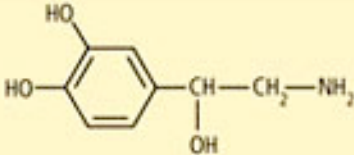
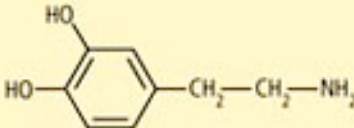
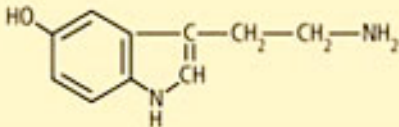
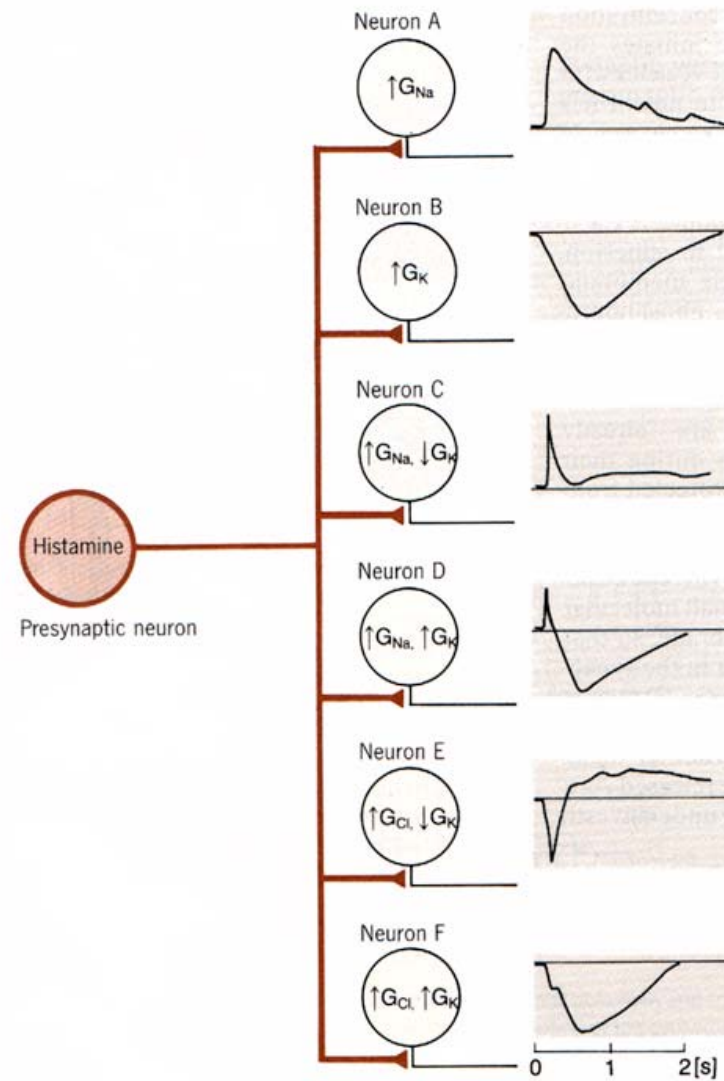
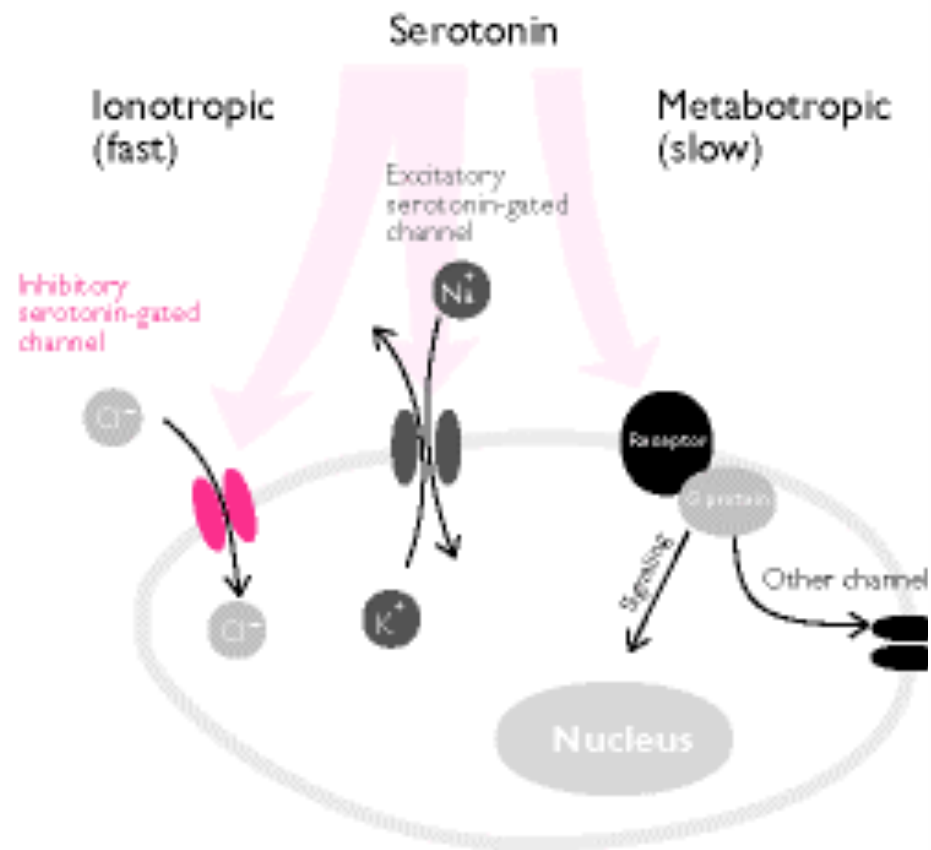


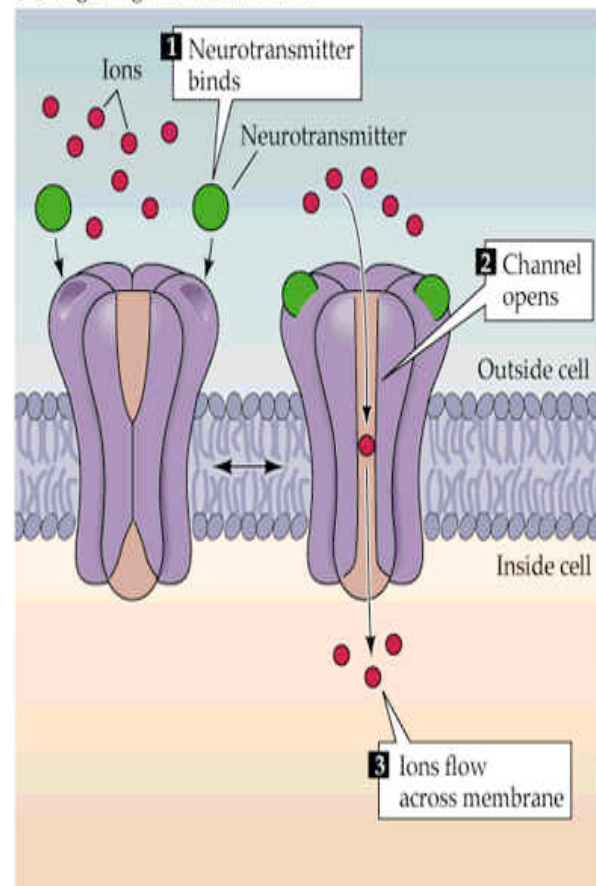
Table 48.1 Major Neurotransmitters

Neurotransmitter	Structure	Functional Class	Secretion Sites
Acetylcholine	$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}^+-(\text{CH}_3)_3$	Excitatory to vertebrate skeletal muscles; excitatory or inhibitory at other sites	CNS; PNS; vertebrate neuromuscular junction
Biogenic Amines			
Norepinephrine		Excitatory or inhibitory	CNS; PNS
Dopamine		Generally excitatory; may be inhibitory at some sites	CNS; PNS
Serotonin		Generally inhibitory	CNS
Amino Acids			
GABA (gamma aminobutyric acid)	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOH}$	Inhibitory	CNS; invertebrate neuromuscular junction
Glycine	$\text{H}_2\text{N}-\text{CH}_2-\text{COOH}$	Inhibitory	CNS
Glutamate	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{CH}_2-\text{CH}_2-\text{COOH} \\ \\ \text{COOH} \end{array}$	Excitatory	CNS; invertebrate neuromuscular junction
Aspartate	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{CH}_2-\text{COOH} \\ \\ \text{COOH} \end{array}$	Excitatory	CNS
Neuropeptides (a very diverse group, only two of which are shown)			
Substance P	Arg—Pro—Lys—Pro—Gln—Gln—Phe—Phe—Gly—Leu—Met	Excitatory	CNS; PNS
Met-enkephalin (an endorphin)	Tyr—Gly—Gly—Phe—Met	Generally inhibitory	CNS

Serotonin Is Gatekeeper of New Fast Recepto

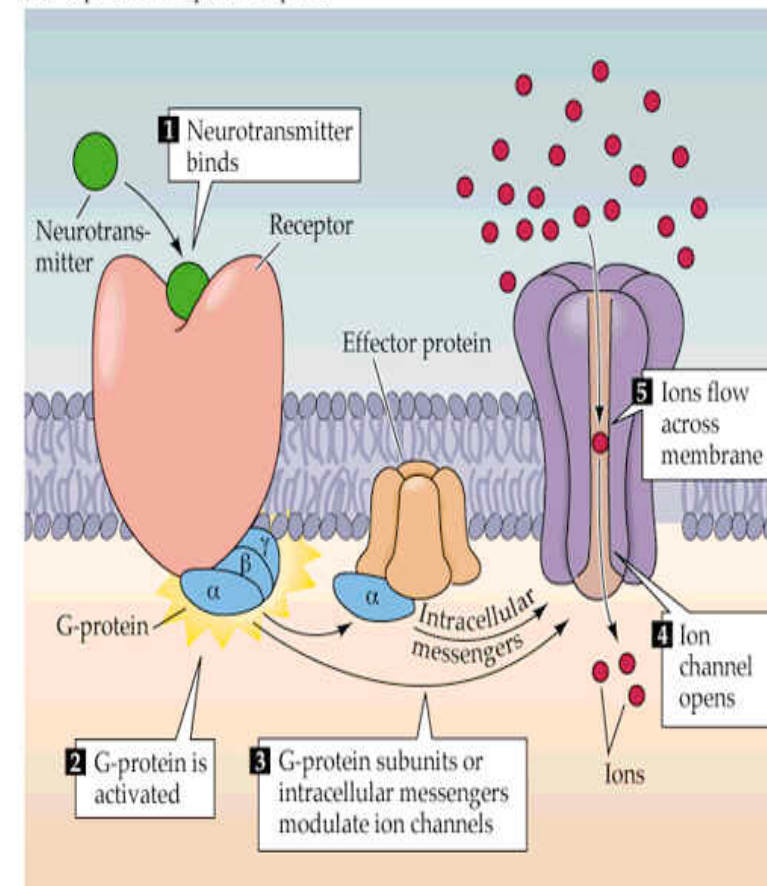


(A) Ligand-gated ion channels

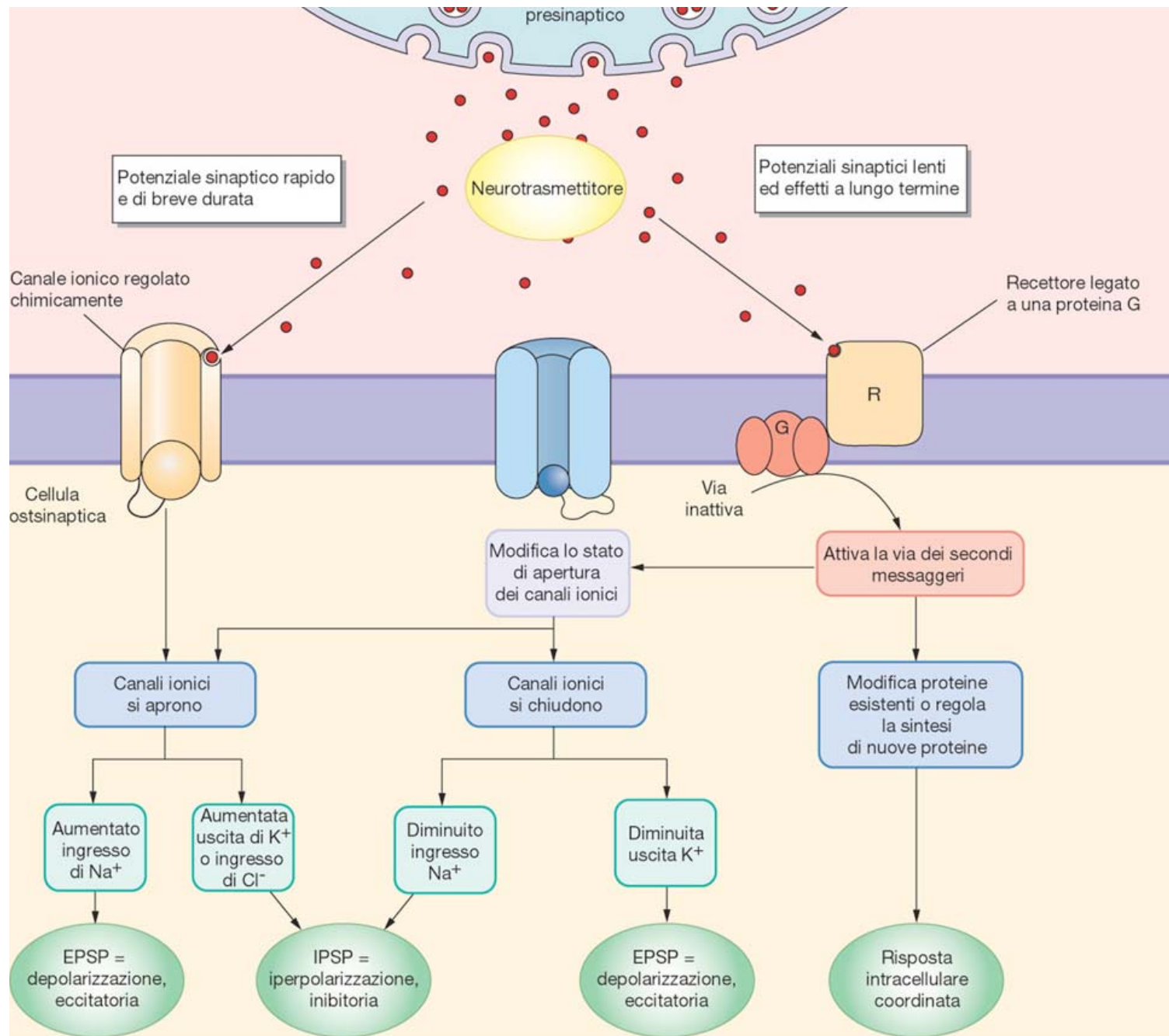


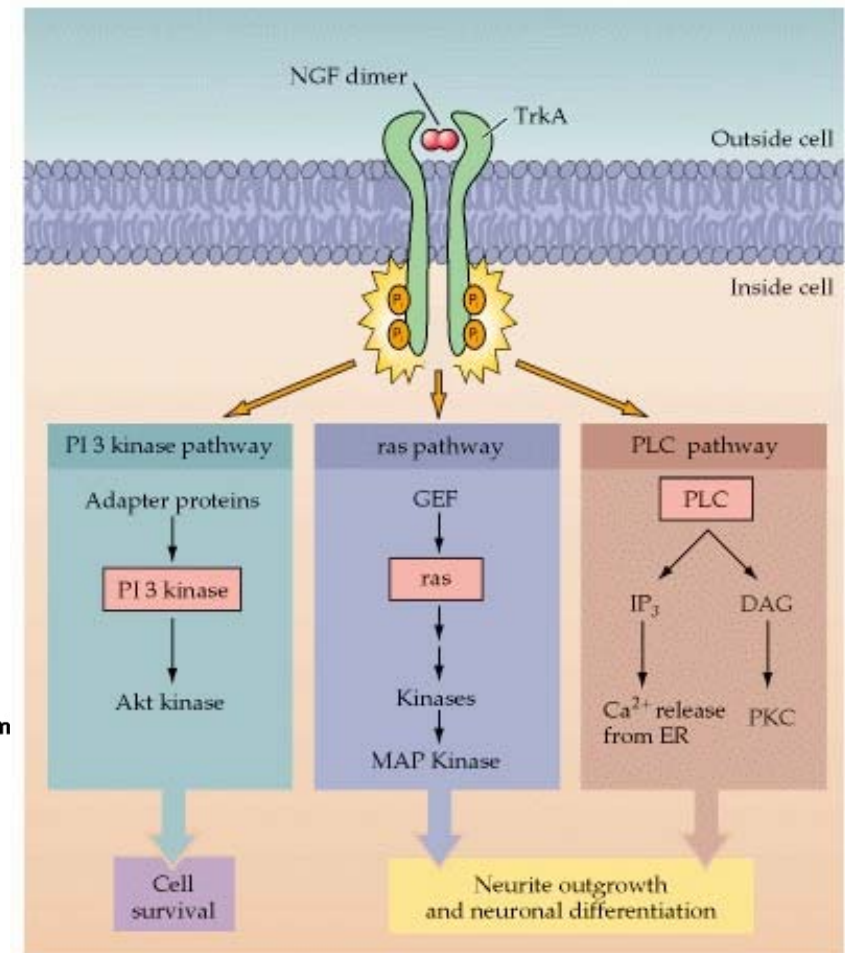
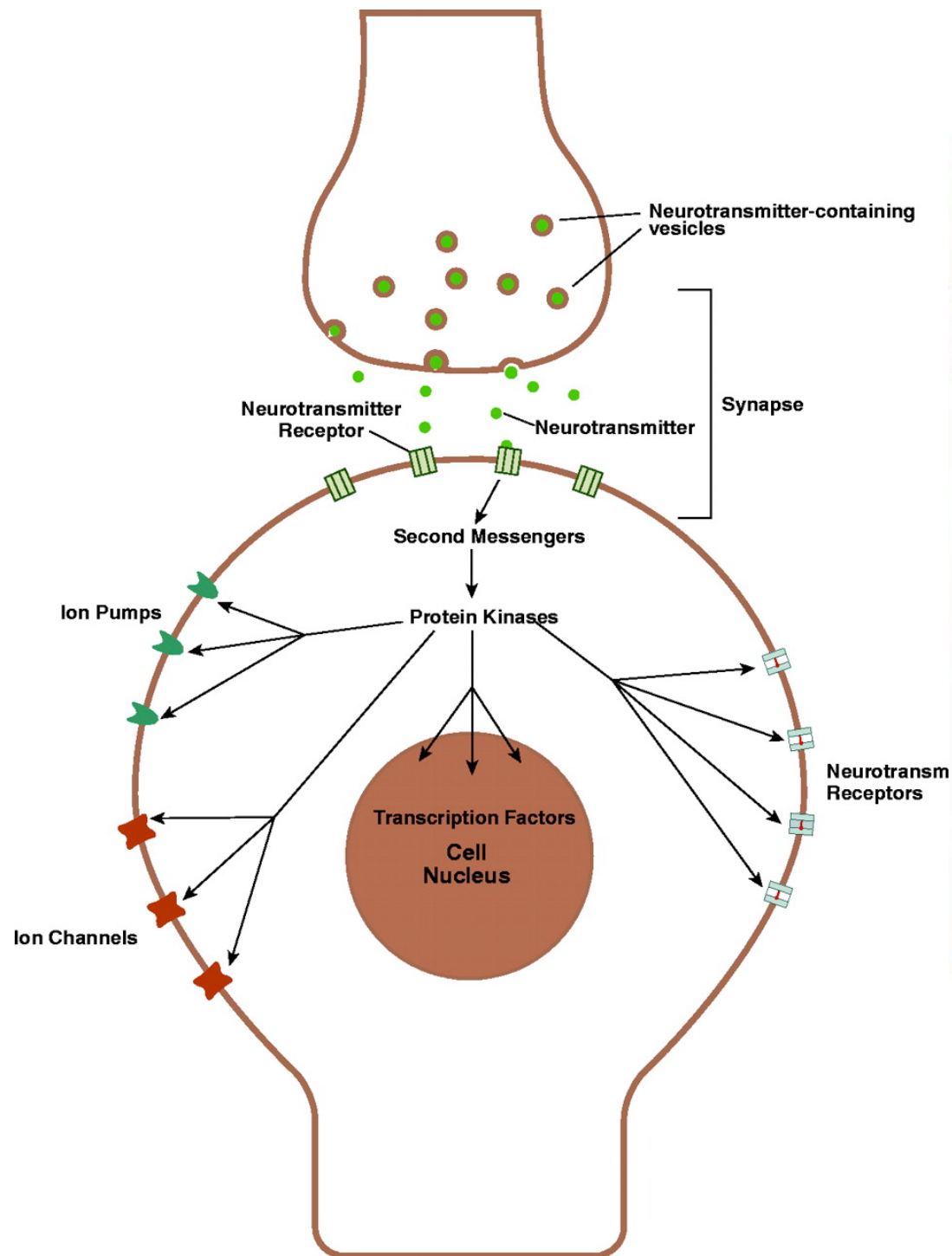
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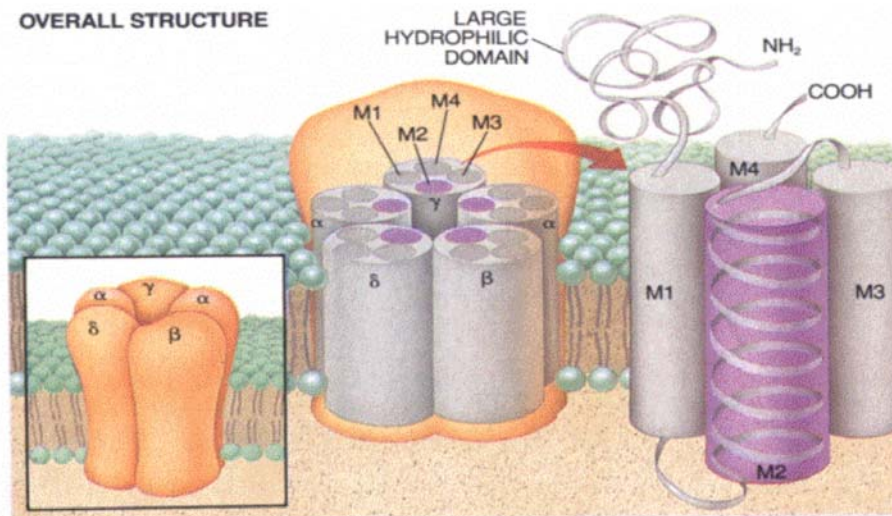
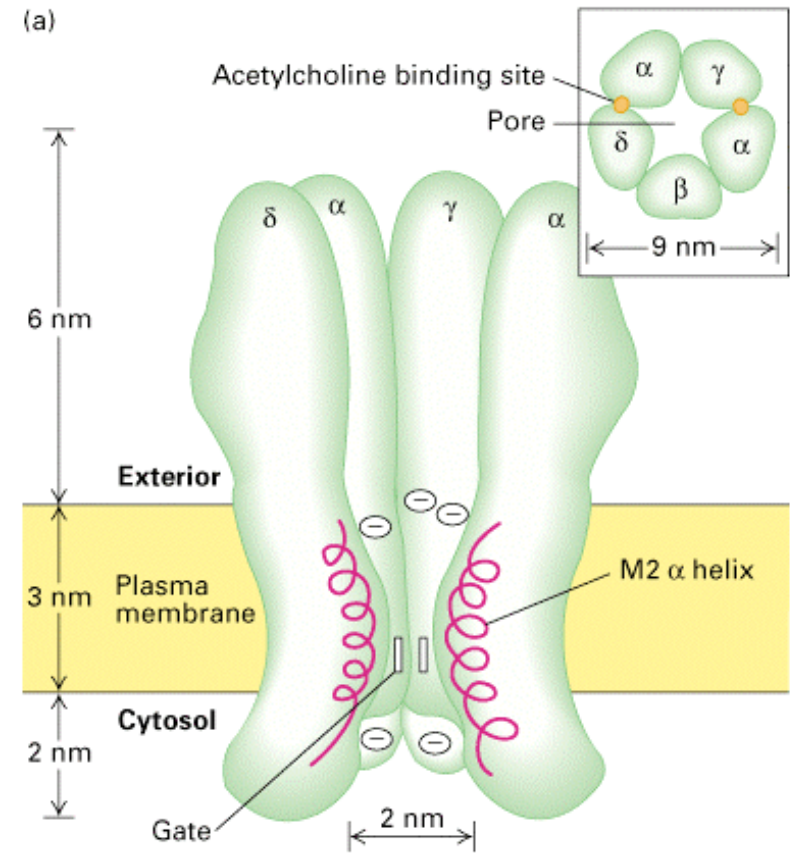
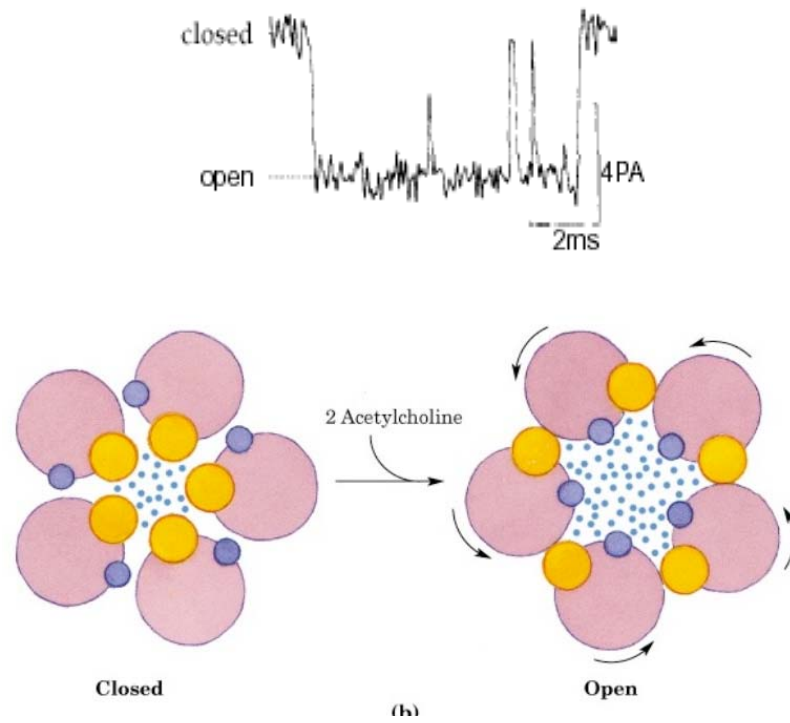
(B) G-protein-coupled receptors



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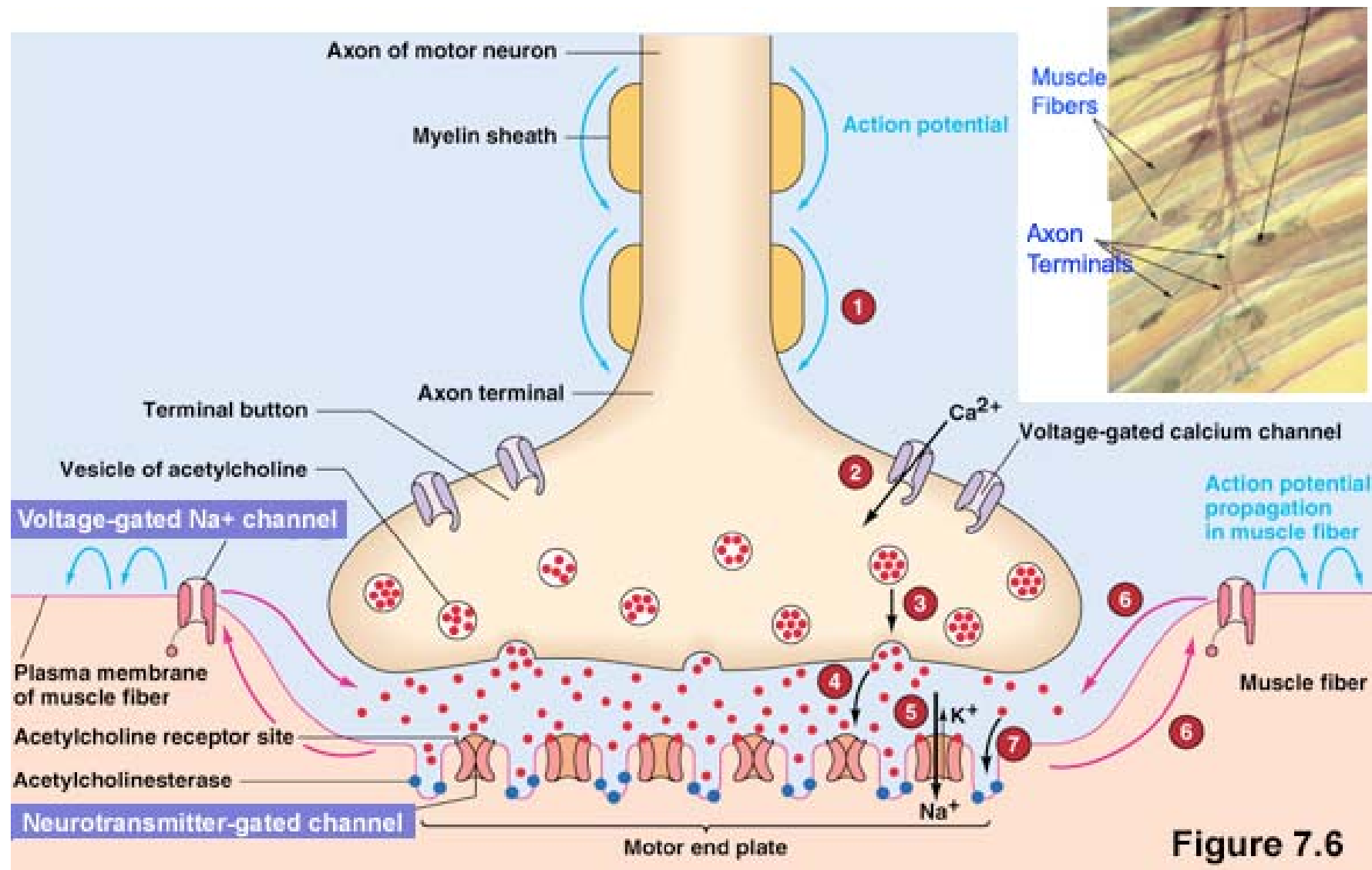


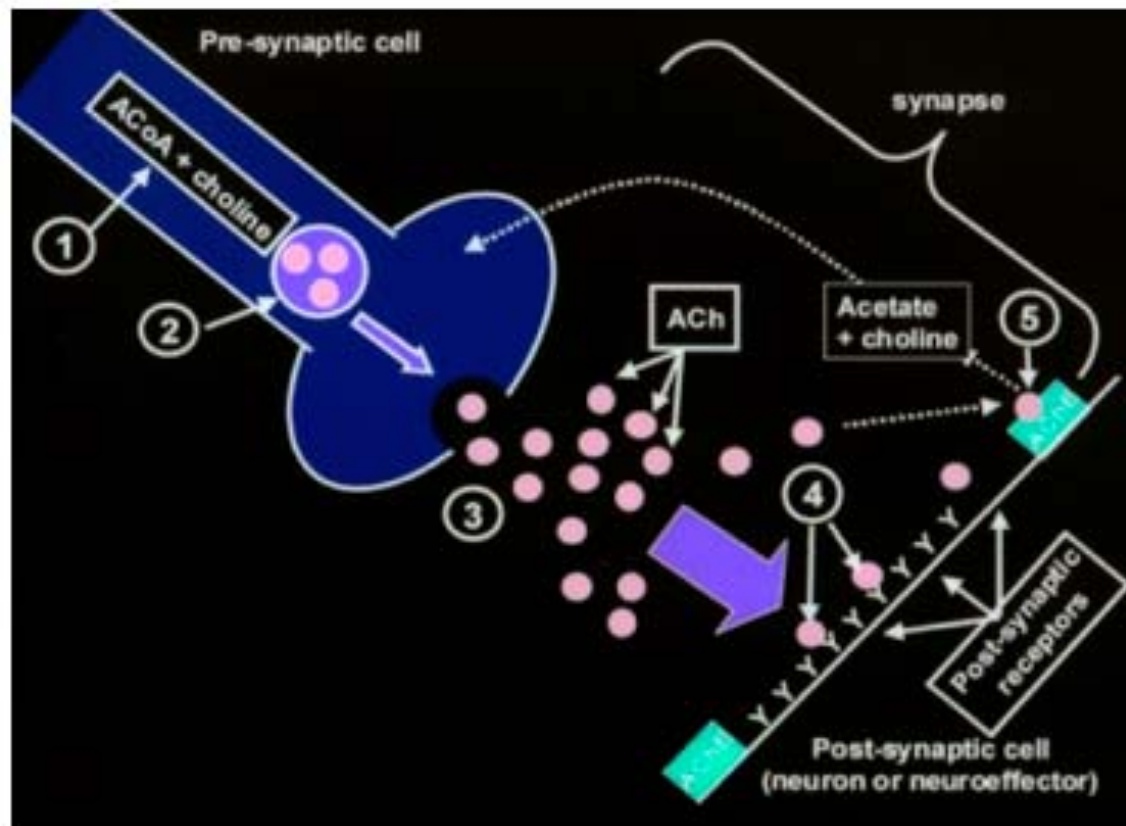
Figure 7.6

Acetylcholine is formed from two precursors:

choline: which is derived from dietary and intraneuronal sources

acetyl coenzyme: which is made from glucose in the mitochondria of neurons.

Acetylcholine is synthesized from choline and acetyl-CoA by the enzyme **choline acetyl transferase (ChAT)** to form acetylcholine, which is immediately stored in small vesicular compartments closely attached to the cytoplasmic side of presynaptic membranes. ChAT is a selective marker for cholinergic neurons.



Synthesis of acetylcholine (ACh)

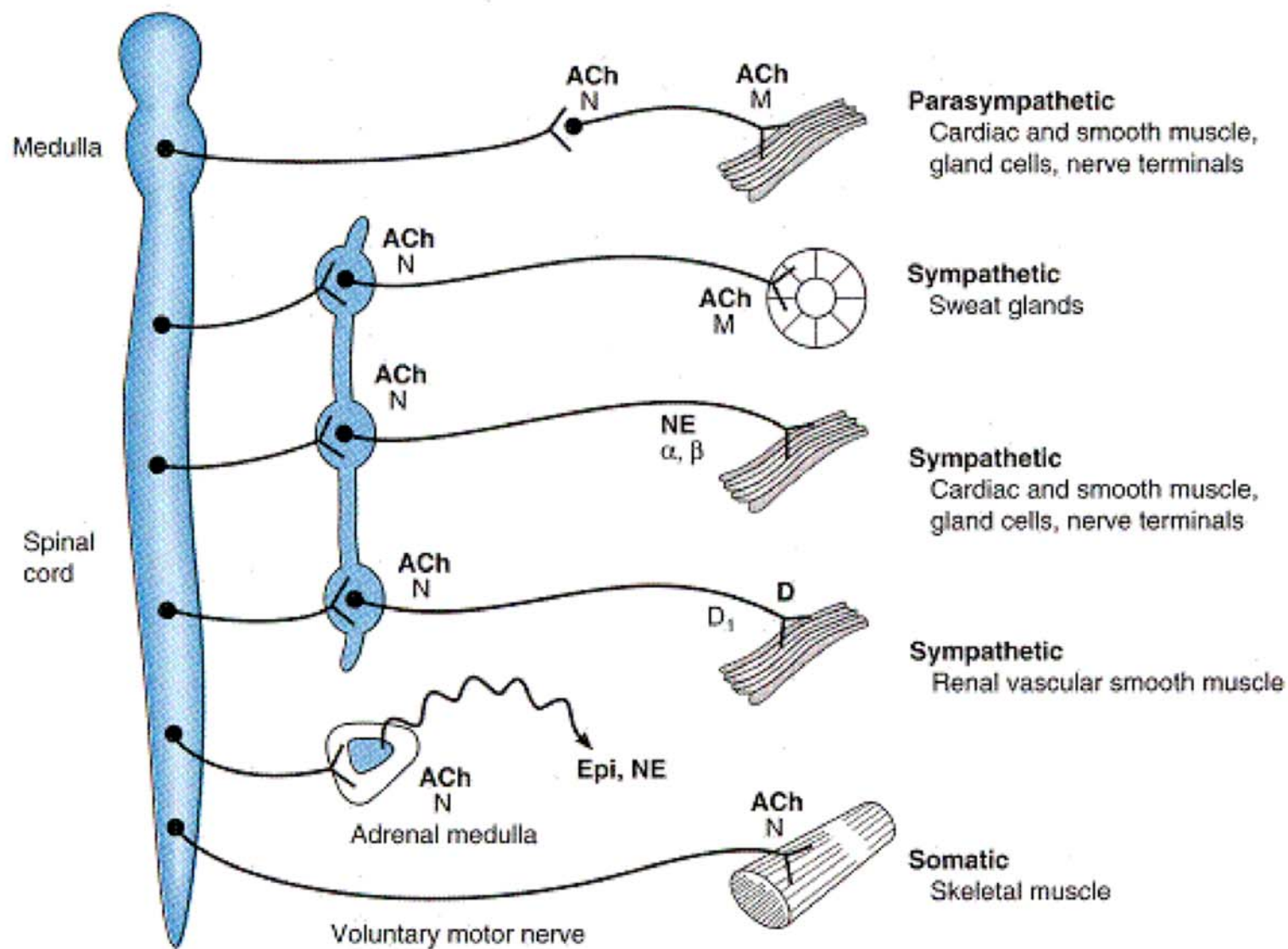
from **acetyl CoA** and **choline**

Storage of ACh in synaptic vesicles

Release of ACh (fusion of synaptic vesicle with presynaptic membrane and release of ACh into the synapse)

Action of ACh by binding to and activating receptors (**nicotinic** in *autonomic ganglia* and *neuromuscular junction* and, **muscarinic** in many sites)

Inactivation by enzymatic breakdown of ACh by **acetylcholinesterase (AChE)** located in the synapse. ACh is degraded in the synaptic cleft by **acetylcholinesterase** to **choline** and **acetate**.



Cholinergic projections in the brain:

The site of greatest acetylcholine synthesis in the brain is:

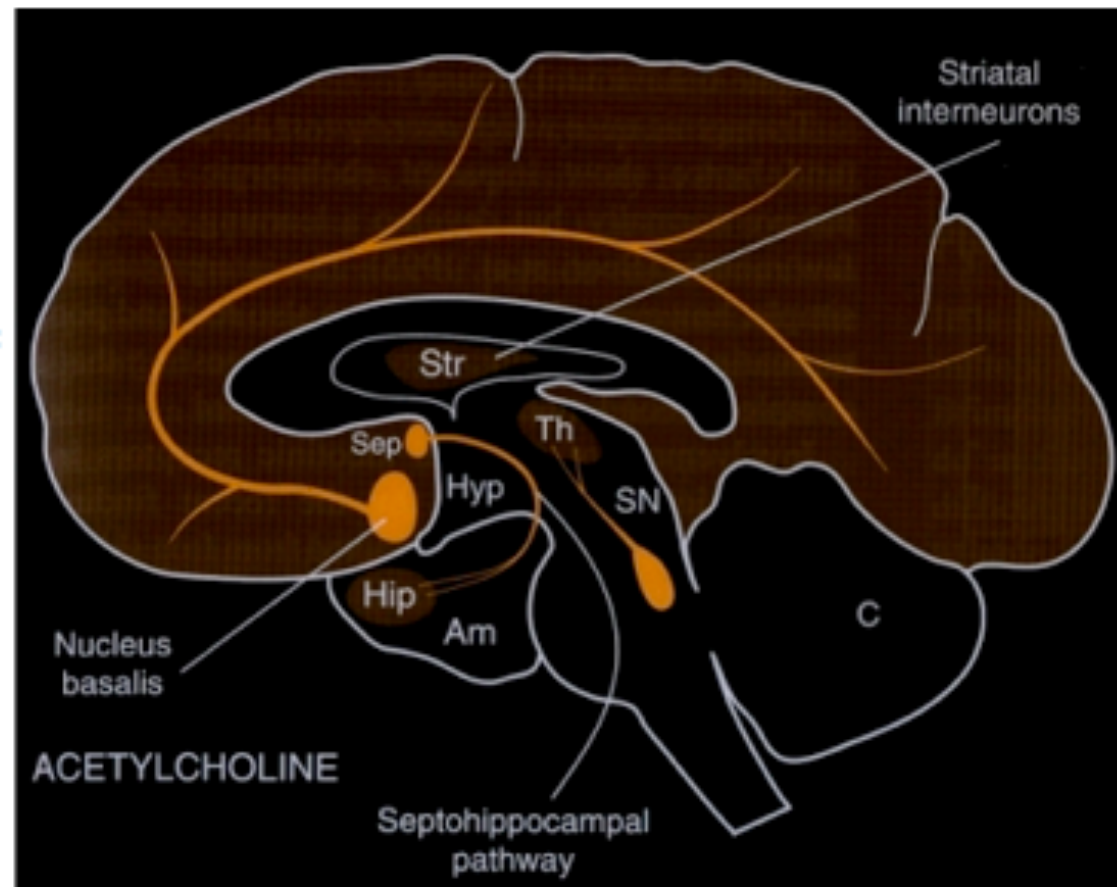
The *interpeduncular nucleus* (located near the *substantia nigra* in the *midbrain*).

All of the interneurons in the *striatum* (*caudate nucleus* and *putamen* of the *basal ganglia*) and the *nucleus accumbens* are cholinergic.

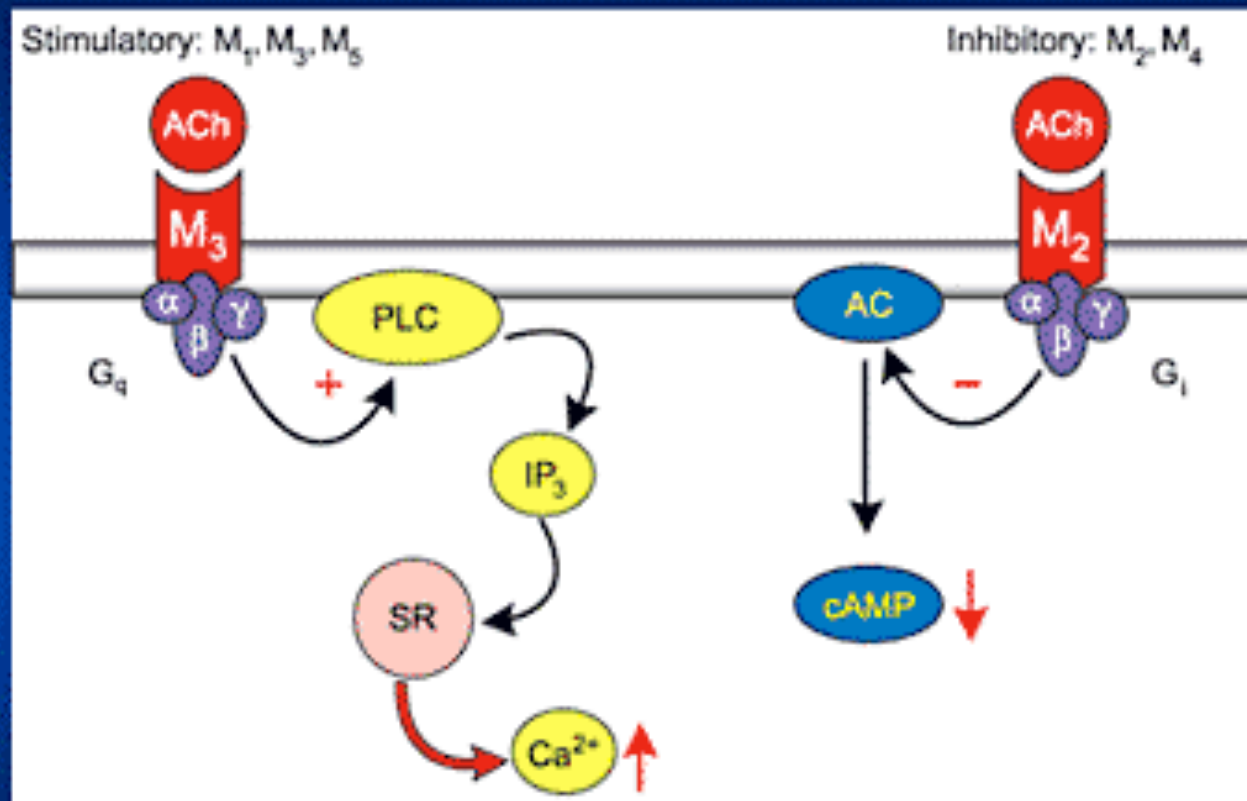
The *septum* provides cholinergic fibers to the *septal-hippocampal tract*.

The primary cholinergic input to the *cerebral cortex* comes from the *basal nucleus of Meynert*, which is the most prominent structure in the *substantia innominata* (ventral to the anterior half of the *globus pallidus*, and adjacent to the *hypothalamus*).

Meynert's nucleus also innervates the *basolateral amygdala*, the *basal ganglia* and the *reticular nucleus of the thalamus*.



Muscarinic Receptor Subtypes (M₁- M₅): Signal Transduction



PLC = phospholipase C; AC = adenylyl cyclase; SR = sarcoplasmic reticulum.

nervous system, and at synapses in several parts of the nervous system.

There are several receptors for Ach. The major distinction is between **muscarinic** and **nicotinic** receptors. Muscarinic receptors are dominant in the CNS.

Five muscarinic receptor subtypes, known as **M1–M5**, have been demonstrated and localized in the central nervous system (CNS). **Acetylcholine** has mainly excitatory effects but some muscarinic receptors are inhibitory.

Each receptor shares common features including specificity of binding for the agonists **acetylcholine** and **carbamylocholine** and the classical antagonists **atropine** and **quinuclidinyl benzilate**. All have a slow response time. Each receptor subtype couples to a second messenger system through an intervening **G-protein**. **M1**, **M3** and **M5** receptors stimulate **phosphoinositide** metabolism while **M2** and **M4** receptors inhibit **adenylate cyclase**. When activated, the final effect can be to open or close channels for K^+ , Ca^{++} , or Cl^- .

The tissue distribution differs for each subtype. **M1** receptors are found in the **forebrain**, especially in the **hippocampus** and **cerebral cortex**. **M2** receptors are found in the **heart** and **brainstem** while **M3** receptors are found in **smooth muscle**, **exocrine glands** and the **cerebral cortex**. **M4** receptors are found in the **neostriatum** and **M5** receptor mRNA is found in the **substantia nigra**, suggesting that **M5** receptors may regulate dopamine release at terminals within the **striatum**.

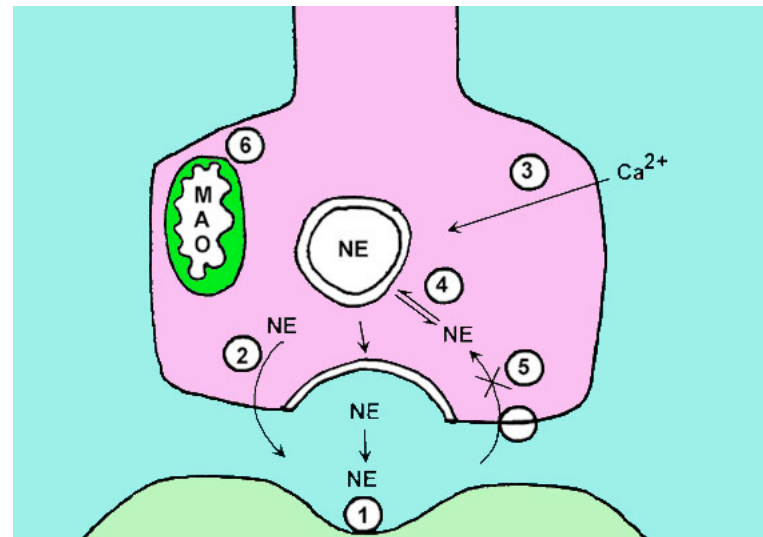
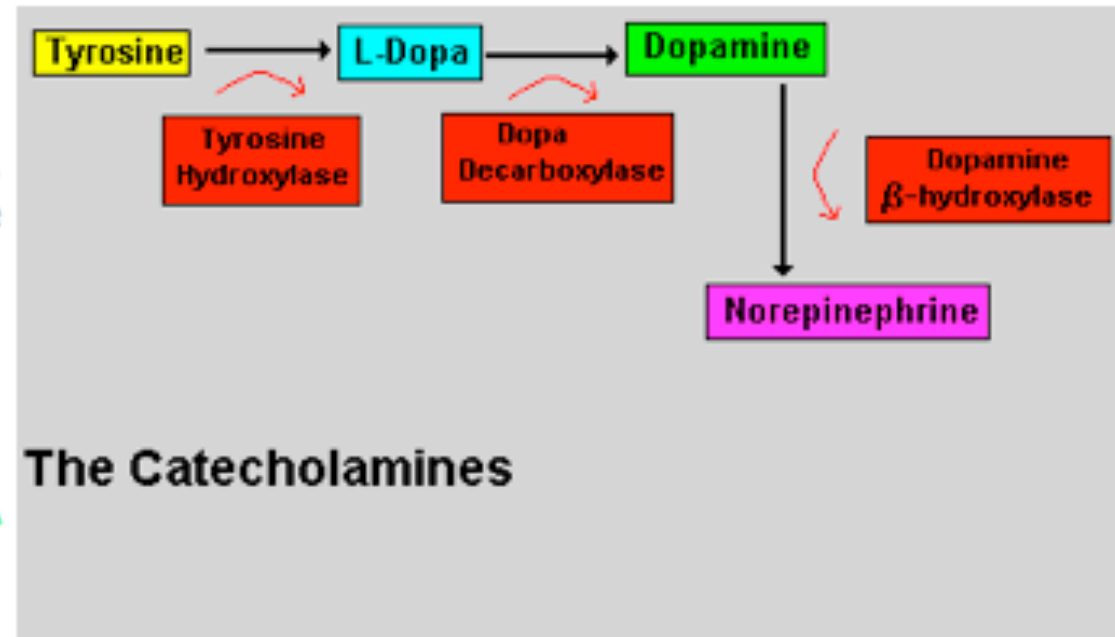
Activation of the **m1**, **m3**, and **m5** receptors causes cellular excitation, whereas activation of the **m2** and **m4** subtypes produces inhibitory effects.

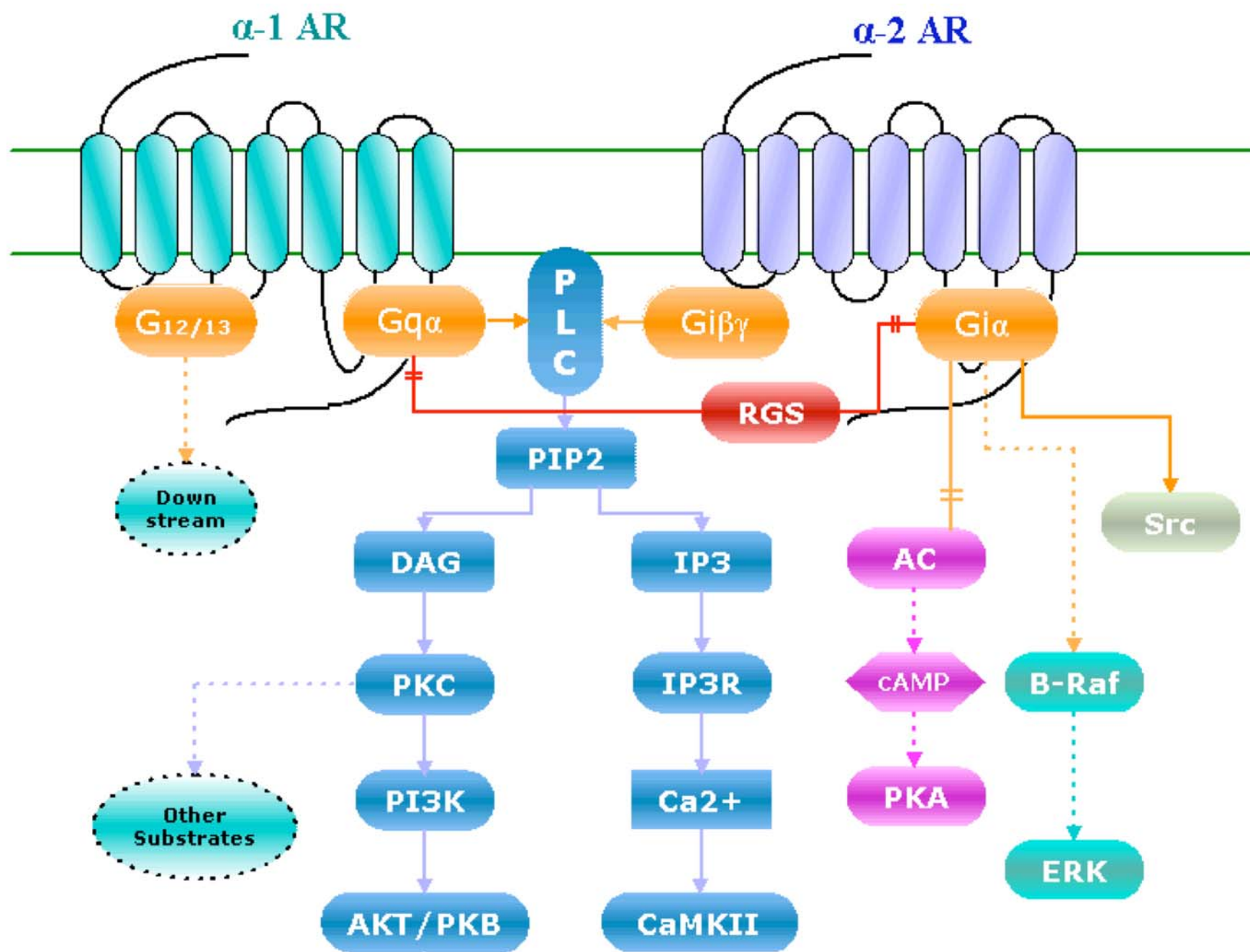
The muscarinic receptors in the brain are predominantly of the **M1** type. In the central nervous system, these receptors are blocked by muscarinic antagonists and stimulated by anticholinesterase.

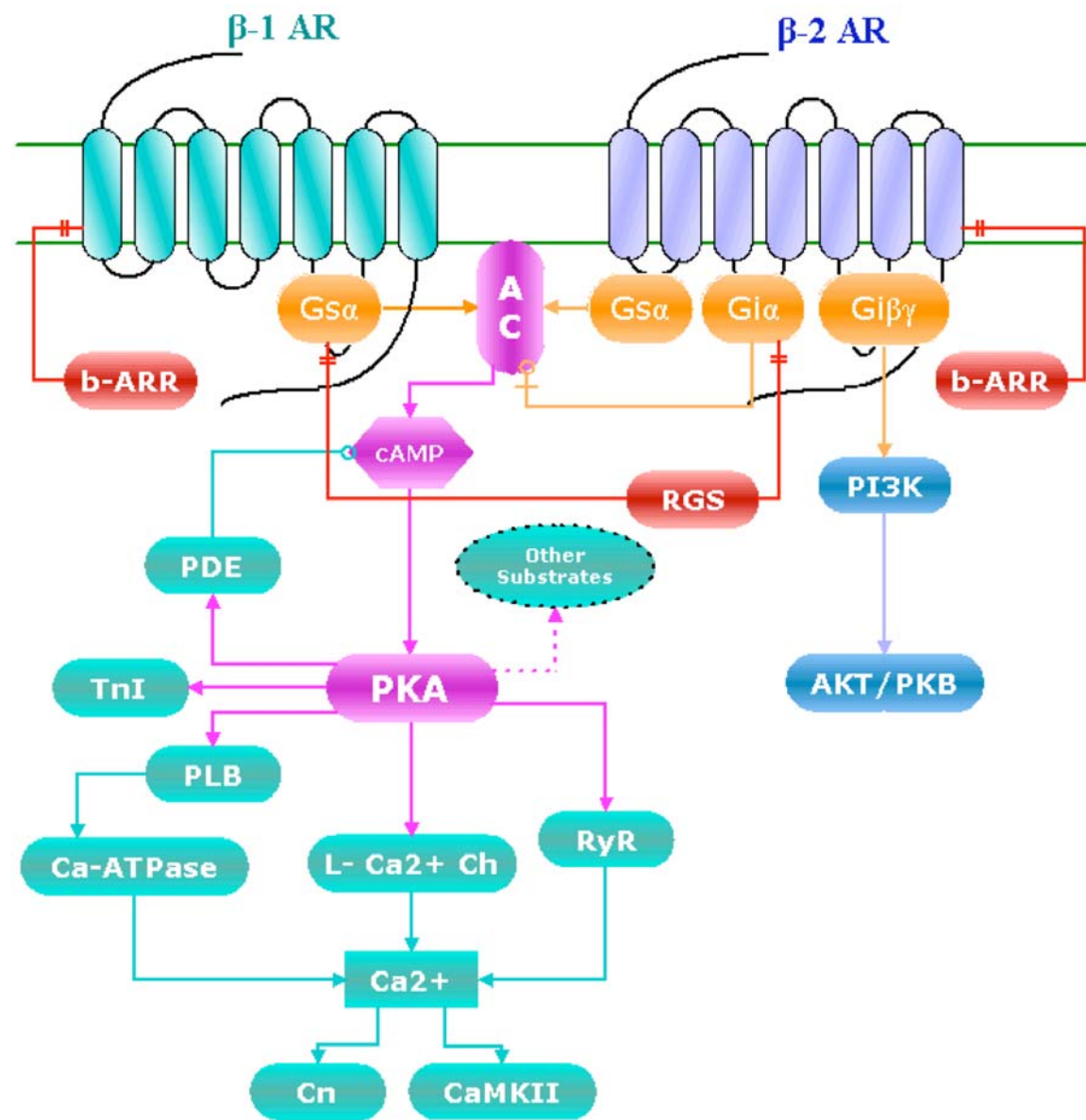
Noradrenaline biosynthesis:

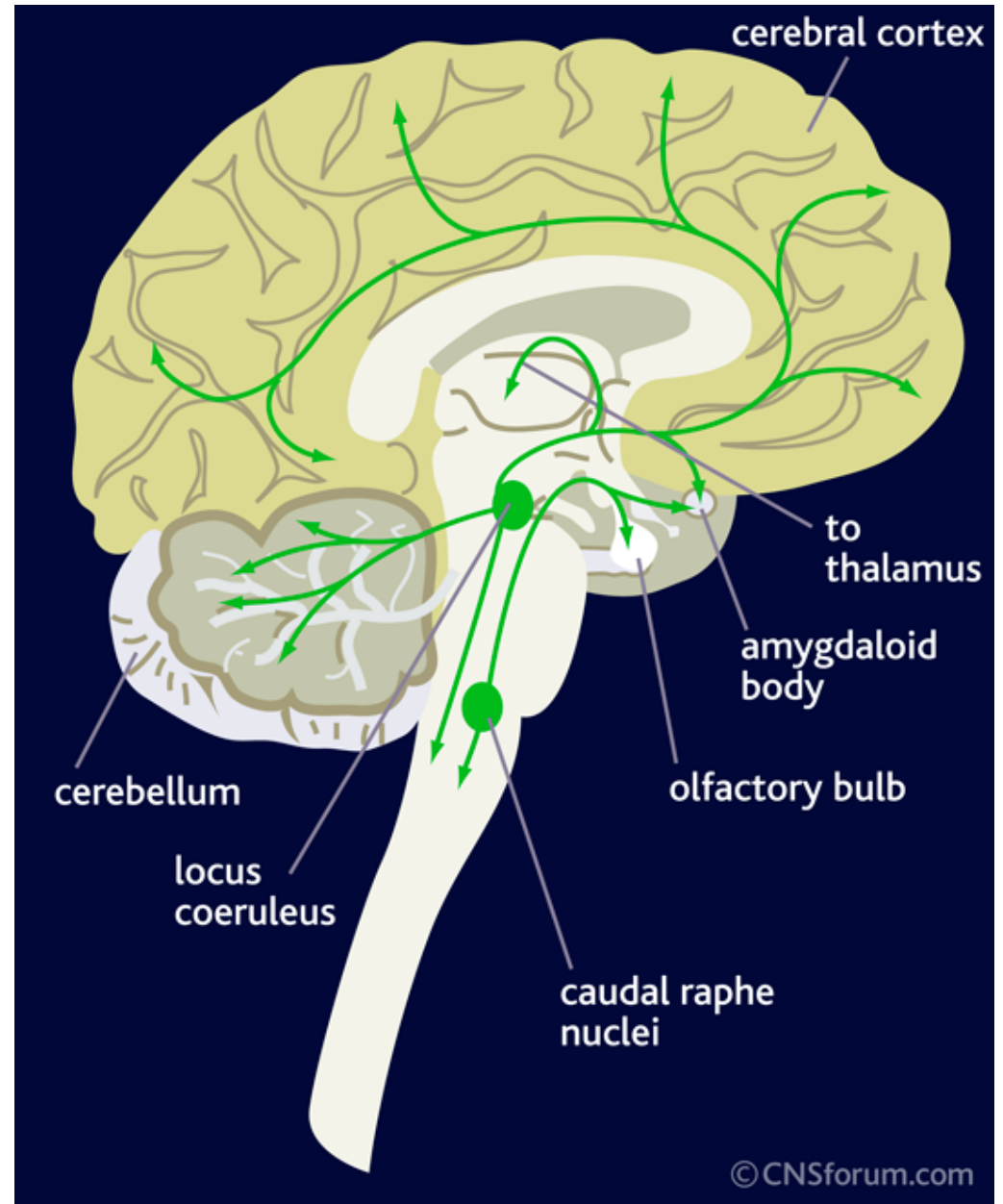
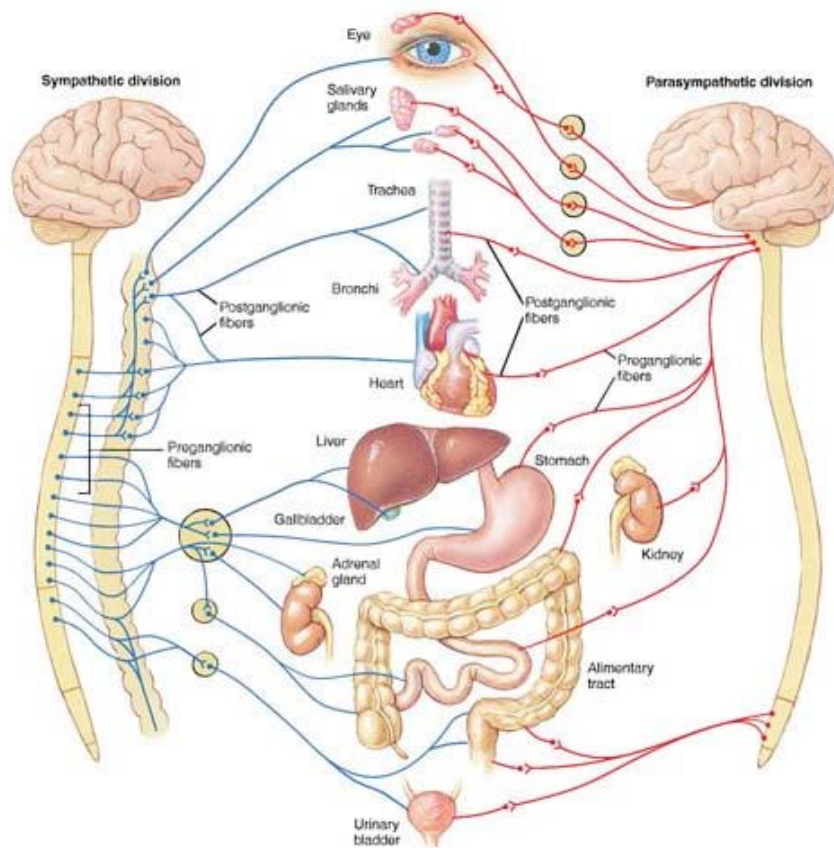
Noradrenaline is produced in noradrenergic neurons. The process starts with the amino acid precursor of NA, **Tyrosine**. Tyrosine is transported into the nervous system from the blood. Once tyrosine is inside the neuron, it undergoes transformation by the action of three enzymes in sequence:

Tyrosine hydroxylase converts the amino acid **tyrosine** into **DOPA**
DOPA decarboxylase converts **DOPA** into **Dopamine (DA)**.
Dopamine beta hydroxylase (DBH) converts **DA** into **NA**







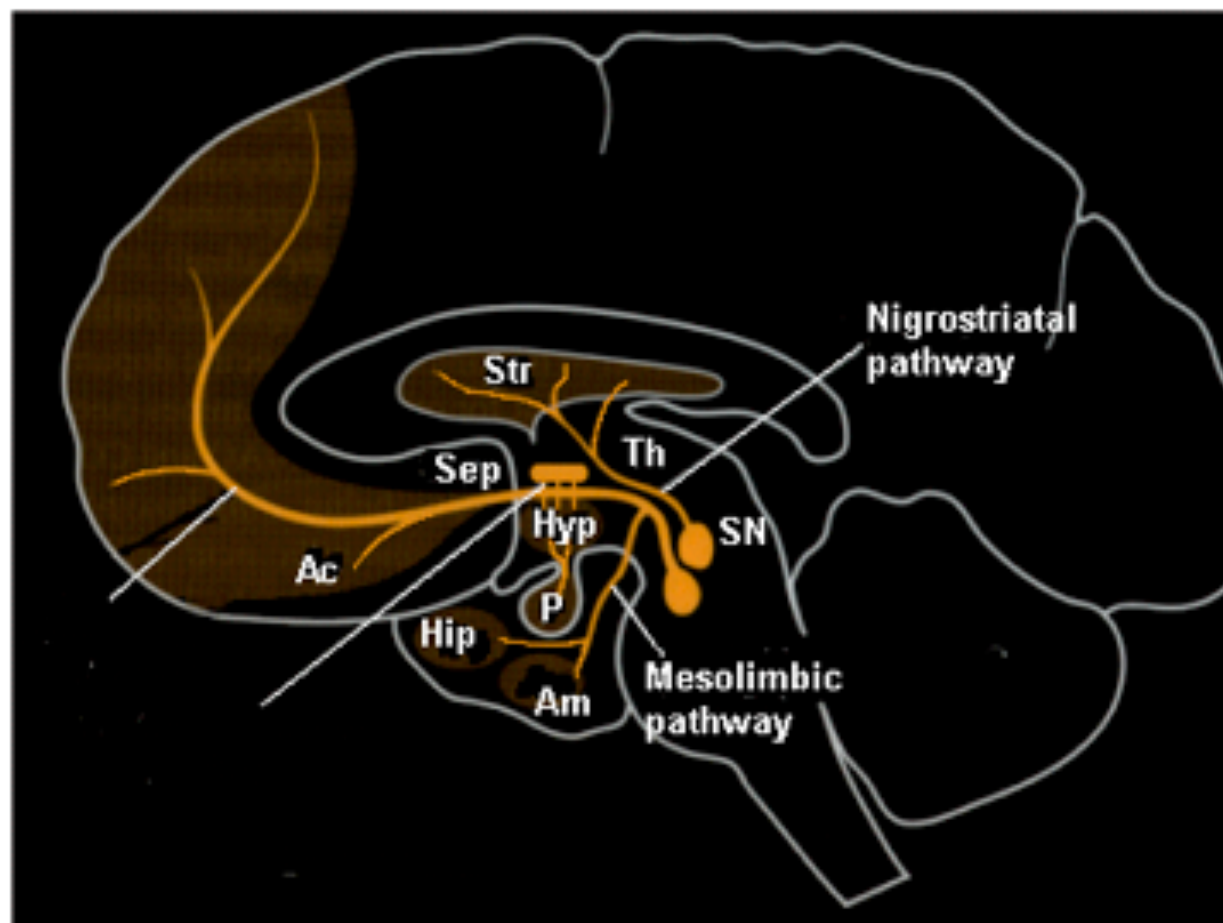


Nigrostriatal pathways: with cell bodies in the substantia nigra, terminating in the striatum. The fibers run the medial forebrain bundle along with many NA and 5HT containing fibers.

Mesolimbic/mesocortical pathways: whose cell bodies occur in groups in the midbrain and fibers projecting via the medial forebrain bundle to parts of the limbic system, especially the nucleus accumbens, the amygdaloid nucleus, and to the cortex.

Tuberohypophyseal system: is a group of short neurons running from the arcuate nucleus of the hypothalamus to the median eminence and pituitary gland.

others: There are many local DA interneurons in the olfactory cortex, medulla and in the retina.



Dopaminergic functions:

Motor control (nigrostriatal system): bilateral lesion of the substantia nigra in rats, destroys the nigrostriatal neuron, causes profound catalepsy. Animals with such lesion become so inactif that they die unless artificially fed.

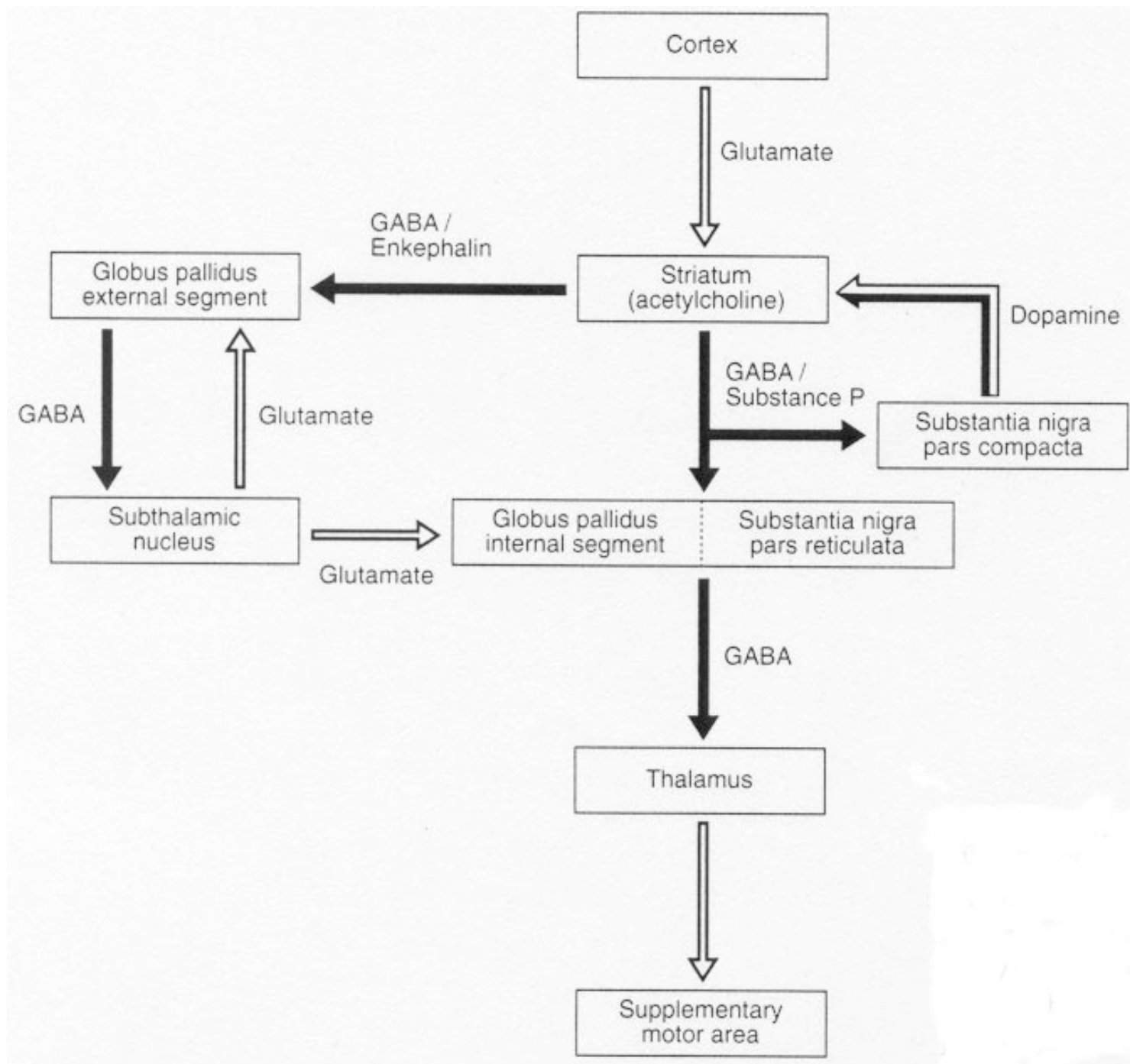
Unilateral lesions produced by 6-hydroxydopamine (6-OHDA) injection cause the animal to turn in circle toward the lesioned side because of imbalance of the DA in the striatum between the two sides of the brain.

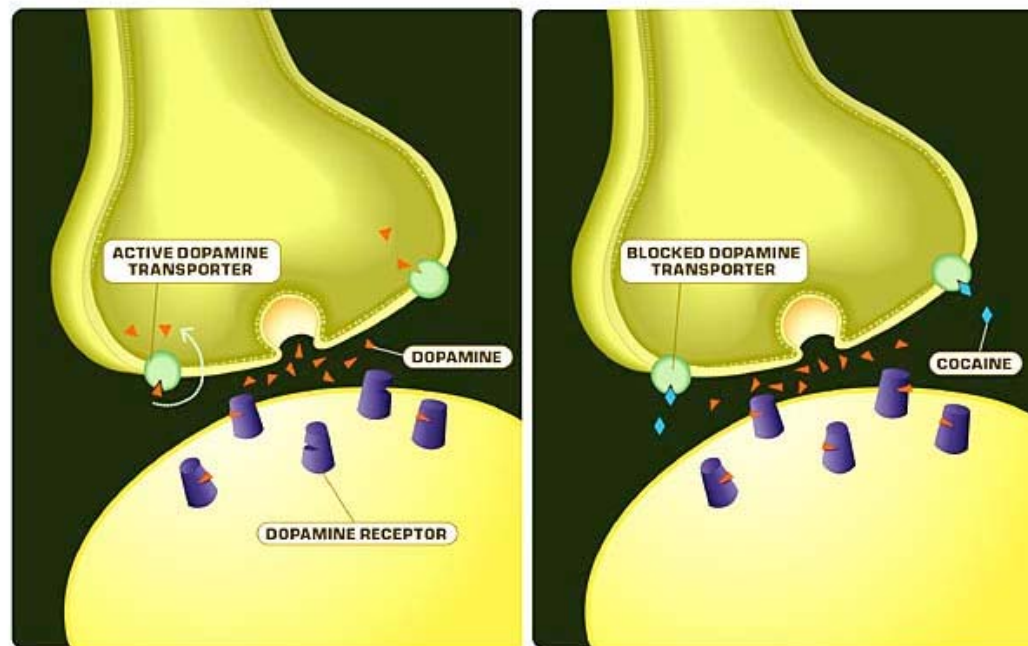
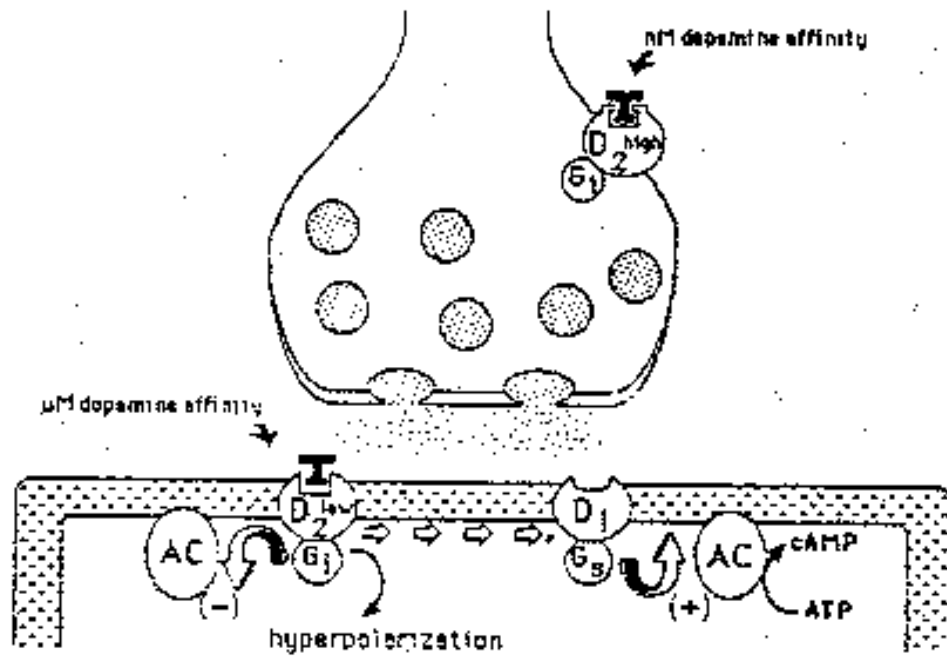
Unilateral injection of apomorphine (DA-like agonist) into the striatum causes circling away from the injected side.

Parkinson s Disease is associated with a deficiency of nigrostriatal dopaminergic neurons.

Behavioral effects: an excess of dopaminergic activity produced stereotyped behaviour patterns, and can be produced by dopamine-releasing agents such as amphetamine or doapmine agonists such as apomorphine.

Neuroendocrine: Hormone release from the anterior pituitary gland is regulated by DA, especially prolactin release (inhibted) and growth hormone release (stimulated).





Serotonin biosynthesis:

The biosynthesis of serotonin (5-HT) follows a pathway similar to that of noradrenaline, except that the precursor is tryptophan instead of tyrosine.

5-HT is formed from dietary tryptophan which is converted to 5-hydroxytryptophan by *tryptophan hydroxylase* (an enzyme confined to 5-HT producing cells).

5-hydroxytryptophan can cross the blood brain barrier to increase central levels of 5-HT.

The 5-hydroxytryptophan is then decarboxylated to 5-HT by the same amino acid that participates in the synthesis of catecholamines and histamine, *L-aromatic acid decarboxylase* (*dopa decarboxylase*).

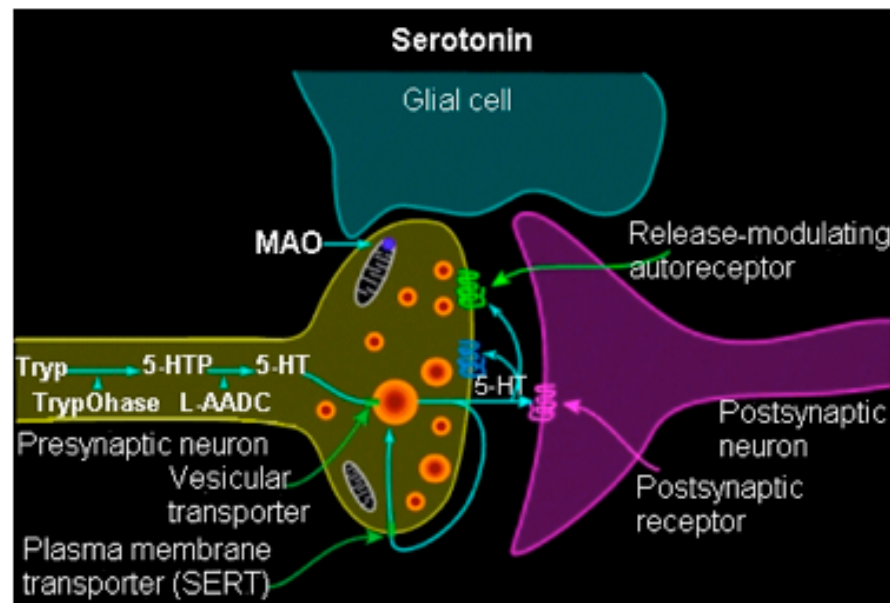
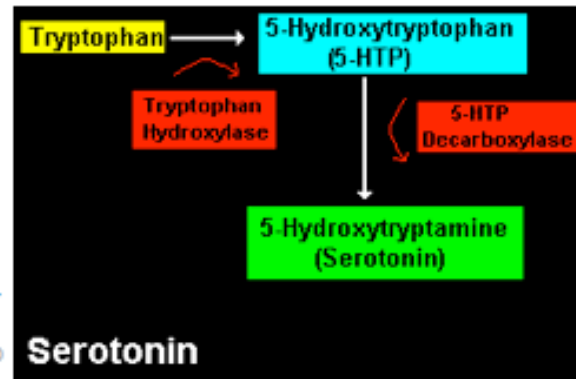
Tryptophan hydroxylase can be selectively and irreversibly inhibited by *p-chlorophenylalanine* (PCPA).

After release 5-HT is recovered by neuronal uptake.

Tricyclic anti-depressants that inhibit catecholamines block the neuronal uptake mechanisms of 5-HT.

SSRIs are *selective serotonin reuptake inhibitors* and constitute an important group of anti-depressants and anxiolytics.

5-HT is degraded almost entirely by MAO which converts it to 5-hydroxyindole acetaldehyde, most of which is dehydrogenated to form 5-hydroxyindole acetic acid (5-HIAA) which is excreted in urine.



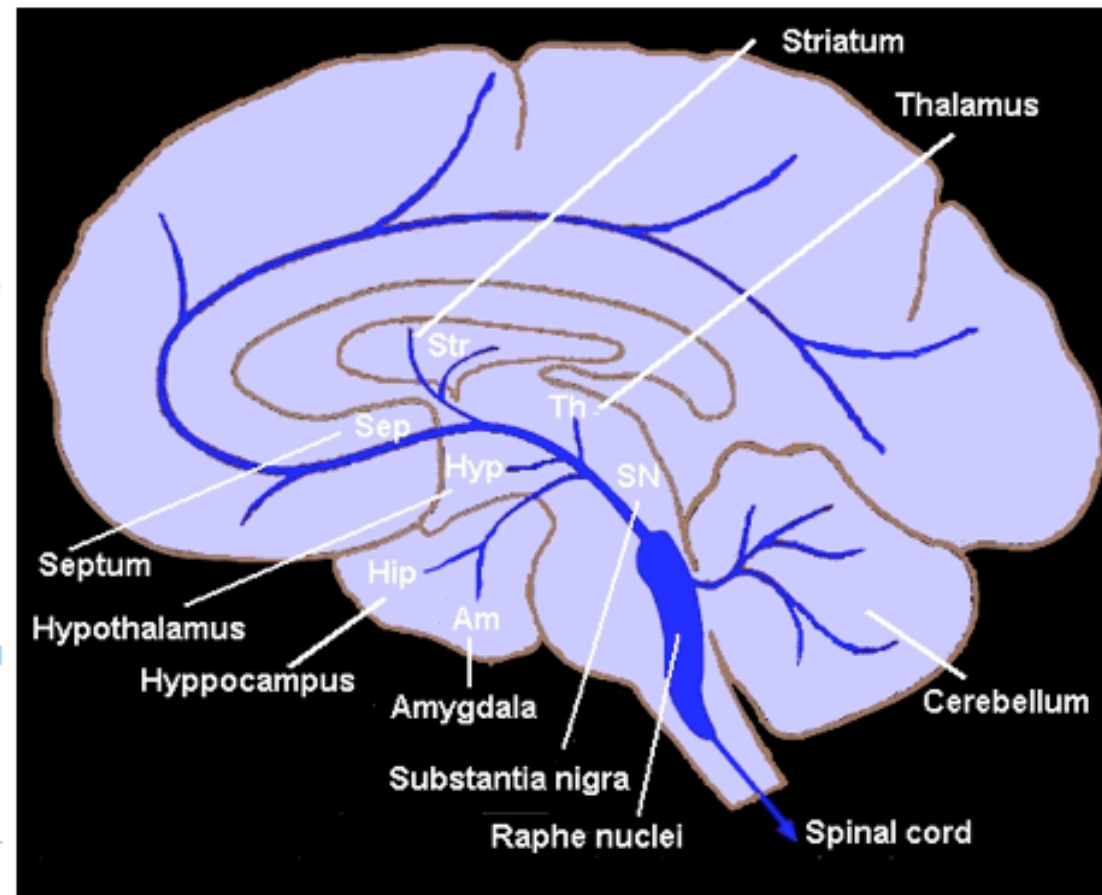
Serotonergic
projections in the
brain:

5-HT
neurotransmitter
neurons occur in
several large nuclei
in the pons and
upper medulla,
often called **raphe**
nuclei.

The caudal nucleus
of the raphe
projects largely to
the cerebellum, the
medulla and spinal
cord for the
regulation of pain
perception.

The rostral nucleus
of the raphe
projects via the
medial forebrain
bundle to many
parts of the cortex,
hippocampus, basal
ganglia, limbic
system and
hypothalamus.

In the limbic
system, 5-HT is co-
localized with
norepinephrine
receptors -- and
the two
transmitters seem
to work in
conjunction in the
regulation of
arousal.



Serotonin receptors and functions:

There are several 5-HT receptors and multiple subtypes. The main receptor subtypes in the CNS are: 5HT1A, 5HT1B, 5HT1D, 5HT2, 5HT3.

5HT1A receptors are expressed as autoreceptors by the 5-HT neurons in the raphe nuclei. They are widely distributed in the cortex and amygdala. They are the main target of drugs used to treat anxiety and depression.

5-HT2 receptors exert an excitatory post-synaptic effect and are abundant in the cortex and hippocampus. They are the target of hallucinogenic drugs. LSD inhibits the firing of 5-HT neurons in the raphe nuclei, apparently by acting as an agonist on the inhibitory autoreceptors of these cells.

Serotonin pathways are associated with:

- hallucinatory behavior, wet-dog shake
- feeding behavior
- control of mood and emotion
- control of sensory pathways, including nociception
- control of body temperature
- vomiting
