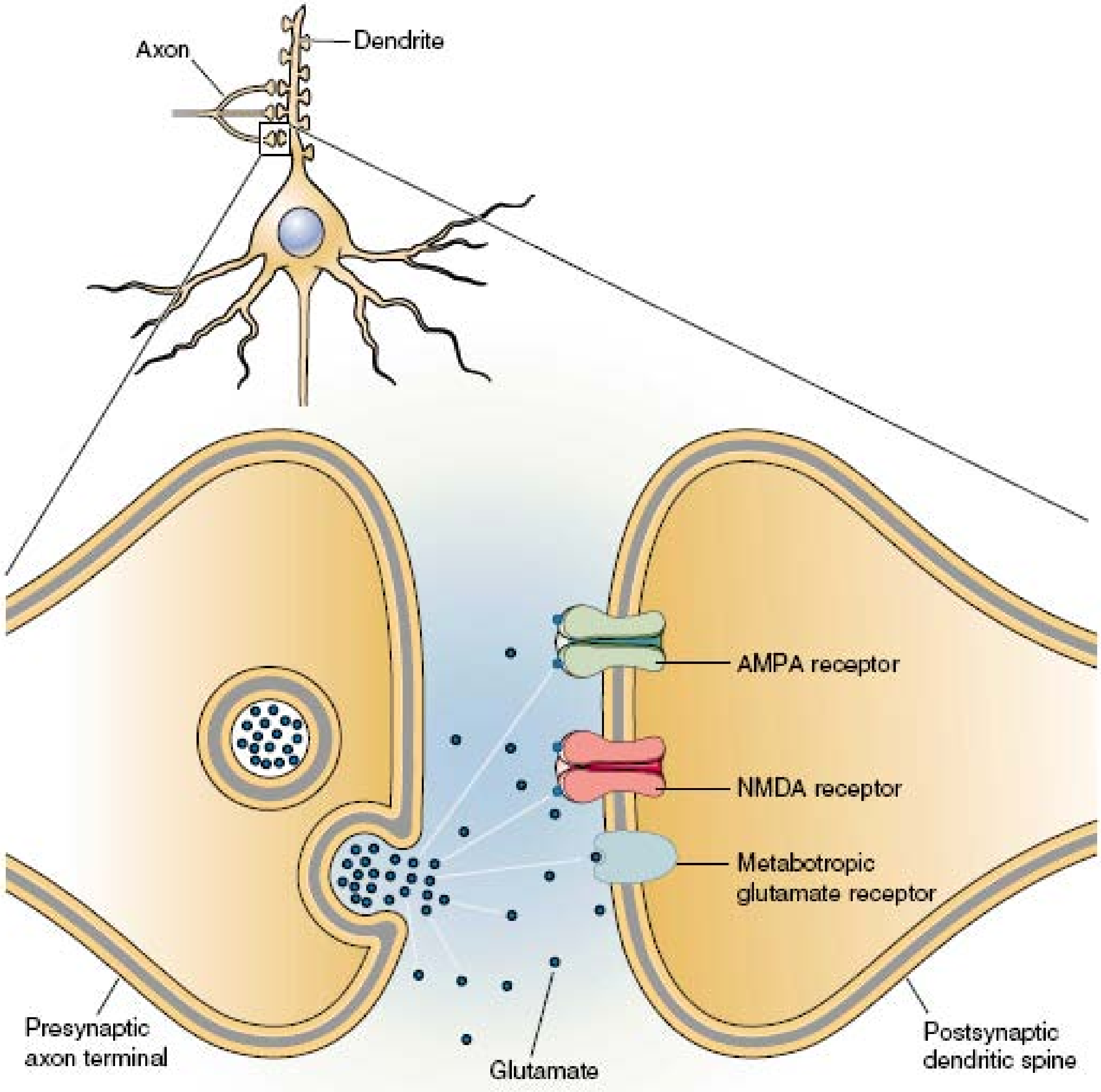
$$\begin{array}{l} COOH \\ | \\ NH_3CH_2 \end{array}$$

GABA
γ-aminobutyric acid

$$NH_3CH_2CH_2CH_2COOH$$

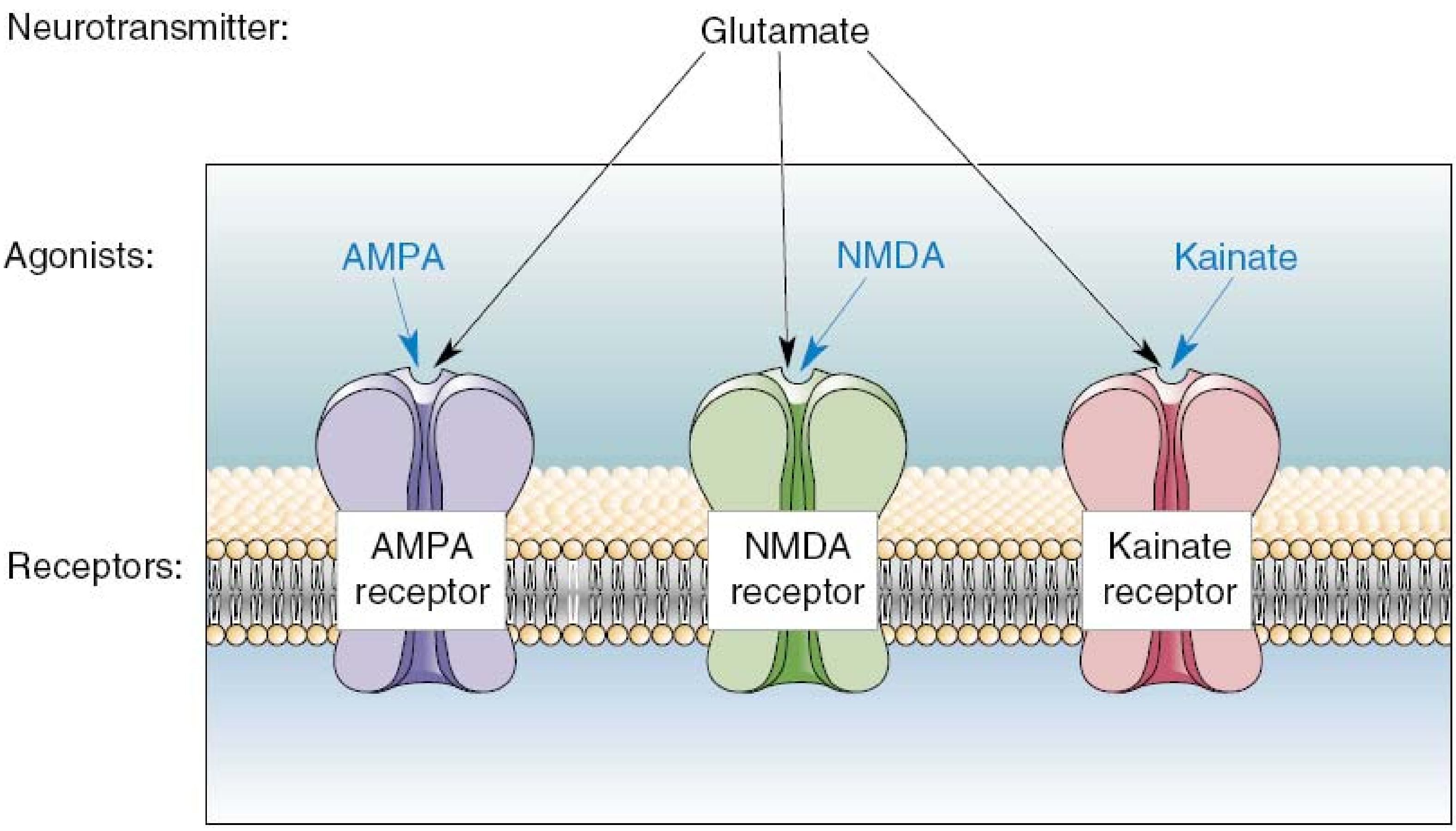
Glutamate as the major excitatory neurotransmitter in the brain



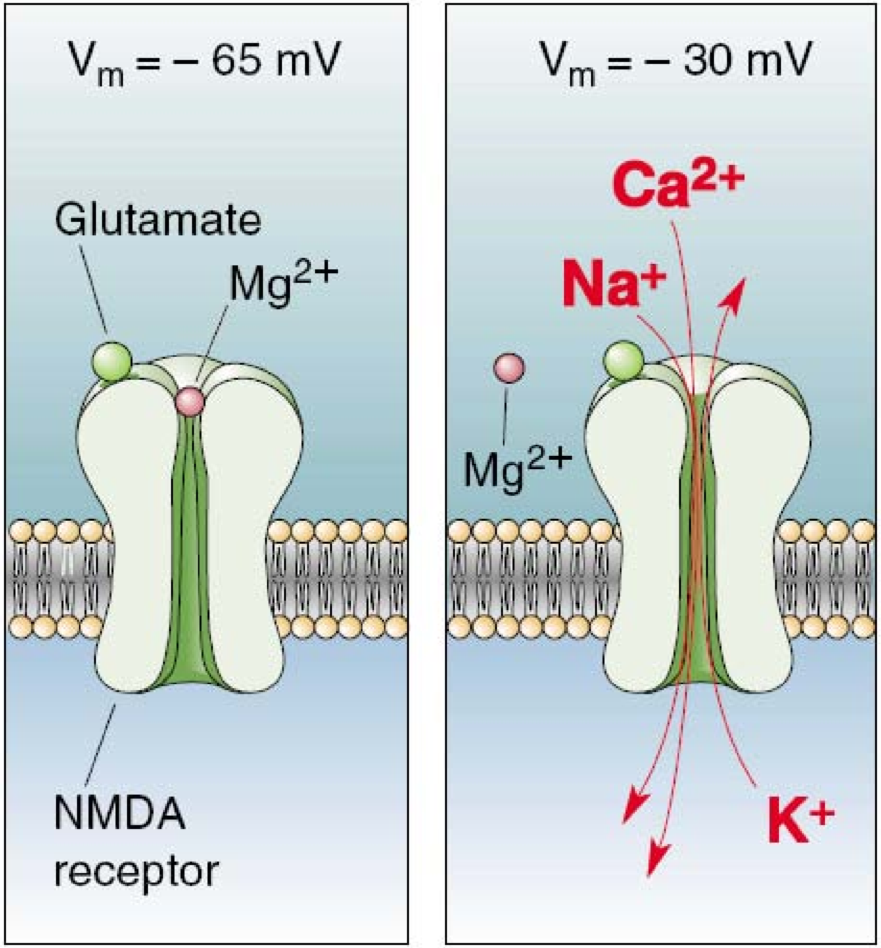


Axon
Dendrite
AMPA receptor
NMDA receptor
Metabotropic
glutamate receptor
Presynaptic
axon terminal
Glutamate
Postsynaptic
dendritic spine

The neuropharmacology of glutamatergic transmission



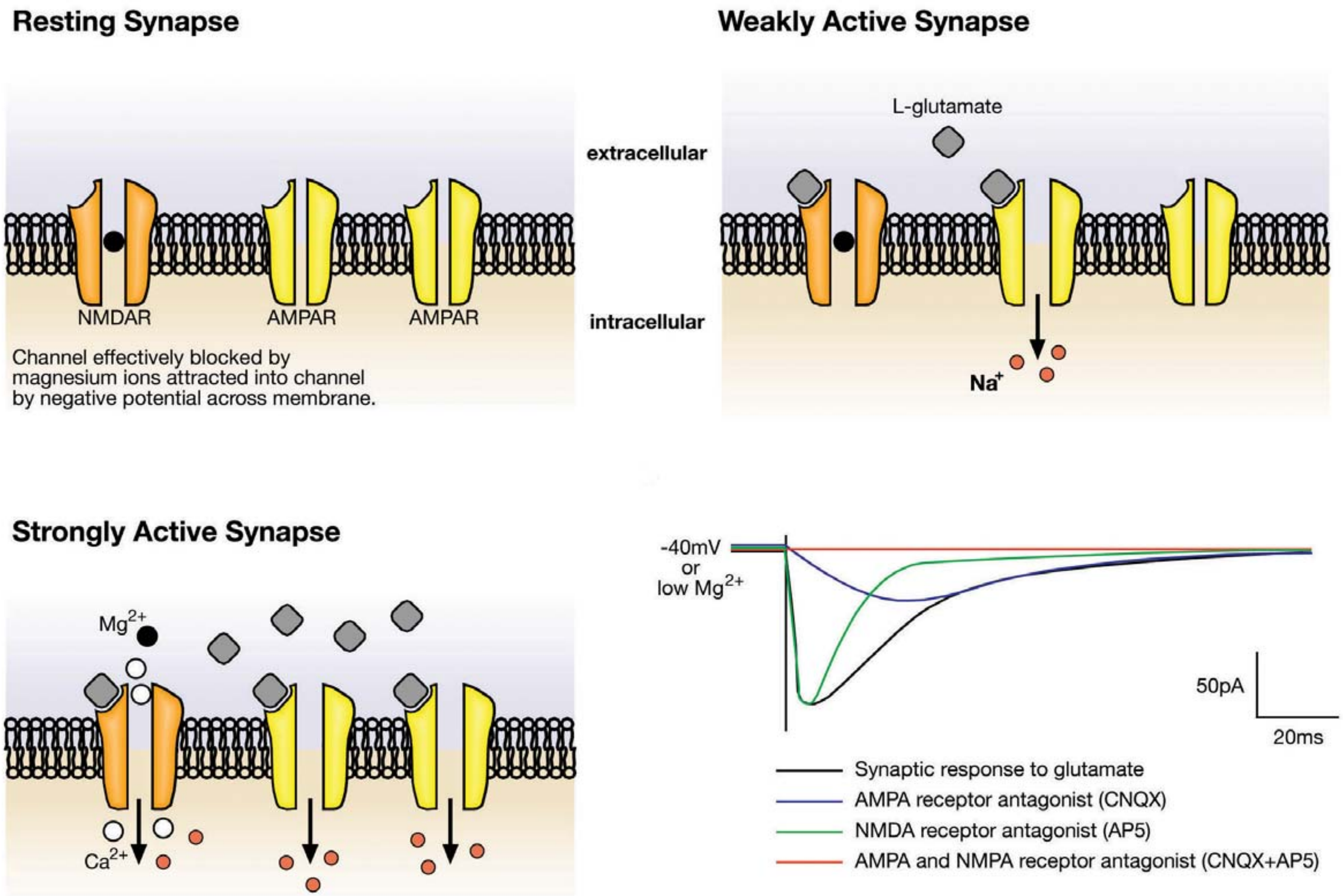
The inward flow of ions through the NMDA receptor



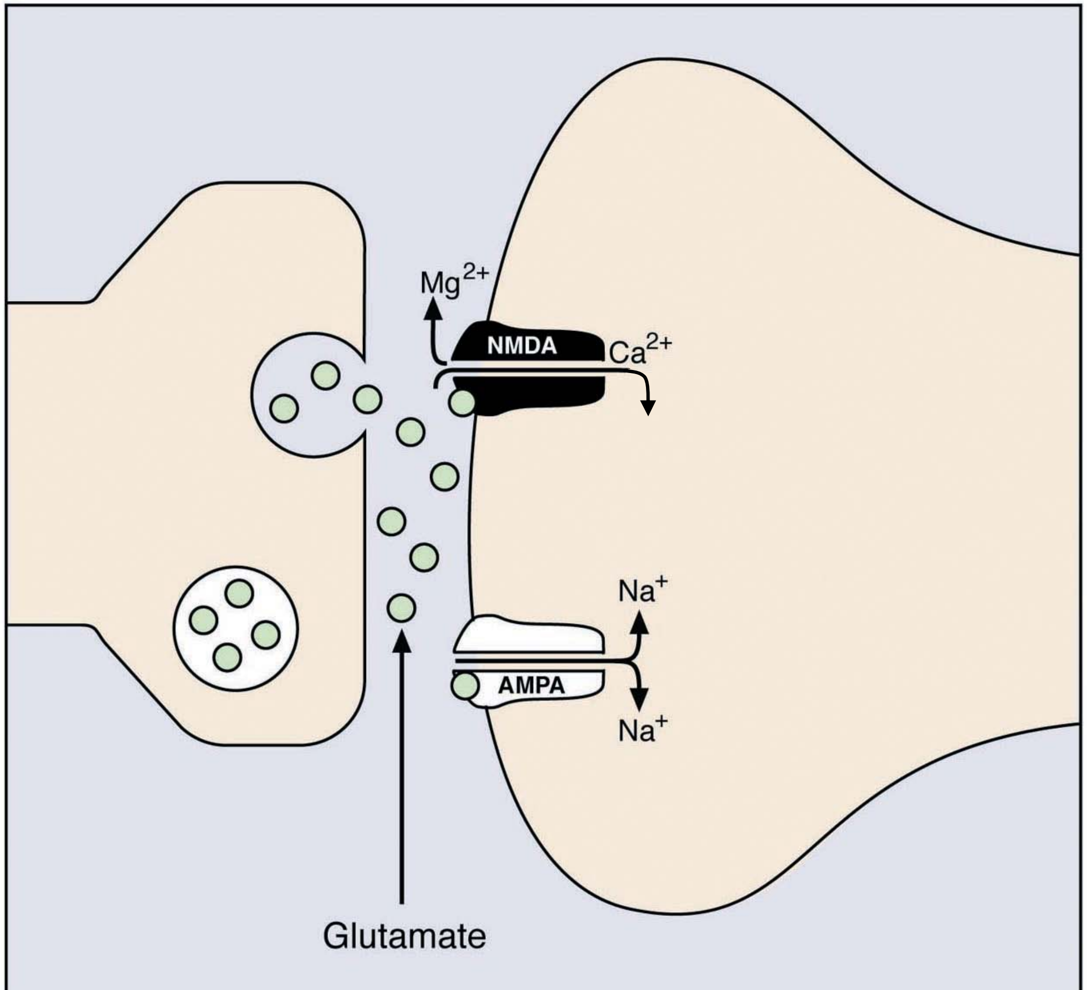
(a) Glutamate

(b) Glutamate and depolarization

The NMDA receptor as a coincidence detector



The NMDA receptor channel only opens when both pre and post-synaptic cells are co-active



The synthesis of GABA from glutamate

Glutamate

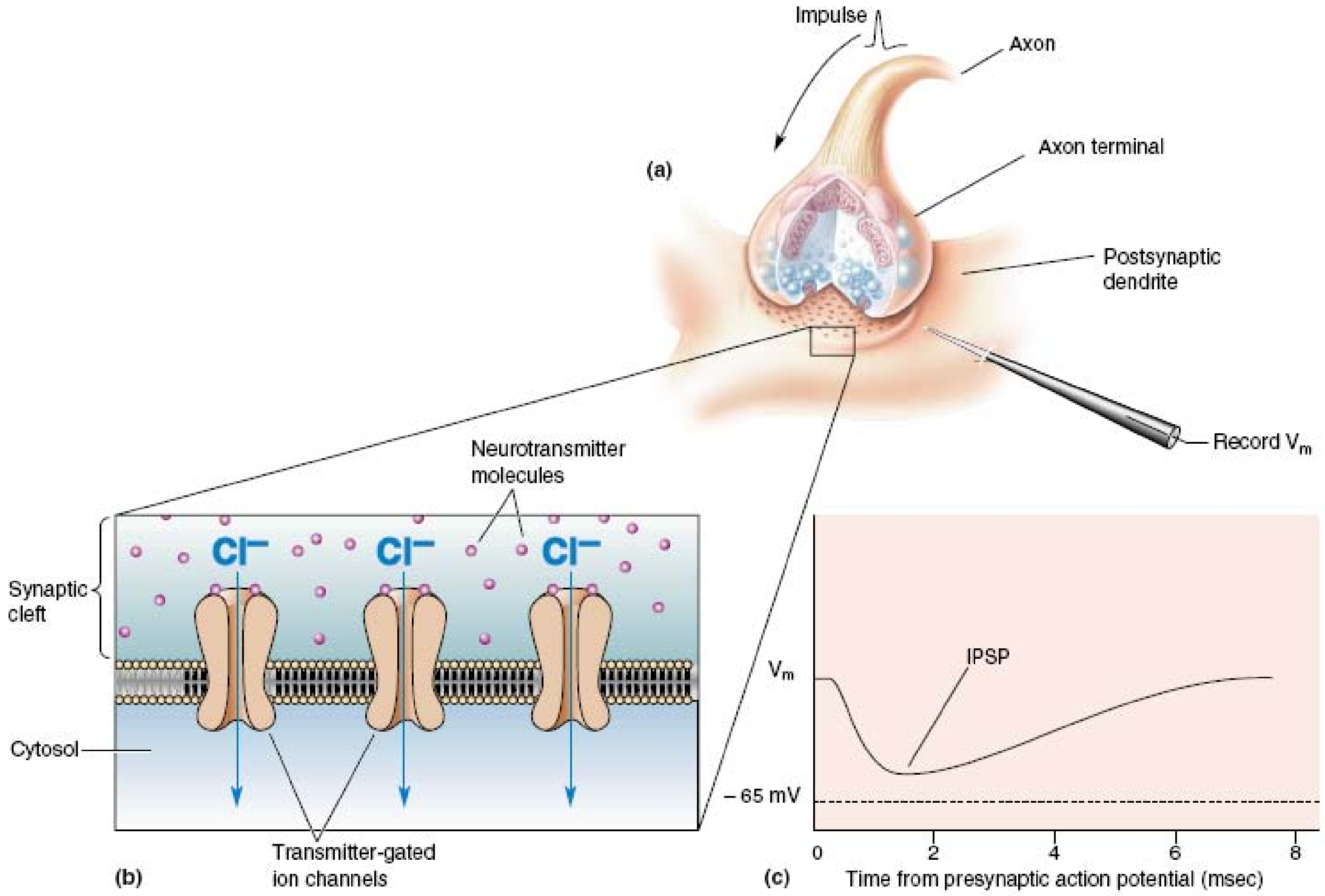
$$\overset{\boxed{COOH}}{|}$$
$$NH_3CHCH_2CH_2COOH$$

$\downarrow$ Glutamic acid decarboxylase (GAD)

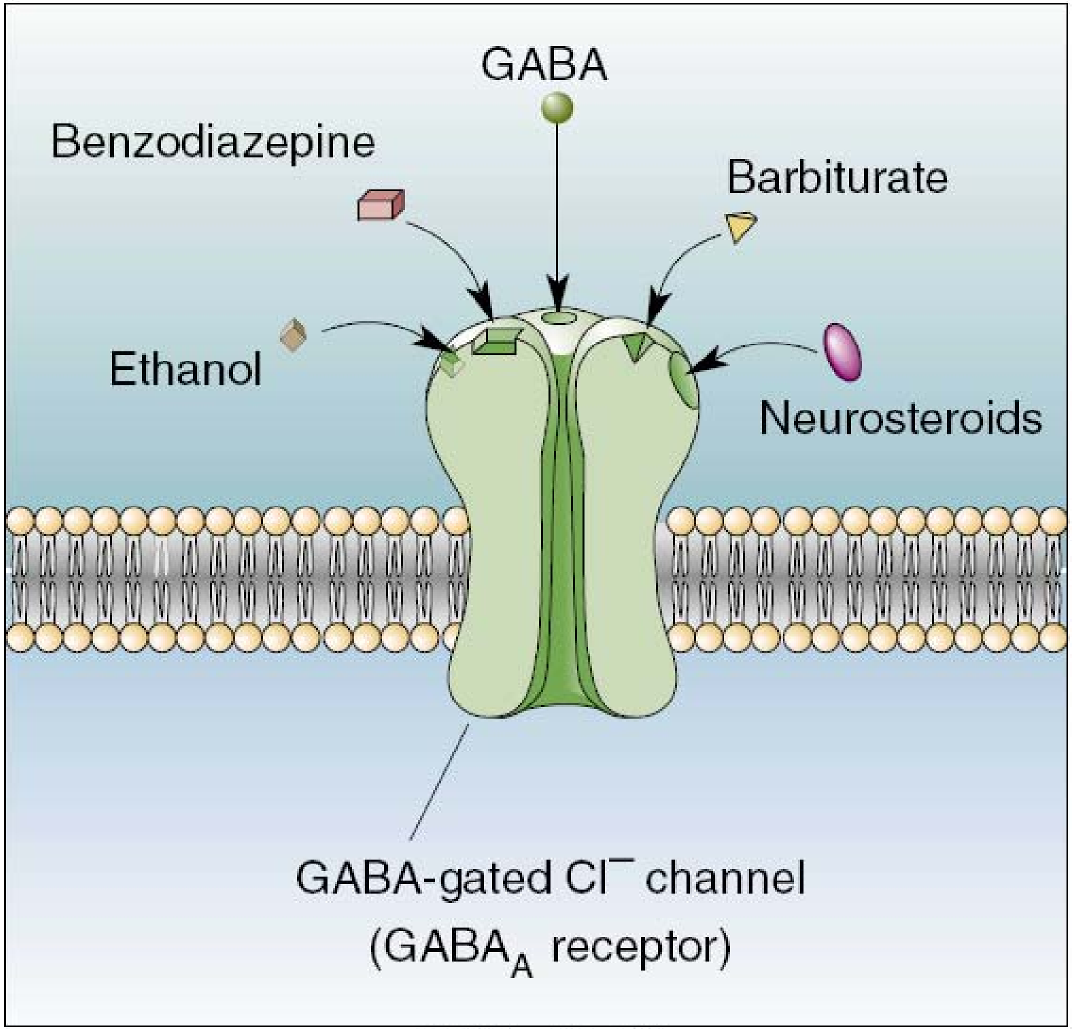
GABA

$$\overset{+}{N}H_3CHCH_2CH_2COOH$$

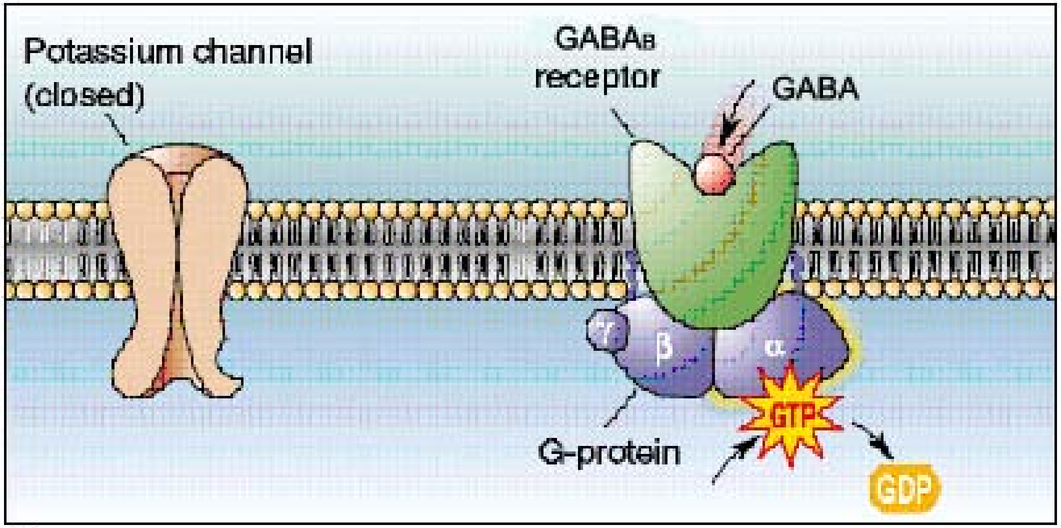
The generation of an IPSP



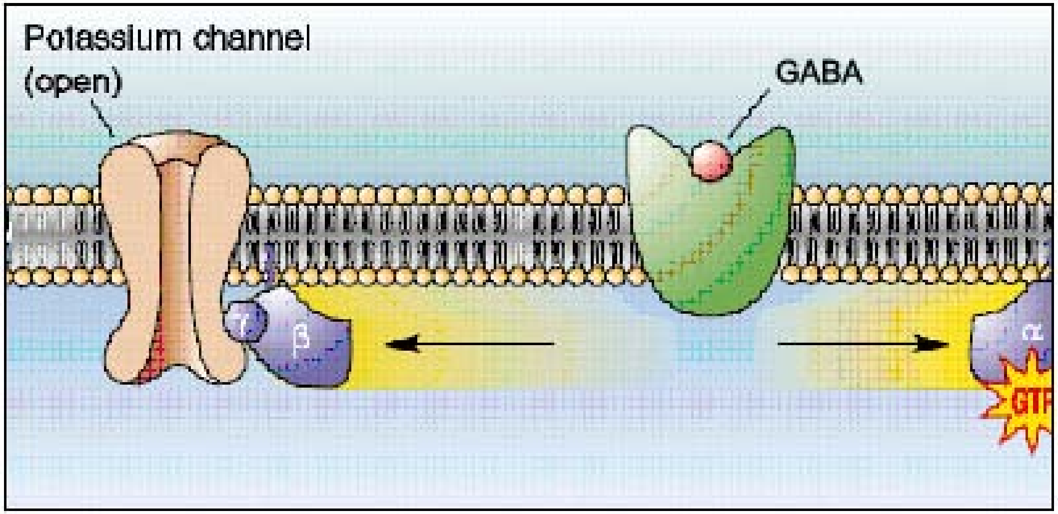
The binding of drugs to the $GABA_A$ receptor



The $GABA_B$ receptor



(a)



Summary of amino acid mediated transmission in the brain

1. In the brain, fast excitatory transmission is predominantly mediated by glutamate and fast inhibitory transmission by GABA (glycine performs this role in the spinal cord)

2. Fast excitatory transmission is mediated by several classes of ionotropic glutamate receptors (AMPA, Kainiate and NMDA).

3. The NMDA receptor has special properties that allow it to detect coincidence between pre and post-synaptic depolarisation

4. There are also metabotropic glutamate receptors

5. Fast inhibitory transmission is mediated by $GABA_A$ receptors

6. Modulation of ionotropic receptor conformation by systemic substances such as ampakines, ethanol, barbiturates or benzodiazepines alters their kinetics and can thereby enhance or repress fast transmission

7. $GABA_B$ receptors are metabotropic

Amine transmitters

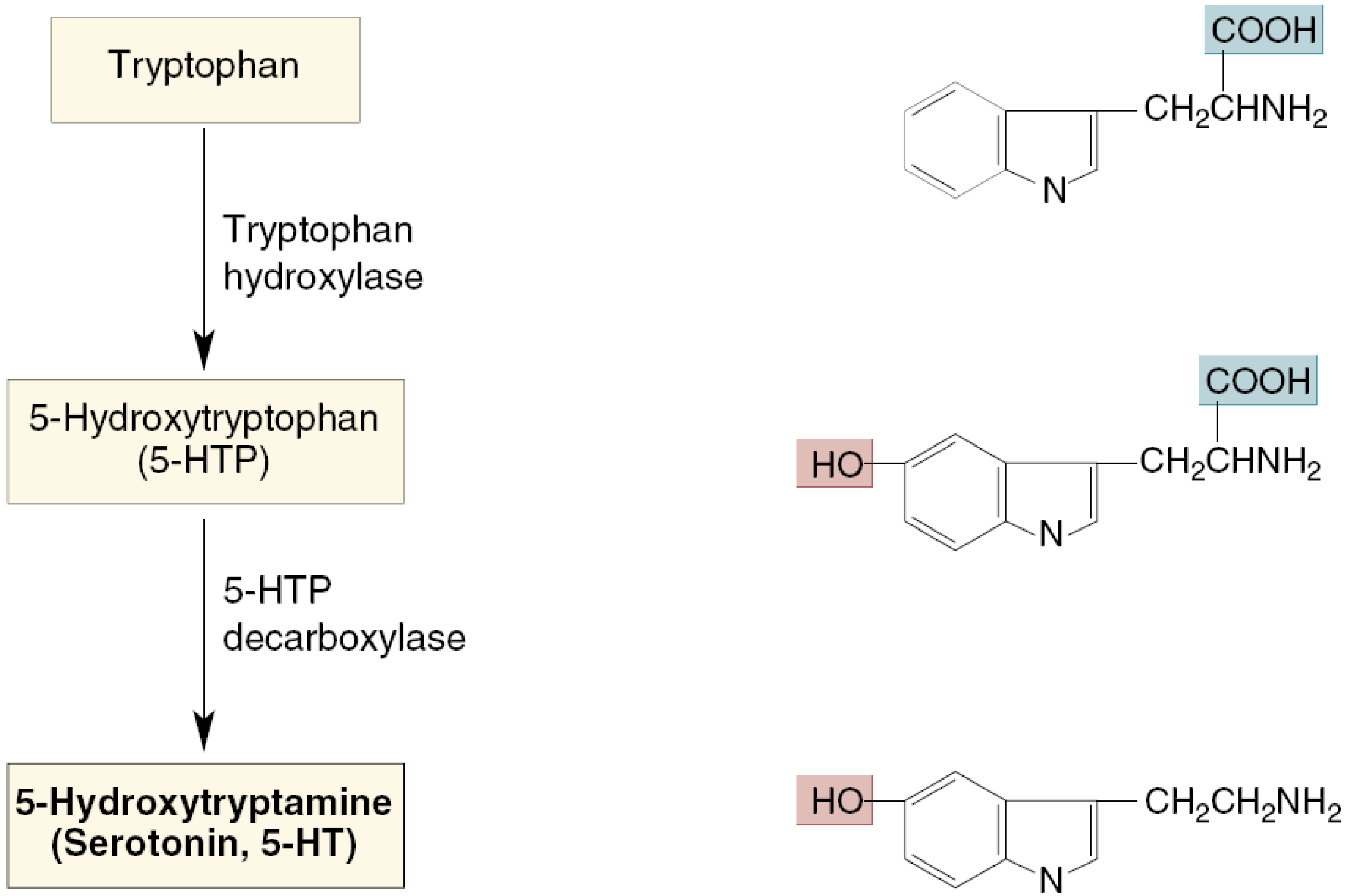
1) 5-HT (Serotonin)

2) Catecholamines:

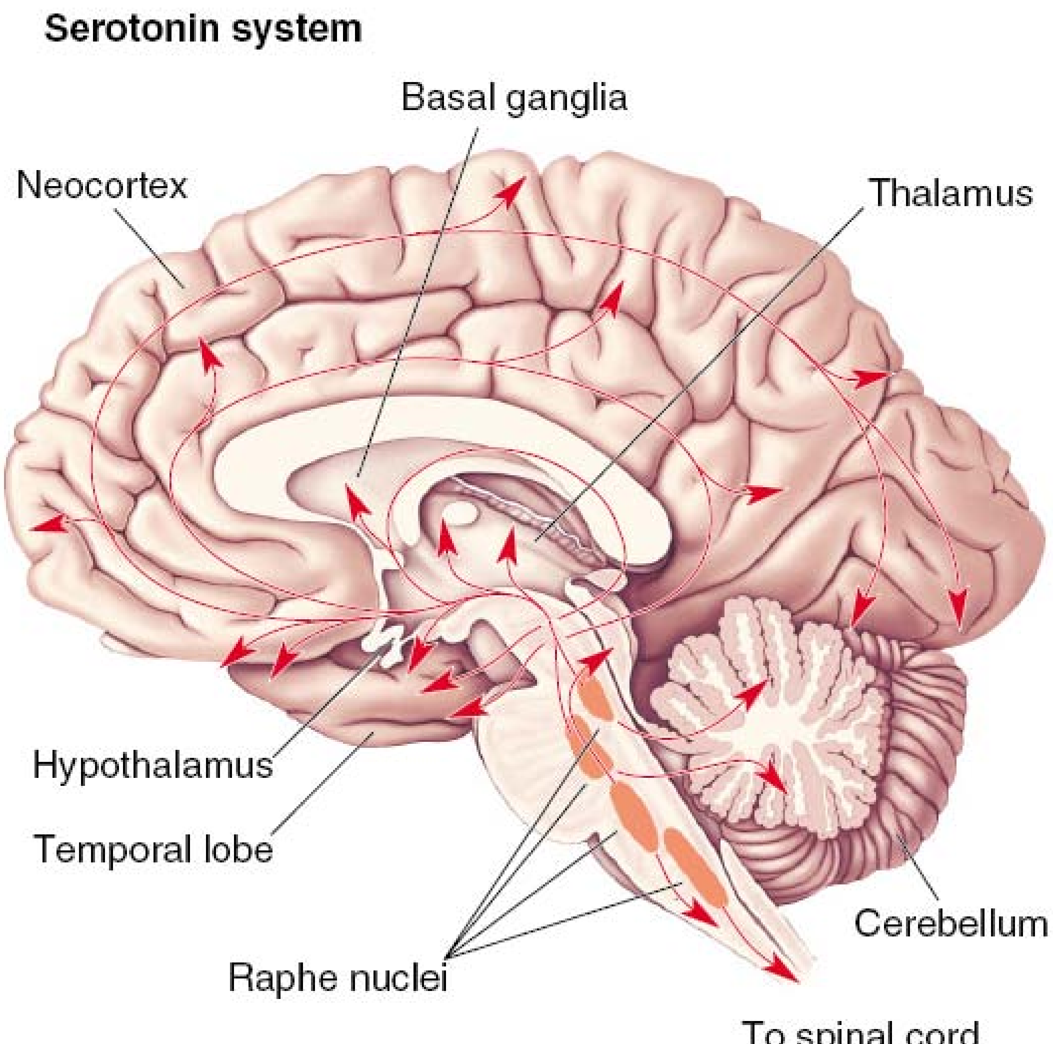
a) Dopamine
b) Norepinephrine (Noradrenaline)
c) Epinephrine (Adrenaline)

3) Acetylcholine

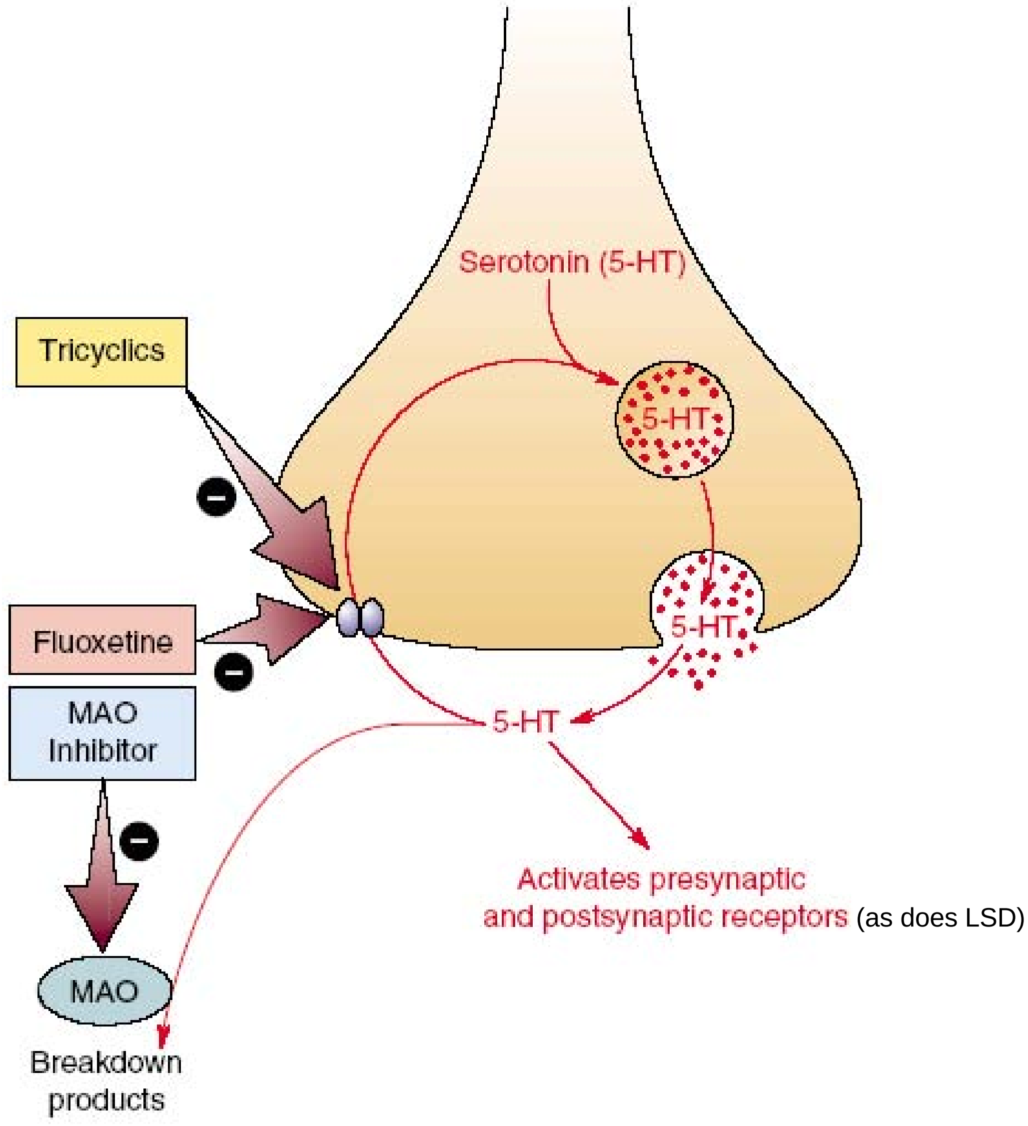
The synthesis of serotonin from tryptophan



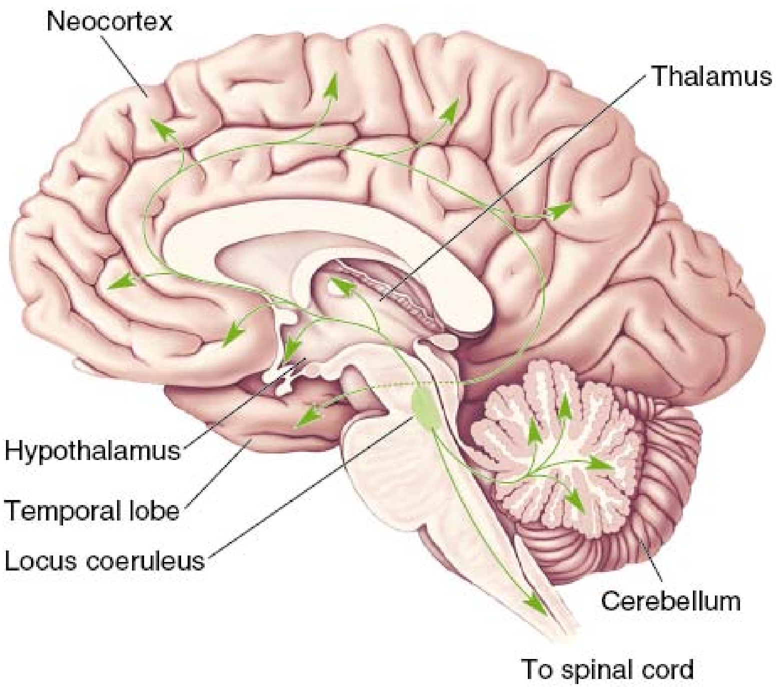
Neuromodulation by Serotonin



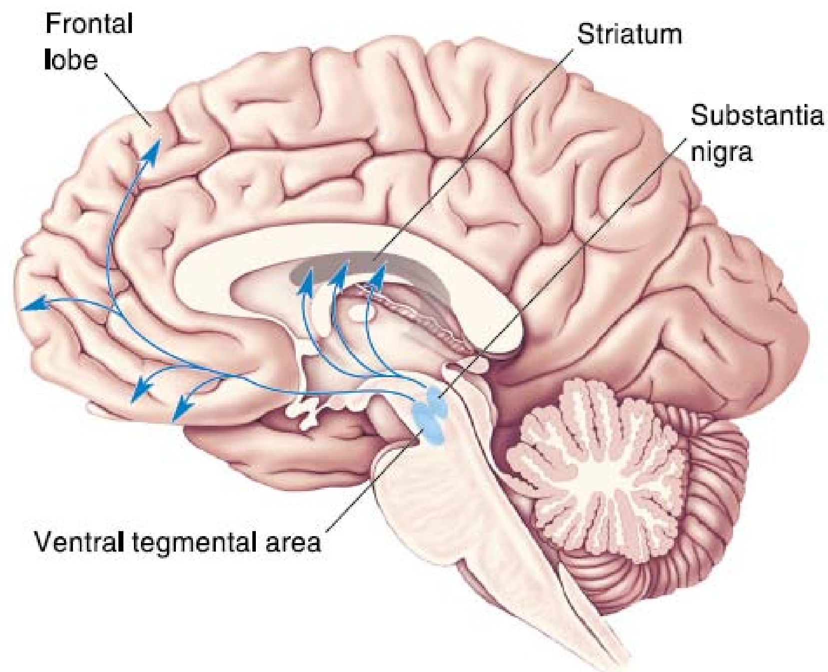
The action of anti-depressants on the serotonergic system



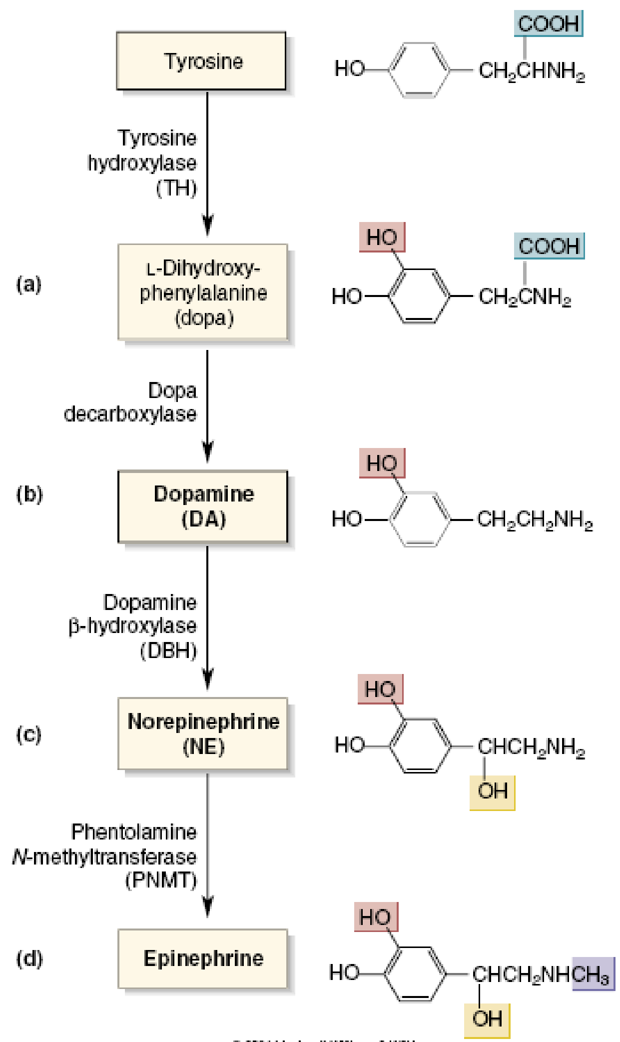
Norepinephrine system

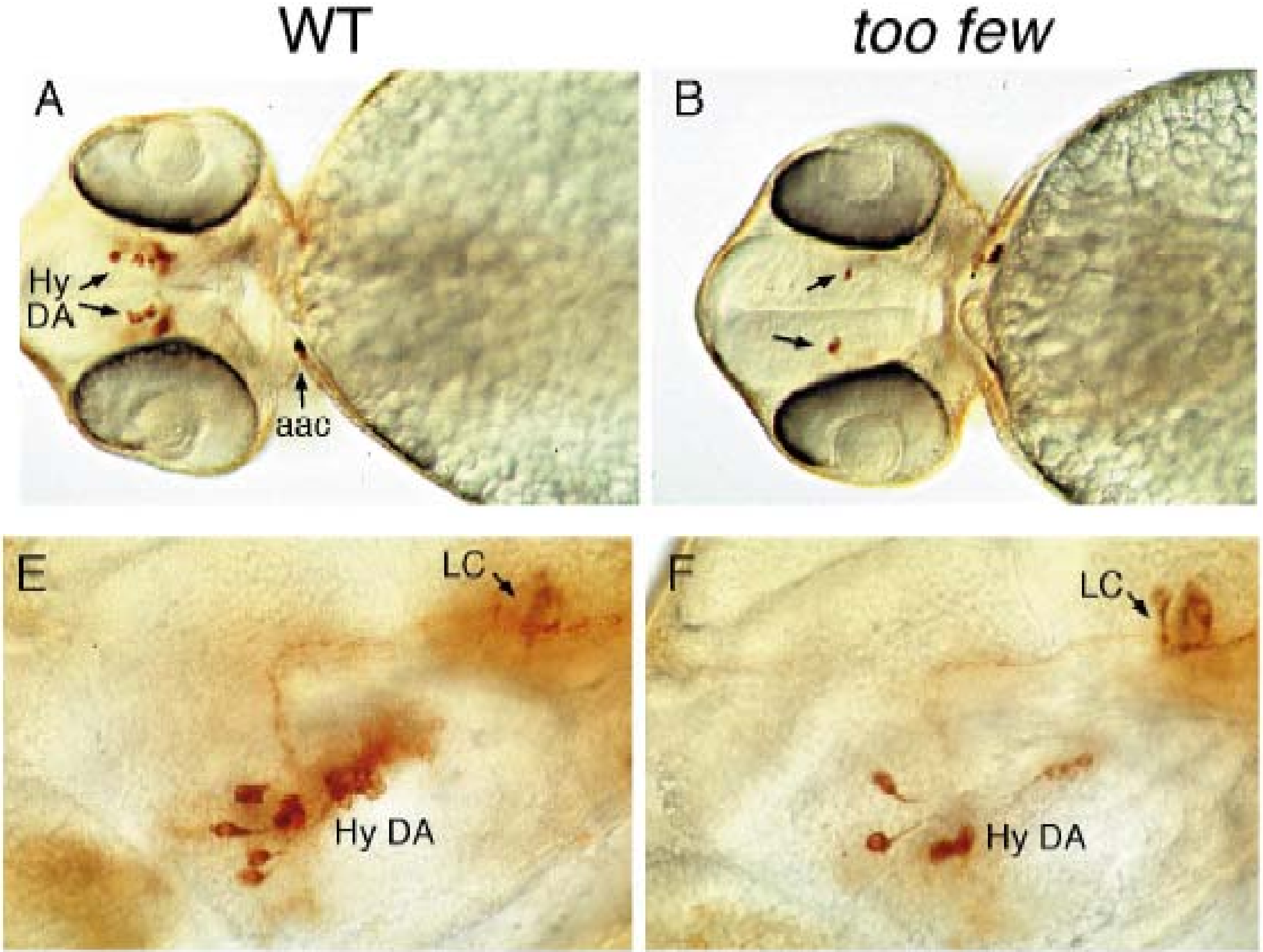


Dopamine system

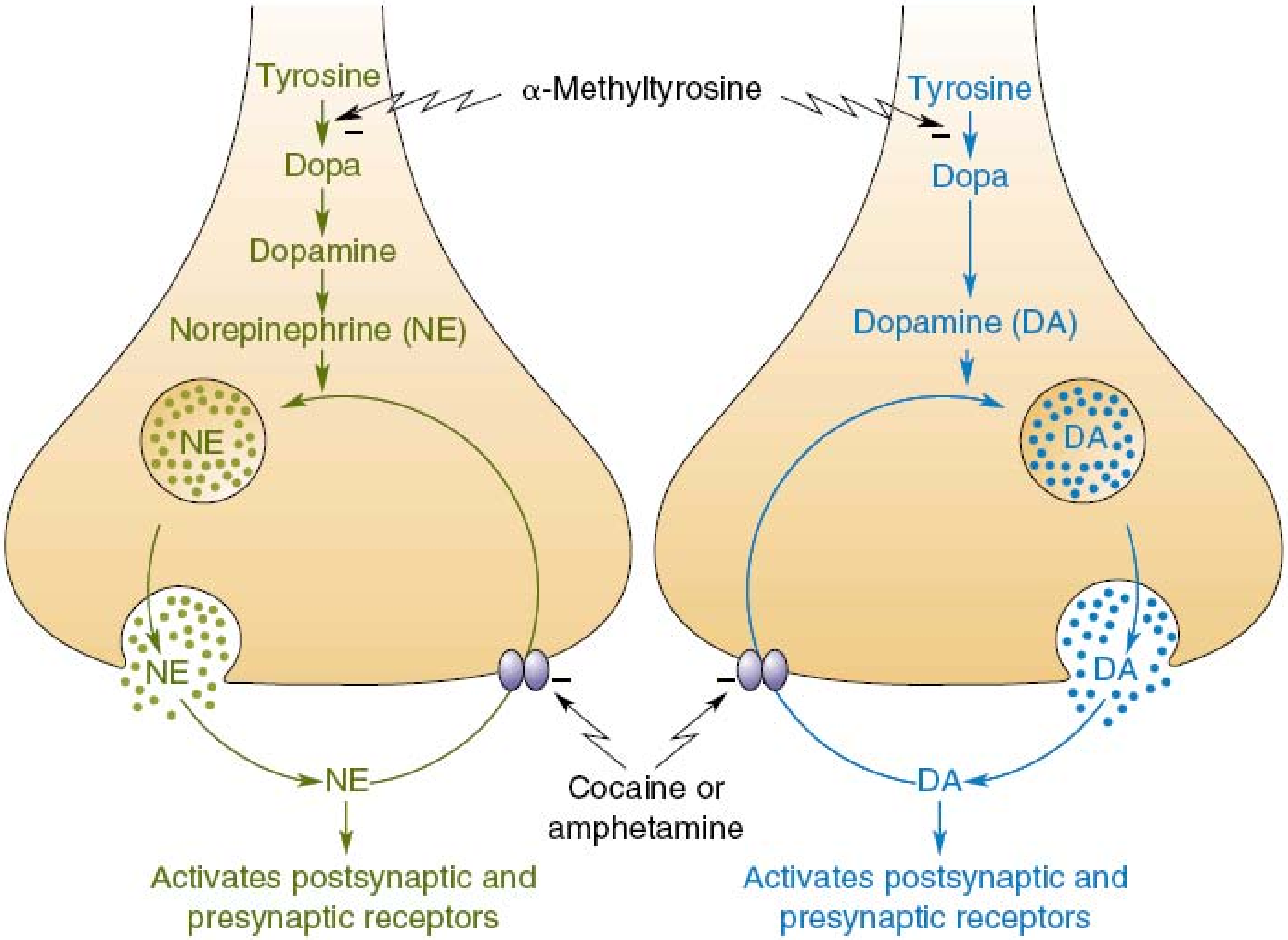


The synthesis of catecholamines from tyrosine



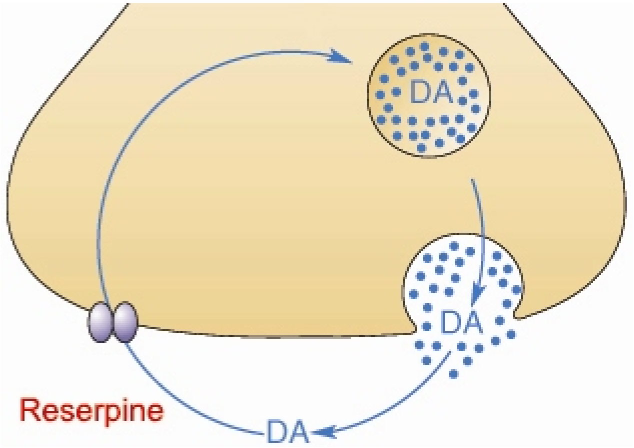

WT
too few
A
Hy
DA
aac
B
E
LC
Hy DA
F
LC
Hy DA

Catecholamine recycling is blocked by recreational drugs



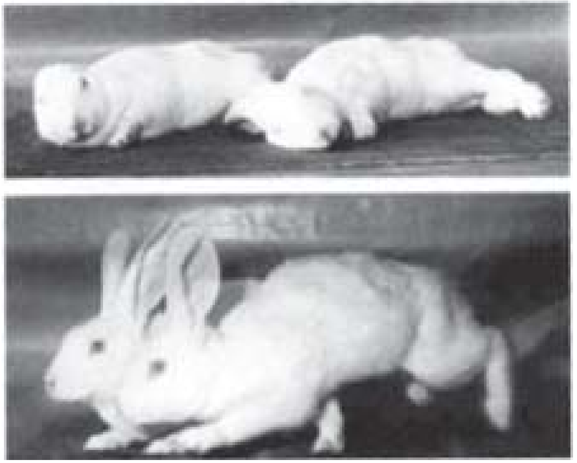
Dopamine as a neurotransmitter

Arvid Carlsson



Reserpine treatment causes catatonia

Indian snakeroot



Reviving reserpine-treated rabbits with L-Dopa

Summary of monoamines

1. The monoamines - serotonin, dopamine and norepinephrine - as well as acetylcholine, seem to perform broad modulatory functions within the brain

2. Monoaminergic and cholinergic neurons emanate from discrete nuclei in the brainstem and innervate most regions of the brain with long, diffuse projections

3. These transmitter systems predominantly act through metabotropic receptors, and therefore have a relatively slow effect, although there are exceptions, such as the nicotinic receptor and the 5-HT_3 receptor

4. Monoaminergic and cholinergic brain systems play important roles in Sleep, arousal, reward and mood.

5. Several degenerative diseases of the nervous system result from selective loss of one or more of these systems – Parkinson's disease (dopamine), Alzheimer's disease (acetylcholine)

6. Many recreational drugs, such as amphetamines, cocaine, LSD, ecstacy and nicotine, have their effects due to interference with monoamine transmitter systems

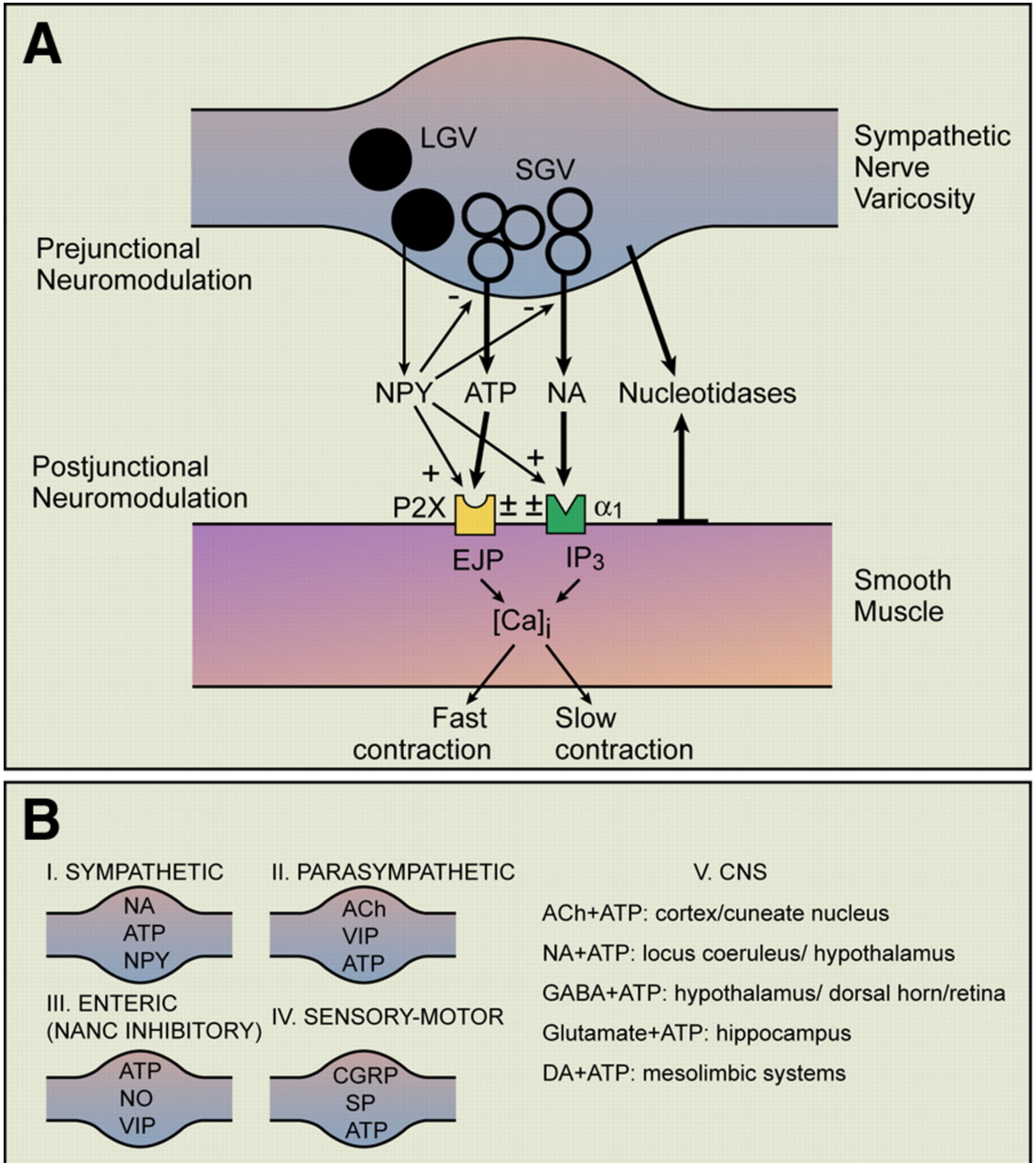
Co-transmission

Henry Dale

Dale's principle:

Each neuron uses one neurotransmitter and one transmitter only – a neuron can be defined by the transmitter it uses.

e.g. Noradrenergic, Cholinergic, Serotonergic, Dopaminergic.


A
LGV
SGV
Sympathetic
Nerve
Varicosity
Prejunctional
Neuromodulation
-
-
NPY
ATP
NA
Nucleotidases
Postjunctional
Neuromodulation
+
+
P2X
±
±
α_1
EJP
IP_3
$[Ca]_i$
Smooth
Muscle
Fast
contraction
Slow
contraction
B
I. SYMPATHETIC
NA
ATP
NPY
II. PARASYMPATHETIC
ACh
VIP
ATP
III. ENTERIC
(NANC INHIBITORY)
ATP
NO
VIP
IV. SENSORY-MOTOR
CGRP
SP
ATP
V. CNS
ACh+ATP: cortex/cuneate nucleus
NA+ATP: locus coeruleus/ hypothalamus
GABA+ATP: hypothalamus/ dorsal horn/retina
Glutamate+ATP: hippocampus
DA+ATP: mesolimbic systems

Endocannabinoids and pre-synaptic regulation