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9.98 Neuropharmacology
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Neurotransmitter systems

Glutamate and GABA

Dopamine

Noradrenaline

Acetylcholine

Serotonin

Catecholamines are synthesized in a multi-step process

Catecholamines:

Dopamine (DA)

Norepinephrine (NE)

Epinephrine (EPI)

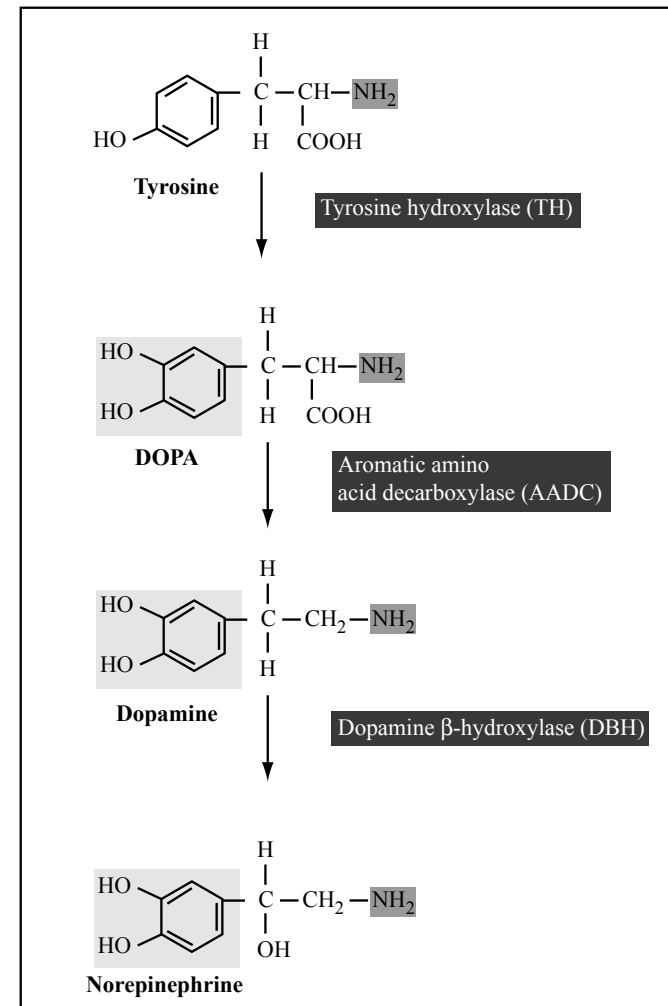


Figure by MIT OpenCourseWare.

The rate-limiting enzyme is TH, which is regulated by the product (feedback) and by stress (up-regulated).

Dopamine vesicular release

Vesicles are loaded with catecholamines by the enzyme Vesicular Monoamine Transporter (VMAT).

VMATS are blocked by the drug **Reserpine** which causes sedation in animals and depressive symptoms in humans

Catecholamine release is inhibited by autoreceptors located on dopaminergic and noradrenergic neurons

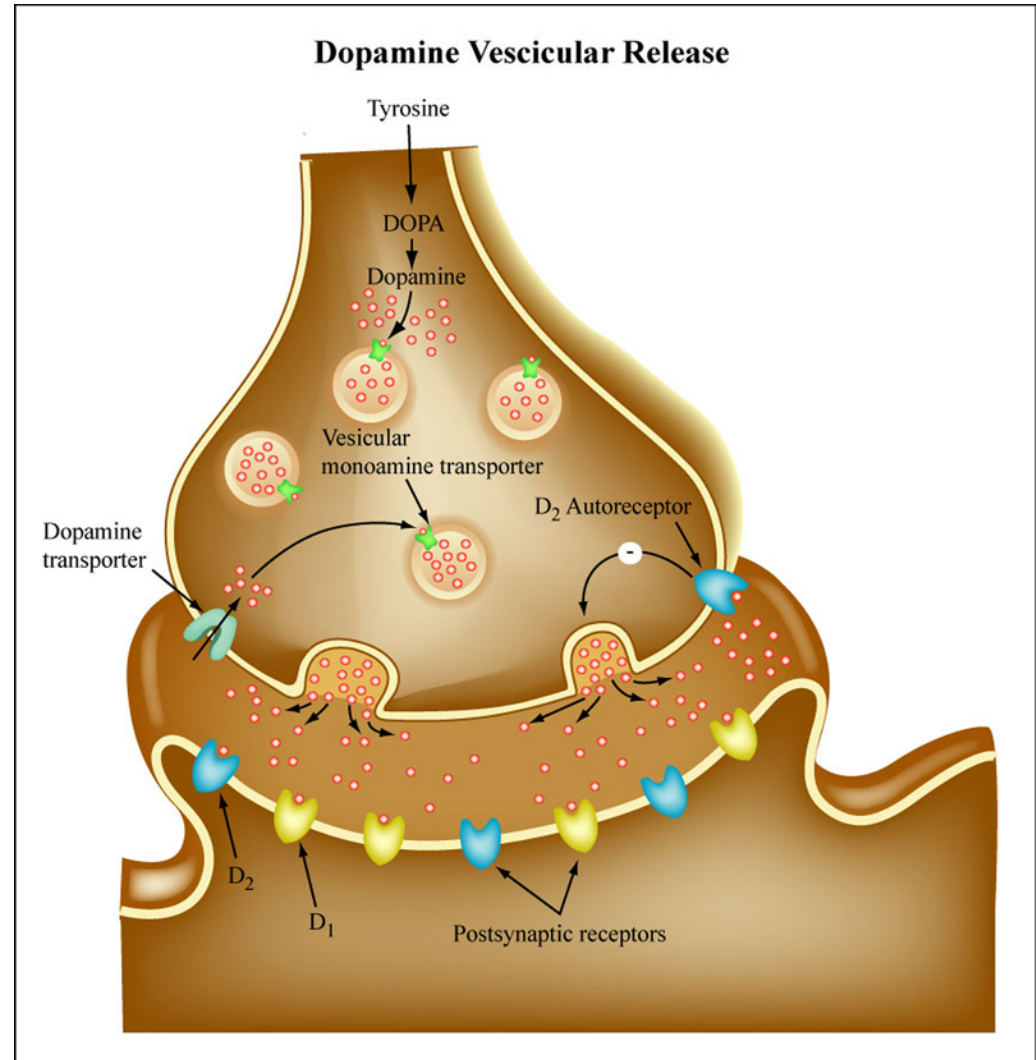


Figure by MIT OpenCourseWare.

Autoreceptors reduce the amount of calcium that enters the terminal in response to a nerve impulse, therefore inhibiting catecholamine release

Modulation of catecholamine action

1. Modulation of release

Release of catecholamines is dependent on neuronal cell firing

Some drugs induce the release independently from nerve cell firing.

In animal models increase in catecholamine release produces increased locomotor activity and stereotyped behavior

Psychostimulants such as **amphetamine** and **methamphetamine** in humans cause increased alertness, euphoria, insomnia.

2. Modulation of autoreceptors

Stimulation of autoreceptors inhibits catecholamine release

Autoreceptor antagonists, increase catecholamine release

3. Modulation of reuptake

Dopaminergic (DA) and Noradrenergic (NE) neurons have specific transporters on their membranes for the reuptake of neurotransmitter. These transporters are different from the autoreceptors described in point 2.

Drugs that block the transporters increase the amount of neurotransmitter in the Synaptic cleft therefore potentiating catecholamine transmission.

Reboexitine is a drug that specifically blocks NE uptake

Cocaine blocks the transport of DA, NE and 5-HT

4. Modulation of metabolism

Inside the terminal the transmitters are also catabolized by 2 enzymes:

Catechol-O-methyltransferase (COMT) and monoamide oxidase (MAO)

Degradation of catecholamines produces metabolites: homovanillic acid (HVA) for DA and 3-methoxy-4hydroxy-phenylglycol (MHPG) (CNS) and vanillymandelic acid (VMA) (PNS) for NE.

The levels of these metabolites in blood or urines gives important indications for the catecholaminergic activity and therefore contributes to the diagnosis of mental disorders

MAO inhibitors (phenelzine or tranylcypromine) have been used in the treatment of Depression. COMT inhibitors: entacapone (Comtan) and tolcapone (Tasmar) are used As supplementments in the treatment of Parkinson disease.

Transgenic animals are useful for the characterization of neurotransmitters action

Mutant mice lacking the dopamine
Transporter DAT show an increase
In locomotor activity

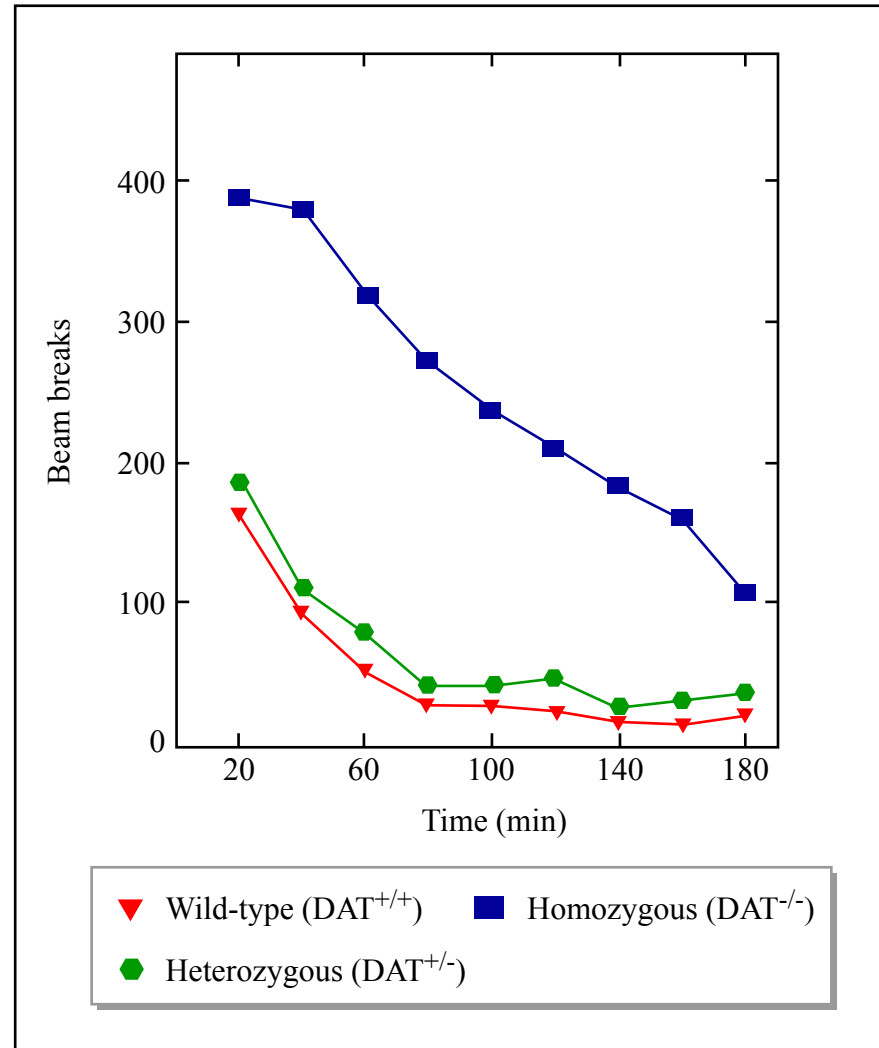


Figure by MIT OpenCourseWare.

Dopaminergic pathways

Dopaminergic neurons are localized in the mesencephalon (midbrain)

Nigrostriatal tract:

cells from the substantia nigra project to the striatum in the forebrain

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This pathway is affected in Parkinson disease. It is involved in control of movements

Mesolimbic dopamine pathway:

Dopaminergic cells in the Ventral Tegmental Area (VTA) in the mesencephalon project to structures of the limbic system: nucleus accumbens, septum, amygdala, hippocampus

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Mesocortical dopamine pathway:

Dopaminergic cells in the Ventral Tegmental Area (VTA) in the mesencephalon project to cerebral cortex

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Figure 5.7 (Part 3) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Mesolimbic and mesocortical pathways have been implicated in drug abuse and schizophrenia

Other dopaminergic neurones are present in the retina and in the hypothalamus these last control the secretion of prolactin

Localized application of the neurotoxin 6-hydroxydopamine (6-OHDA) is used to Examine the role of specific pathways in behavior.

This neurotoxin is similar to DA, and therefore is taken selectively by dopaminergic Neurons which are damaged and die

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Figure 4.1 (Part 1) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Dopamine receptors are found in the afferent structures of dopaminergic neurons

There are 5 known receptors: D1-D5 and they are all metabotropic receptors

D1 receptors stimulate cAMP production, while activation of D2 receptors inhibits the production of cAMP.

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Figure 5.9 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

This happens through the stimulation of 2 different G-proteins (D1/Gs-D2/Gi)

In addition, D2 also activates potassium channels

Dopamine receptors agonists and antagonists control dopaminergic-related functions

Apomorphine is an agonist of both D1 and D2 receptors

SFK38393 is an activator of D1 receptors and in mice it enhances self-grooming behavior

Quinprole affects D2 and D3 receptors. It causes an increase in locomotion and Sniffing behavior

Antagonists of dopaminergic receptors cause catalepsy: lack of spontaneous movements

Haloperidol causes catalepsy through D2 receptors, SCH acts through D1 receptors

After prolonged treatment with D receptor antagonists the animals develop behavioral supersensitivity, meaning that their reaction to dopaminergic stimulants is increased

Mice that lack D1 receptors are insensitive to locomotor stimulating effects induced by cocaine

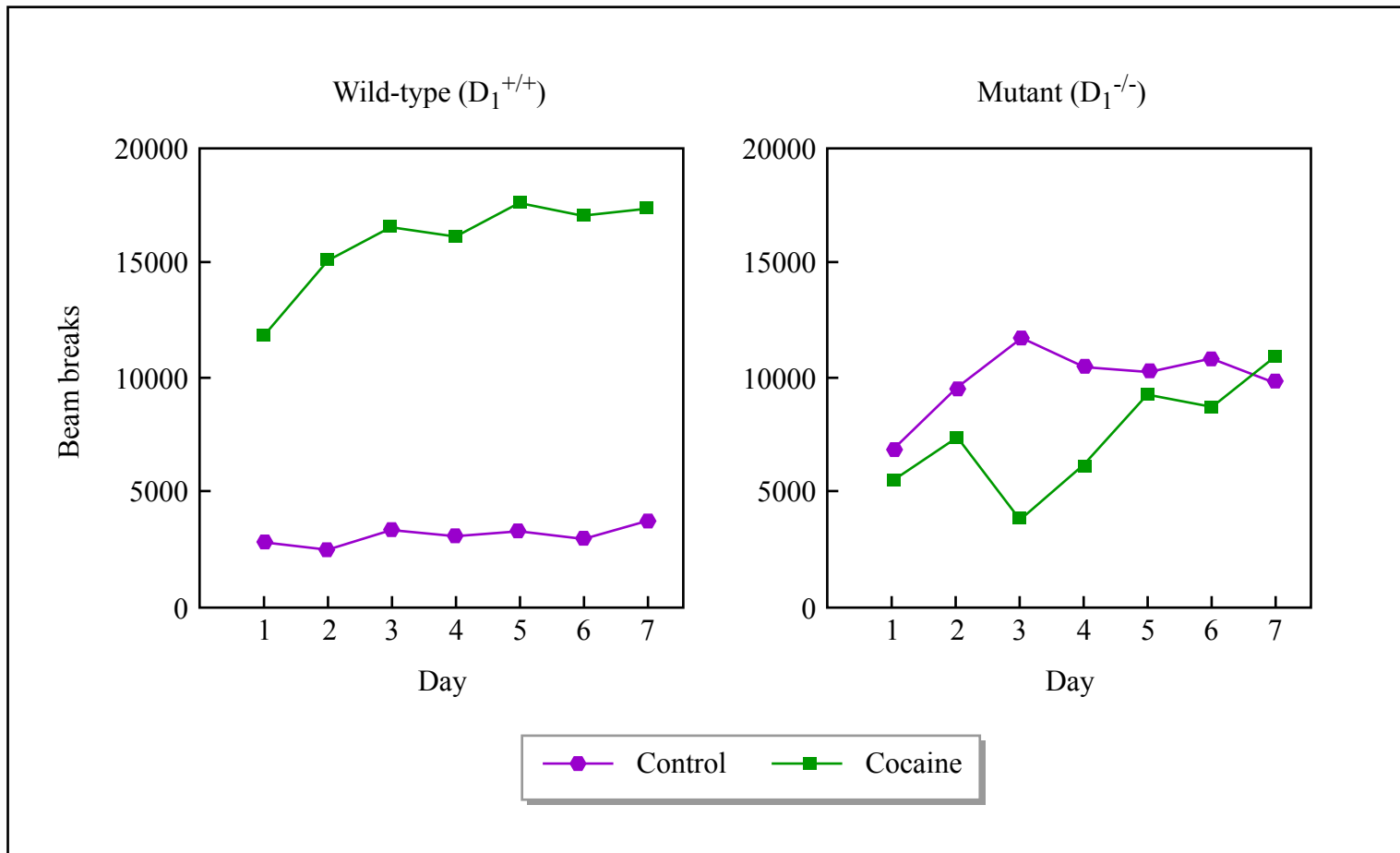


Figure by MIT OpenCourseWare.

Drugs that affect the dopaminergic system

<i>Drug</i>	<i>Action</i>
DOPA	Converted to DA in the brain
Phenelzine	Increases catecholamine levels by inhibiting MAO
α -Methyl- <i>para</i> -tyrosine (AMPT)	Depletes catecholamines by inhibiting tyrosine hydroxylase
Reserpine	Depletes catecholamines by inhibiting vesicular uptake
6-Hydroxydopamine (6-OHDA)	Damages or destroys catecholaminergic neurons
Amphetamine	Releases catecholamines
Cocaine and methylphenidate	Inhibit catecholamine reuptake
Apomorphine	Stimulates DA receptors generally (agonist)
SKF 38393	Stimulates D ₁ receptors (agonist)
Quinpirole	Stimulates D ₂ and D ₃ receptors (agonist)
SCH 23390	Blocks D ₁ receptors (antagonist)
Haloperidol	Blocks D ₂ receptors (antagonist)

Parkinson disease

The major symptoms include deficits in movement, but some patients also show Cognitive dysfunctions

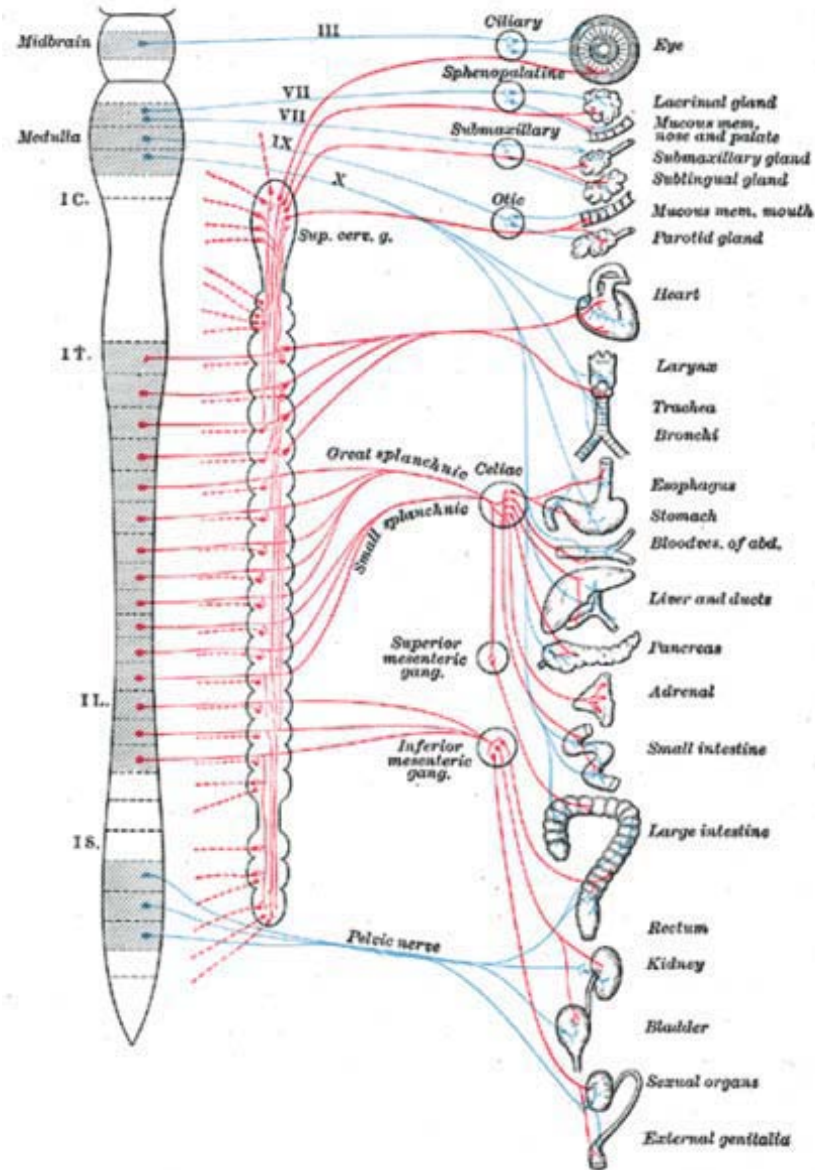
Caused by death of dopaminergic neurons in the substantia nigra

Possible cause: oxyradical-induced oxidative stress that damages/kills DA neurons

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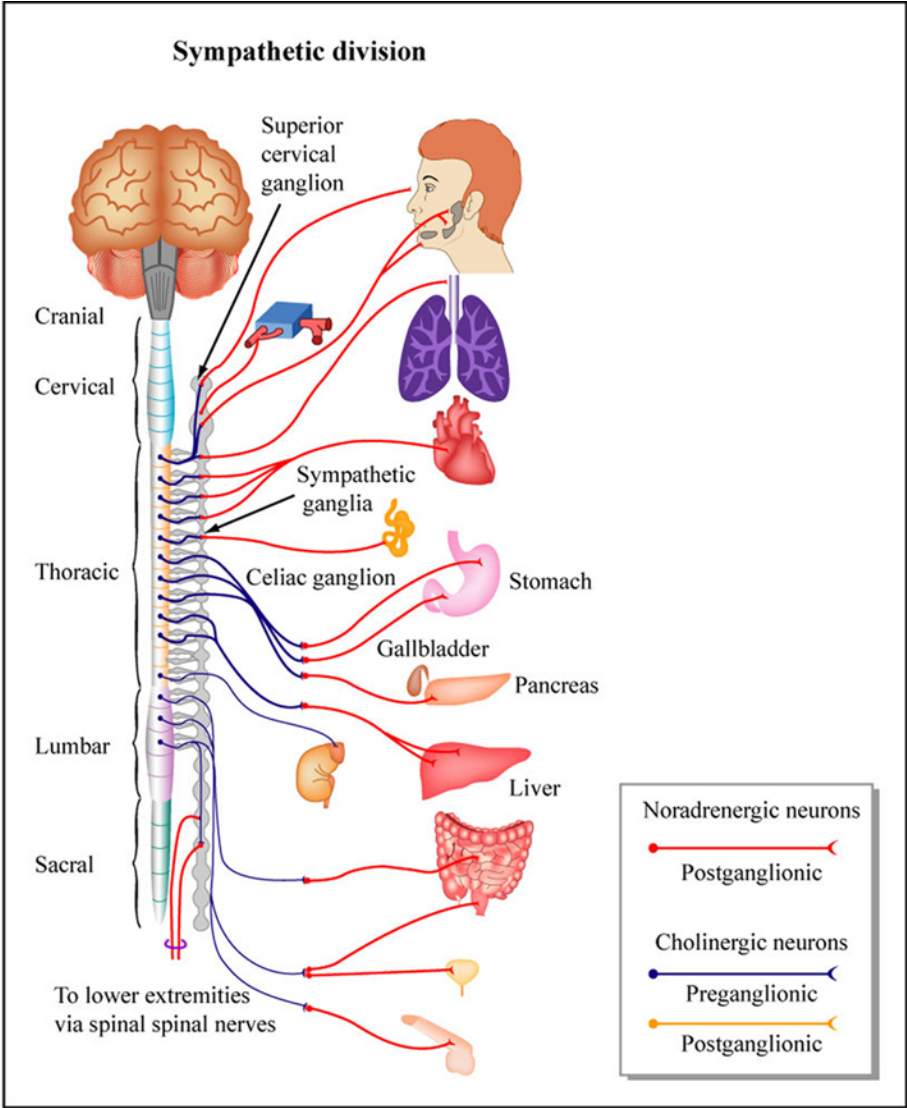
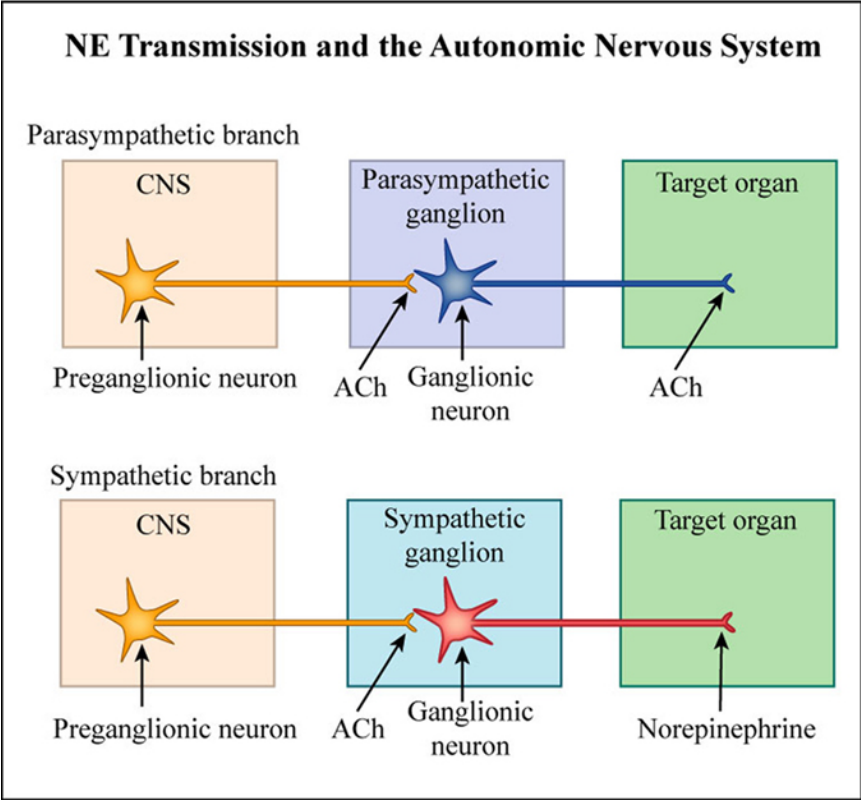
Box 5.1 (Part 1) in Meyer, and Quenzer, *Psychopharmacology*, 2004.

The autonomic Nervous System



Source: Grey's Anatomy. Courtesy of Wikipedia.

NE transmission and the autonomic nervous system



Figures by MIT OpenCourseWare.

The NE-containing neurons are localized mostly in the LOCUS COERULEUS (LC): an area in the pons (brain stem). These cells provide inputs to cords, cerebellum, and to several areas in the forebrain.

Image removed due to copyright restrictions. Figure 5.11 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Also NE neurons are in the ganglia of the sympathetic branch of the autonomic nervous system, therefore playing an important role in PNS.

The NE neurons in the LC play an important role in the state of VIGILANCE: being alert to external stimuli.

In vivo electrophysiological recordings from the LC showed that the firing depends on the status of the animal and the external stimuli

Image removed due to copyright restrictions. Figure 5.12 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

The receptors of NE and EPI are called ADRENERGIC RECEPTORS and they are Metabotropic receptors.

They are distinguished in alpha (α_1 and α_2) and beta (β_1 and β_2)

β_1 and β_2 receptors increase the levels of cAMP.

α_2 receptors inhibit adenyl cyclase and increase K channels opening

α_1 receptors act with phosphoinositide as second messenger inducing an increase of Ca^{++} in the postsynaptic cell

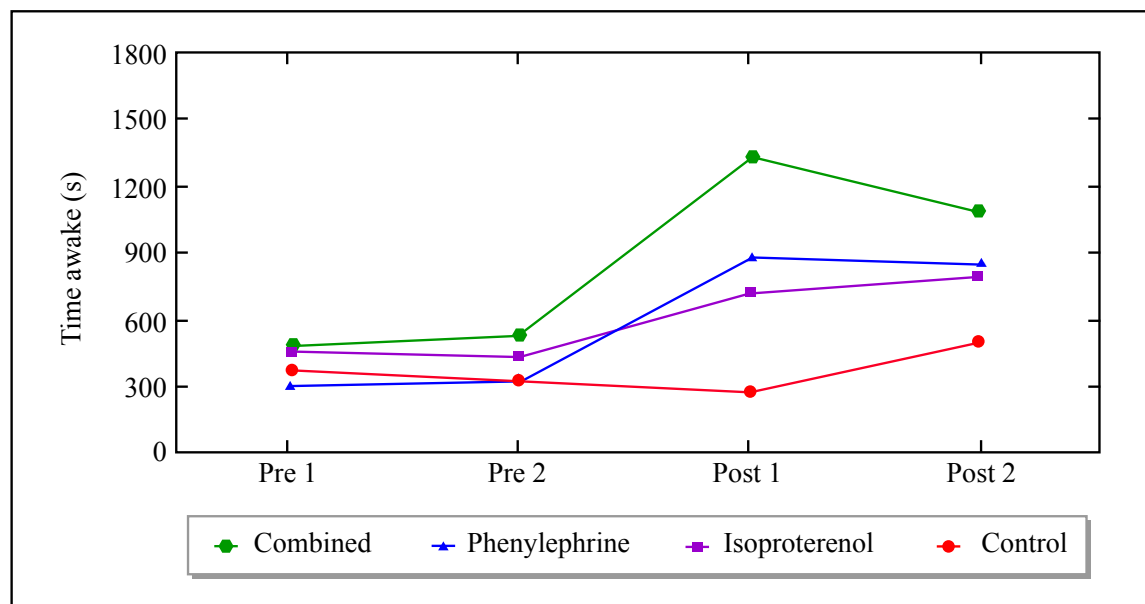


Figure by MIT OpenCourseWare.

The effects of drugs for the NE system are measured by looking at the vigilance: phenylephrine is α_1 receptor agonist, while isoproterenol is a β receptors agonist

NE modulates:

vigilance

anxiety

pain

hunger and eating behavior

autonomic functions

It is important to consider the localization of receptor subunits in specific areas

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Figure 5.14 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Effects

Agonists:

α receptors stimulation leads to constriction of the blood vessels in the bronchial lining, this reducing congestion and edema.

The agonist phenylephrine is the ingredient in Neosynephrine (a nasal spray)

β receptors stimulation induce relaxation of the bronchial muscles, therefore providing a wider airway. In fact albuterol is a very popular local medication in asthma

Antagonists:

Prazosin is a α_1 receptors antagonist and causes a relaxation of the blood vessels

Propranolol is a β receptors blocker that reduces the heart's contractile force.

They are both used as treatment for high blood pressure

Blockers are in general used to treat the symptoms of anxiety disorders: palpitation, tachycardia

Location and physiological actions of peripheral α - and β -adrenergic receptors

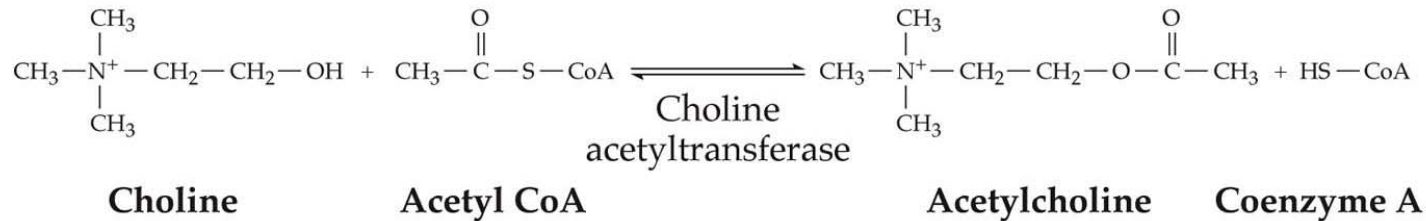
<i>Location</i>	<i>Action</i>	<i>Receptor subtype</i>
Heart	Increased rate and force of contraction	β
Blood vessels	Constriction	α
	Dilation	β
Smooth muscle of the trachea and bronchi	Relaxation	β
Uterine smooth muscle	Contraction	α
Bladder	Contraction	α
	Relaxation	β
Spleen	Contraction	α
	Relaxation	β
Iris	Pupil dilation	α
Adipose (fat) tissue	Increased fat breakdown and release	β

Figure by MIT OpenCourseWare.

Drugs that affect the Noradrenergic system

<i>Drug</i>	<i>Action</i>
Phenelzine	Increases catecholamine levels by inhibiting MAO
α -Methyl- <i>para</i> -tyrosine (AMPT)	Depletes catecholamines by inhibiting tyrosine hydroxylase
Reserpine	Depletes catecholamines by inhibiting vesicular uptake
6-Hydroxydopamine (6-OHDA)	Damages or destroys catecholaminergic neurons
Amphetamine	Releases catecholamines
Cocaine and methylphenidate	Inhibit catecholamine reuptake
Desipramine	Selectively inhibits NE reuptake
Phenylephrine	Stimulates α_1 -receptors (agonist)
Clonidine	Stimulates α_2 -receptors (agonist)
Albuterol	Stimulates β -receptors (partially selective for β_2)
Prazosin	Blocks α_1 -receptors (antagonist)
Yohimbine	Blocks α_2 -receptors (antagonist)
Propranolol	Blocks β -receptors generally (antagonist)
Metoprolol	Blocks β_1 -receptors (antagonist)

Acetylcholine



Acetylcholine is a neurotransmitter in:
Neuromuscular junctions
Peripheral Nervous System
Central Nervous System

Factors that regulate Ach synthesis:

- Availability of reagents
- Firing rates

Since so far there are no drugs that control ChAT, the control of cholinergic system happen at different steps of transmission

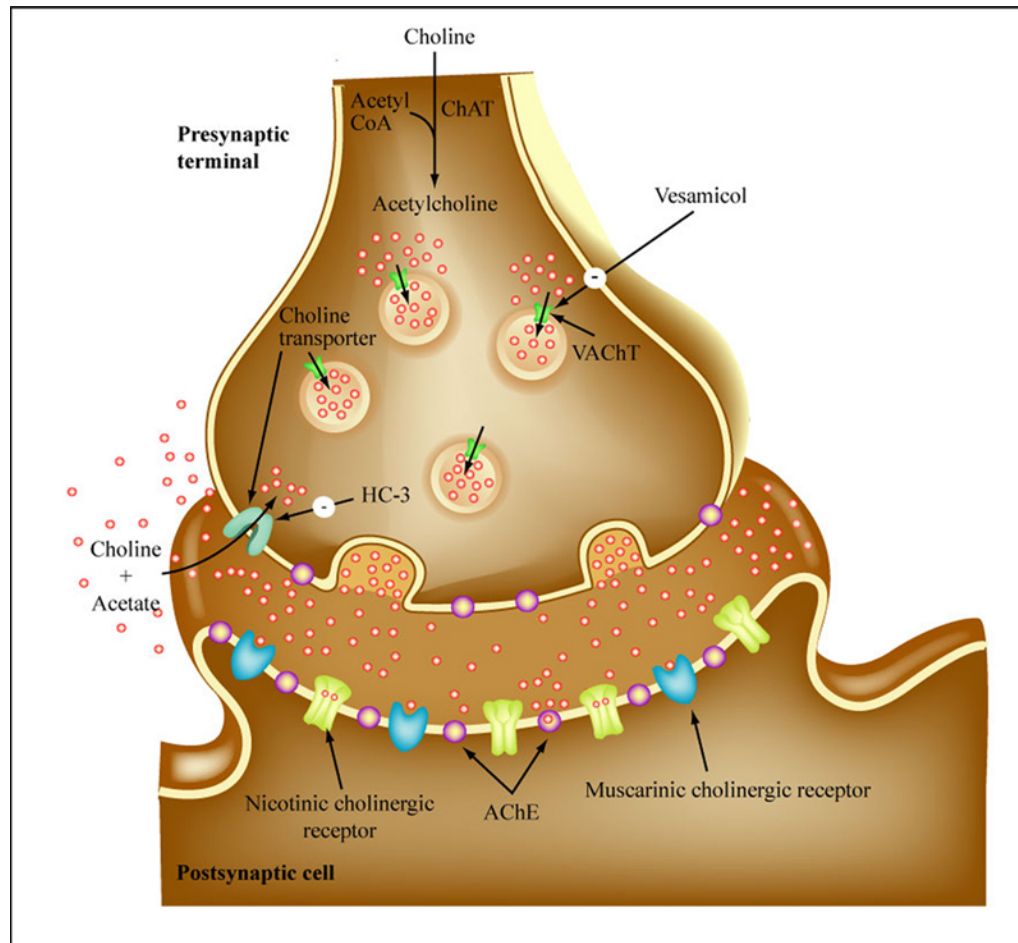


Figure by MIT OpenCourseWare.

Vesamicol is a drug that blocks the vesicular ACh transporter, therefore decreasing ACh transmission: ACh can only be released through vesicles

A Choline transporter takes back ACh into the presynaptic terminal. If this transporter is blocked (hemicolinium-3 (HC-3)) the production of ACh declines. This suggests that there is recycling. HC-3 has to be administered locally.

Factors that modulate Ach release:

Toxin in the venom of the black widow spider

Induce a massive release of Ach, thereby causing:
tremors, pain, vomiting, salivation, sweating

Botulinum toxins: blocks Ach release

The toxins are picked up by cholinergic neurons at the neuromuscular junction, thereby causing muscle paralysis.

Symptoms: blurred vision, difficulty speaking and swallowing, muscle weakness

At low dosage Botox is used also for therapeutic purposes:

Diseases caused by permanent muscle contraction: dystonias

Also used for reducing wrinkles

Acetylcholinesterase (AChE) degrades ACh

It is localized in the presynaptic terminal, in the membrane of the postsynaptic terminal, and at the neuromuscular junctions

Drugs that block AChE increase the effects of Ach transmission

Reversible inhibitors:

Physostigmine (Eserine) blocks AChE therefore causing: loss of reflexes, mental confusion, allucination, convulsions, slurred speech. It crosses the BBB.

Neostigmine (Prostigmin) and pyrodostigmine (Mestinon) are analogous of Physostigmine that do not cross the BBB. They are used for the treatment of Myasthenia gravis: an autoimmune disorder where antibodies attack cholinergic Receptors at the neuromuscular junction, therefore in these patients the muscles are less sensitive to Ach.

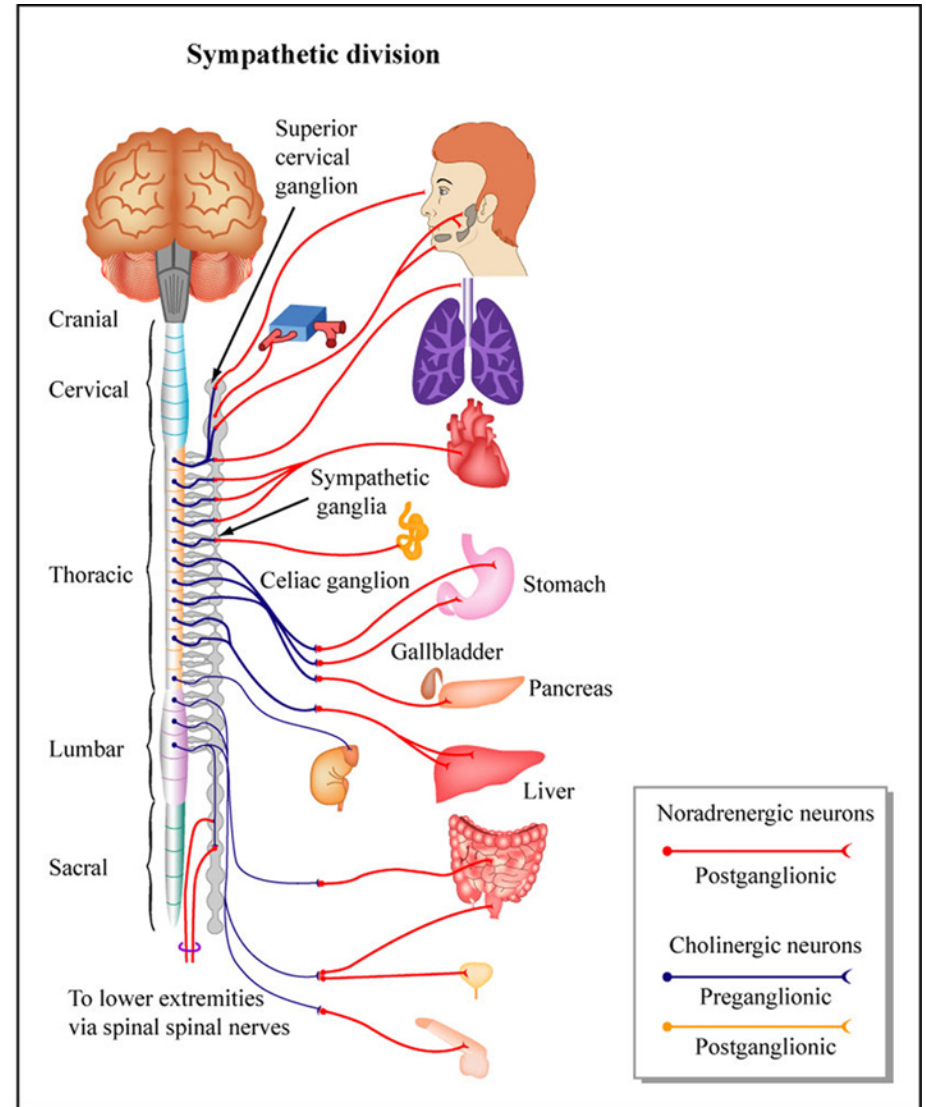
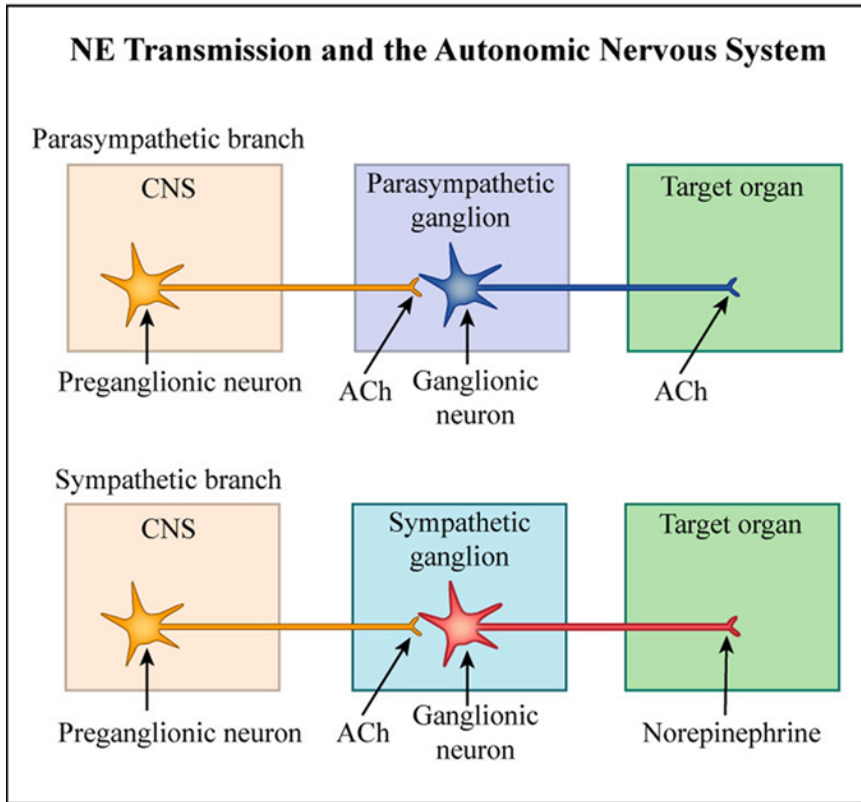
These substances are used at low dosage also in pesticides

Irreversible inhibitors of AChE:

Sarin and Soman: chemical gases developed in chemical warfare.
They causes paralysis of the diaphragm, hence death

Some analogous – but reversible- blockers of AChE are used as antidote

Acetylcholine is fundamental in sympathetic and parasympathetic branches of Autonomic nervous system



Figures by MIT OpenCourseWare.

Localization of cholinergic neurons in the CNS

Note that in the striatum (the target of dopaminergic neurons from substantia nigra), there are cholinergic interneurons. The control of movement depends on the balance between cholinergic and dopaminergic transmission. Therefore in Parkinson disease anticholinergic drugs are also used to improve the control of movements: orphenadrine (Norflex), benztropine mesylate (Cogentin), trihexyphenidyl (Artane)

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Figure 6.7 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

Neurons of the BFCS are involved in cognitive functions

Role of cholinergic system in Alzheimer disease

Ach receptors

Nicotinic: ionotropic, distributed mainly in neuromuscular junctions, autonomic nervous system, some neurons in the brain.

When they are activated the Na^+ and Ca^{++} ions flow through the channel, thereby mediating fast excitatory responses (in case of muscle, contraction)

The nicotinic receptor is made by different subunits

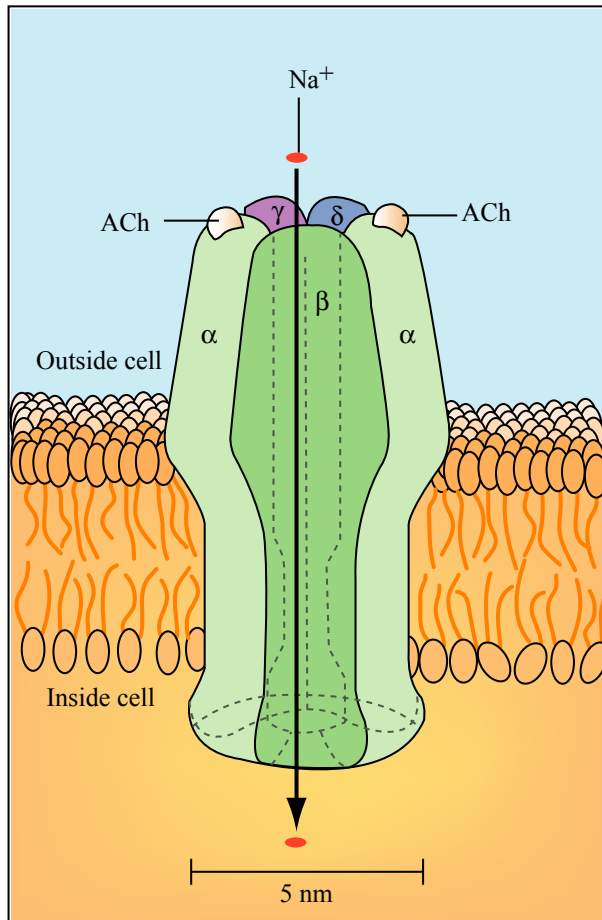


Figure by MIT OpenCourseWare.

The composition at the neuronal and muscular synapses are different.

For example the effects of nicotine are different in the brain and in the muscles

A nicotinic receptor antagonist is D-tubocurarine, That is the main active ingredient of curare.

Curare blocks cholinergic transmission at the neuromuscular junction therefore causing respiratory paralysis.

Interestingly, treatment with neostigmine (anti AChE) overcomes the effects of curare

Muscarinic receptors

Metabotropic receptors (M1-M5) that activate different second messenger pathways:

Activation of phosphoinositide

Decrease of cAMP

Stimulation of K⁺ channels opening

These receptors play an important role in cognitive functions, and those in the striatum are involved in motor function.

M5 muscarine receptors are involved in morphine reward and dependence

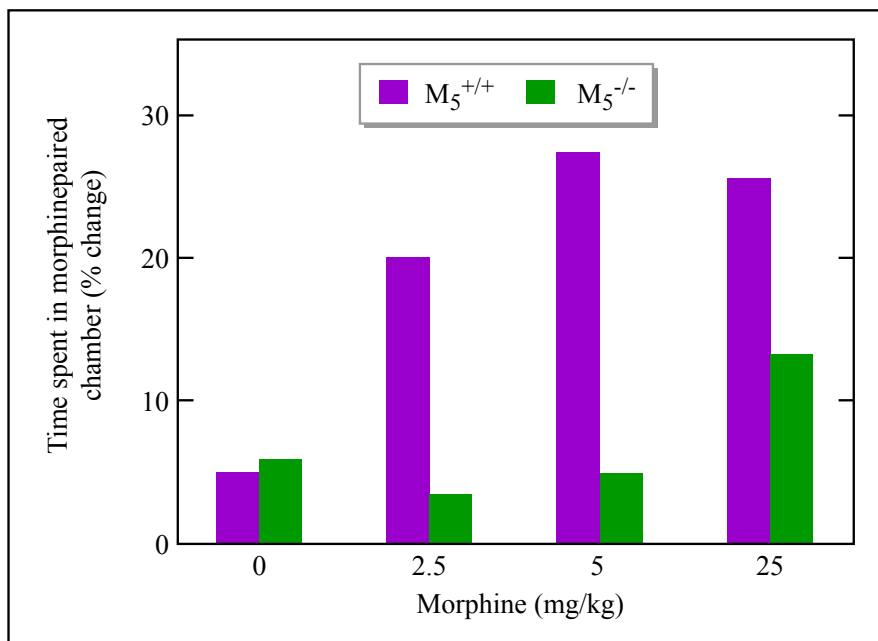


Figure by MIT OpenCourseWare.

Muscarinic receptors outside the nervous system:

Cardiac muscle

Smooth muscles associated with several organs

They modulate heart rate and contractions, salivation, sweating, lacrimation

All these possible side effects need to be taken into account for the cognitive effects related to muscarinic receptors

Muscarinic receptor AGONISTS (muscarine, pilocarpine, arecoline):

Mimic the effects of parasympathetic activation: lacrimation, salivation, sweating, Constriction of the iris, contraction of the smooth muscles of the viscera, diarrhea

Muscarinic receptor ANTAGONISTS (atropine, scopolamine)

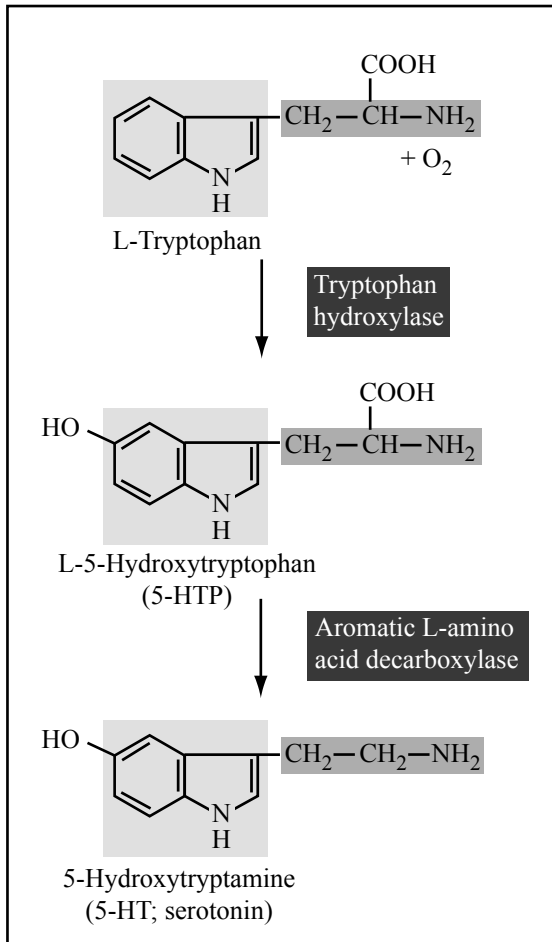
Pupillary dilatation, reduction of secretions

Drugs and Toxins that affect the Cholinergic System

<i>Drug</i>	<i>Action</i>
Vesamicol	Depletes ACh by inhibiting vesicular uptake
Black widow spider venom	Stimulates ACh release
Botulinum toxin	Inhibits ACh release
Hemicholinium-3	Depletes ACh by inhibiting choline uptake by the nerve terminal
Physostigmine, neostigmine, and pyridostigmine	Increase ACh levels by inhibiting acetylcholinesterase reversibly
Sarin and Soman	Inhibit acetylcholinesterase irreversibly
Nicotine	Stimulates nicotinic receptors (agonist)
Succinylcholine	Nicotinic receptor agonist that causes depolarization block
D-Tubocurarine	Blocks nicotinic receptors (antagonist)
Muscarine, pilocarpine, and arecoline	Stimulate muscarinic receptors (agonists)
Atropine and scopolamine	Block muscarinic receptors (antagonists)

5-hydroxytryptamine (5-HT): Serotonin

Involved in depression, anxiety, obesity, aggression and drug addiction



Starting reagent: tryptophan

Tryptophan hydroxylase is specific of Serotonergic neurons

The drug para-chlorophenylalanine (PCPA) selectively inhibits tryptophan hydroxylase, Therefore blocking 5-HT synthesis

Figure by MIT OpenCourseWare.

A diet rich in carbohydrates leads to the increase of insulin which facilitate glucose uptake, and also several other aa, but not tryptophan

Since it is the ratio between tryptophan and other aa that is important for crossing the BBB a carbo-rich diet would increase the uptake of tryptophan and eventually the production of serotonin

Serotonergic transmission is similar to DA and NE transmission

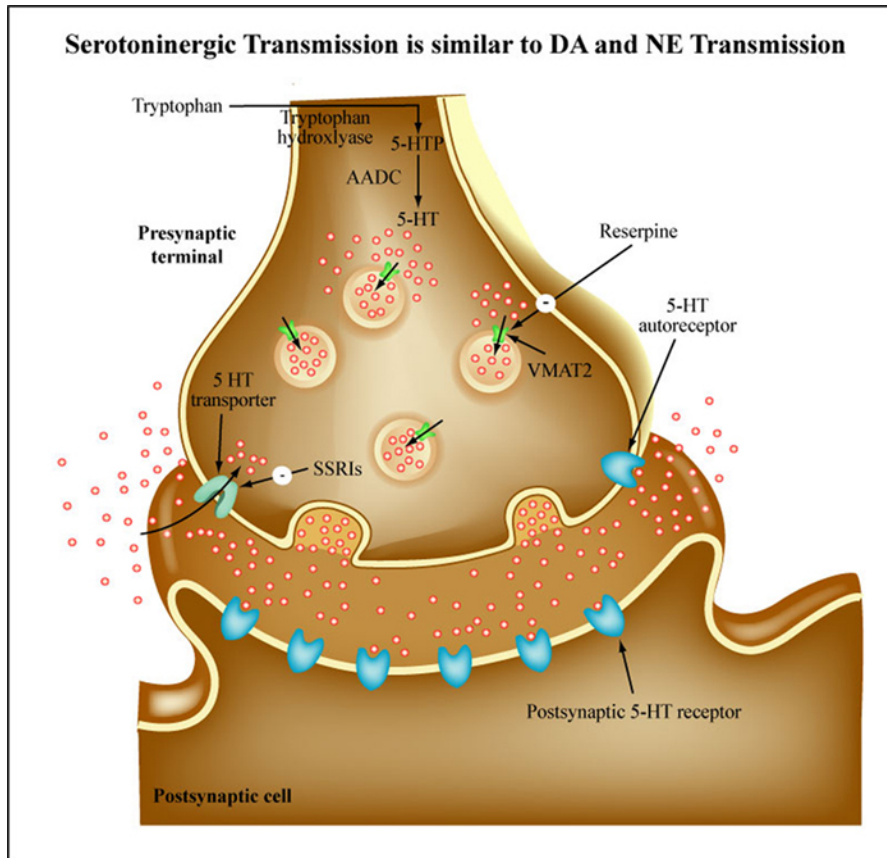


Figure by MIT OpenCourseWare.

VMAT2 transport 5-HT into vesicles (reserpine blocker)

Presence of auto receptors that modulate firing rate- release

5-HT release can be stimulated by drugs with the structure of amphetamines

Once released, 5-HT is removed from the cleft by the e-HT transporter.

A blocker of the transporter is fluoxetine (Prozac) that potentiate 5-HT transmission

Monoamine oxidase (MAO) also catabolites 5-HT producing the metabolite 5-hydroxyindoleacetic acid (5-HIAA)

The majority of serotonergic nuclei are localized in the brainstem (medulla, pons and midbrain)

These nuclei are called the raphe nuclei and they are localized on the midline of the brain stem

They project to all the forebrain regions

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Figure 6.17 in Meyer, and Quenzer, *Psychopharmacology*, 2004.

The firing of the serotonergic neurons is associated with the behavioral status of the animal: the firing slows down with sleep and shut off during REM sleep

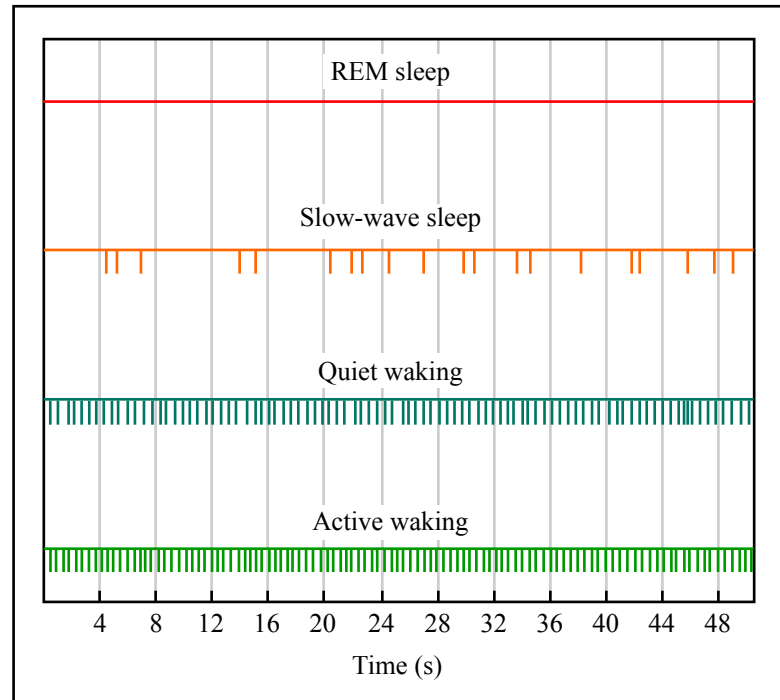


Figure by MIT OpenCourseWare.

In general the firing is constant during repetitive movements, like chewing, and it suddenly stops when a new stimulus is presented

Induced lesions of the serotonergic system in animals show that it modulates food Intake, reproductive behavior, pain sensitivity and learning and memory

5-HT receptors

There are at least 15 receptor subtypes and they are all metabotropic, with the exception of 5-HT₃, which is an excitatory ionotropic receptor

5-HT_{1A} is present in many brain areas, including the hippocampus and the amygdala

It acts by inhibiting adenylyl cyclase and by opening a K⁺ channel leading to membrane hyperpolarization

Administration of 5-HT_{1A} agonists produce hyperphagia

The most studied antagonist (WAY-100861 from the pharmaceutical company Schering-Plough) produced decrease in body weight but it was accompanied by side effects

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Figure 6.19 (Part 1) in Meyer, and Quenzer,
Psychopharmacology, 2004.

5-HT_{1A} stimulation also produced reduction in anxiety, and this is what is used in the medication Buspar-commercial name for busiprone.

Another effect of 5-HT_{1A} agonist is the inhibition of alcohol consumption

5-HT_{2A} receptors act by activating protein kinase C,
They are present in cerebral cortex.

Agonist of this receptor cause Hallucinations, and this
is supposed to be related to the effects of lysergic acid
diethylamide (LSD)

The best known agonist is DOI (1-(2,5-dimethoxy-4-iodophenyl)
-2-aminopropane

Known antagonists are ketanserin and ritanserin.

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Figure 6.19 (Part 2) in Meyer and Quenzer,
Psychopharmacology, 2004.

In general, these antagonists can be used for the treatment of schizophrenia.
Recently, drugs that act on both the DA and 5-HT system have shown
the best results for the treatment of schizophrenia with lower side effects

Drugs that affect the Serotonergic system

<i>Drug</i>	<i>Action</i>
<i>para</i> -Chlorophenylalanine	Depletes 5-HT by inhibiting tryptophan hydroxylase
Reserpine	Depletes 4-HT by inhibiting vesicular uptake
<i>para</i> -Chloroamphetamine, fenfluramine, and MDMA	Release 5-HT from nerve terminals (MDMA and <i>para</i> -chloroamphetamine also have neurotoxic effects)
Fluoxetine	Inhibits 5-HT reuptake
5,7-Dihydroxytryptamine	5-HT neurotoxin
Buspirone, ipsapirone, and 8-OH-DPAT	Stimulate 5-HT _{1A} receptors (agonists)
WAY 100635	Blocks 5-HT _{1A} receptors (antagonist)
DOI	Stimulates 5-HT _{2A} receptors (agonist)
Ketanserin and ritanserin	Block 5-HT _{2A} receptors (antagonists)

Figure by MIT OpenCourseWare.