

Pharmacology of the autonomic nervous system for dental students (minimum requirement)

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2.1. Anatomy and physiology of sympathetic and parasympathetic nerves

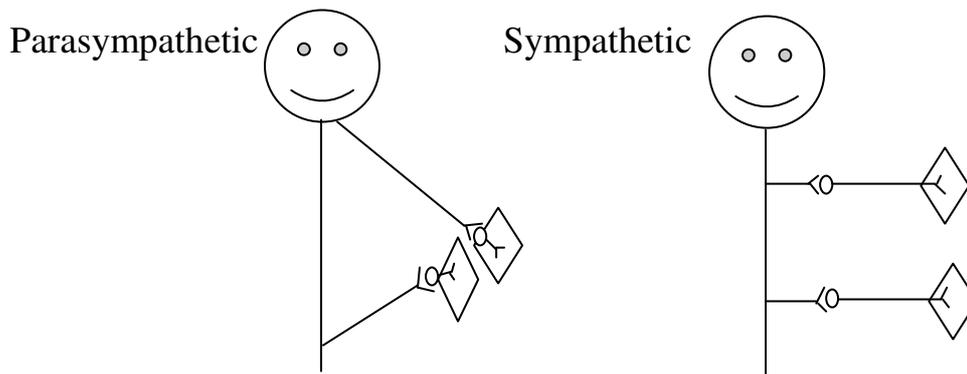
2.1.1. Basic principles

Autonomic nervous system is involuntary, that is, the function of sympathetic and parasympathetic nerves can not be influenced by our mind. With respect to 'global function', the sympathetic distribution is to effectors throughout the body, whereas the parasympathetic distribution is much more limited. In most of the blood vessels, only sympathetic nerves regulate the tone of smooth muscles. The sympathetic system is not essential for life, but its absence would decrease one's ability to respond to stress, especially the correlates of 'flight, fright, or fight'. The parasympathetic system serves mainly to conserve energy and maintain organ functions.

2.1.2. Anatomy

Although all preganglionic efferent fibers (from the spinal cord to ganglia) of the autonomic nervous system are cholinergic (they synthesize and release acetylcholine), the axons of the sympathetic and parasympathetic divisions exit the central nervous system at different levels. The efferent fibers of the parasympathetic division leave the central nervous system at the level of the cranial nerves, the cervical segments, and the sacral segments (S_2 to S_4) of the spinal cord. The sympathetic division is also called the thoracolumbar outflow, since the efferent fibers exit the spinal cord at spinal levels T_1 through L_2 .

The postganglionic fibers of the parasympathetic nervous system tend to be shorter than those of the sympathetic nervous system. The parasympathetic ganglia are found near or even within the effector organ (e.g. the intestine), whereas the sympathetic ganglia are usually located next to the vertebral bodies (paravertebral).



2.1.3. Neurotransmitters

All of the autonomic nerves leaving the spinal cord are cholinergic (they synthesize, store and release acetylcholine). The first synapse outside the spinal cord is in the ganglion. The effector organs are innervated by postganglionic fibers, but an exception is the adrenal medulla (modified ganglion).

The postganglionic fibers of the parasympathetic nervous system are cholinergic: acetylcholine is released from these nerves. The postganglionic fibers of the sympathetic division are almost all noradrenergic (they synthesize, store and release noradrenaline). The exceptions are the cholinergic postganglionic sympathetic fibers to sweat glands and to vascular beds in some skeletal muscles. Unusually, sympathetic postganglionic fibers release dopamine, instead of noradrenaline, in some renal blood vessels.

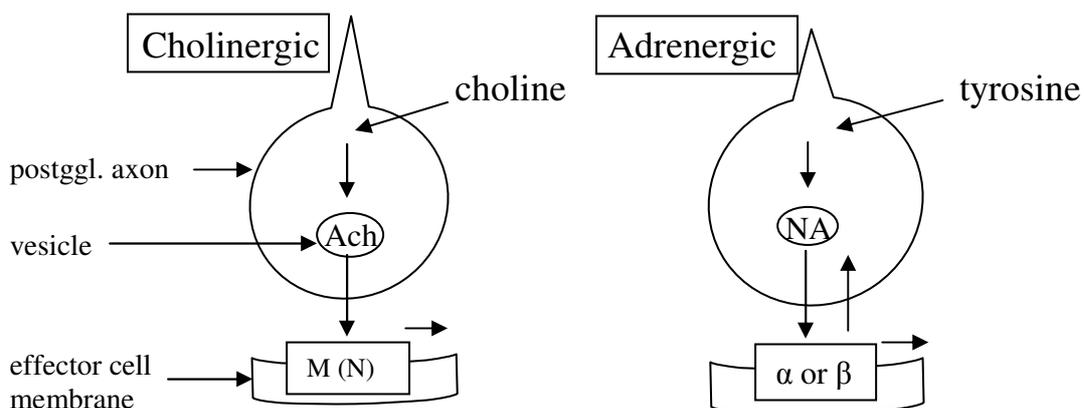
2.1.4. Receptors

On the membranes of sympathetic and parasympathetic ganglionic cells the receptors are nicotinic (N) in nature (nicotine mimics the effects of acetylcholine).

In the parasympathetic division, end organs contain muscarinic (M) receptors. Muscarine mimics the effects of acetylcholine on these receptors, which are located on glands, smooth muscle, and the heart. Oddly, there are muscarinic receptors on blood vessels that are not innervated. Note that non-autonomic, somatic motor nerves are cholinergic nerves and the receptors in the myoneural (neuromuscular) junctions are nicotinic. These nicotinic receptors are somewhat different from those located in autonomic ganglia.

In the sympathetic division, end organs contain adrenergic receptors. These receptors have subtypes: α_1 , α_2 , β_1 , β_2 . α_2 adrenergic receptors are feedback receptors on the postganglionic axon terminals. β_3 receptors are present in fat cells and have no known role in the autonomic nervous system.

2.1.5. Regulation of cholinergic and adrenergic neurotransmission



Precursor for the synthesis of acetylcholine is an amino acid, *choline*. Choline is taken up into the axon terminal by an active transport. Axonal mitochondria synthesize acetyl-CoA and with choline form acetylcholine. This reaction is catalysed by cholineacetylase enzyme. Acetylcholine is stored in axonal vesicles and released by an exocytotic mechanism. This mechanism is triggered by calcium ions. In the synaptic cleft, acetylcholine binds to cholinergic receptors and produces a biological signal(s). After detaching from the receptor, acetylcholine is cleaved into acetate and choline by the acetylcholine esterase, an enzyme located in the postsynaptic membrane.

Precursor for the synthesis of *noradrenaline (norepinephrine)* is the amino acid, tyrosine. Tyrosine is taken up into the axon terminal by an active transport. The enzyme, tyrosine hydroxylase converts tyrosine into *dopa*. Then *dopa* is decarboxylated into dopamine by *dopa decarboxylase (L-aromatic amino acid decarboxylase)* *Dopamine* is transported into the axonal vesicles and, noradrenaline is synthesized by the catalytic action of dopamine beta-hydroxylase. Axonal nerve impulse enhances the calcium ion concentration and, following a releasing mechanism similar to acetylcholine, noradrenaline binds to adrenergic receptors in the synaptic cleft. In contrast to the elimination of acetylcholine, noradrenaline is not completely degraded by enzymatic reactions. Most of the released noradrenaline (~70%) is taken up by the axon terminal, transported into the vesicles and released again during the next electrical impulse. This is called 'reuptake or uptake I.' mechanism. The remaining 30% of noradrenaline flows out of the synapse and it is taken up by the tissues with 'uptake II.'. Within the axon terminal, extravesicular noradrenaline is broken down by monoamine oxidase (MAO). In the tissues, both MAO and catecholamine orthomethyl-transferase (COMT) are responsible for the degradation of noradrenaline.

It is important to note, that there are presynaptic receptors located on the axon terminals and regulate the synthesis and release of neurotransmitters. This negative feed-back is mediated by presynaptic α_2 adrenergic receptors. Agonists inhibit and antagonists facilitate the synthesis/release of noradrenaline.

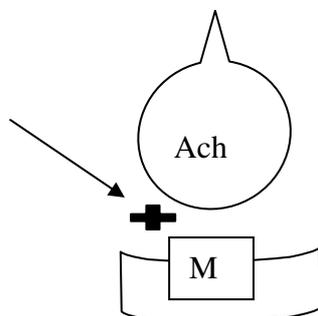
2.2. Drugs affecting cholinergic and adrenergic functions

2.2.1. Cholinergic agonists and antagonists

Cholinergic agonists can be divided into directly and indirectly acting drugs. Direct agonists bind to postsynaptic receptors while indirectly acting agonists inhibit the enzyme activity of the acetylcholine esterase. In the latter case, the effect of endogenous acetylcholine is prolonged.

Cholinergic antagonists inhibit the postsynaptic receptors of acetylcholine. These receptors are mainly muscarinic types.

2.2.1.1. Directly acting parasympathetic agonists



Among the cholinergic receptors, the muscarinic subtype (M) is stimulated by muscarine derived from the mushroom, *Amanita muscaria* (fly-agaric). The nicotinic subtype (N) can be stimulated by the plant alkaloid, nicotine (*Nicotiana tabacum*). None of them are useful therapeutic agents. However, these substances serve the basis of classification: there are muscarinic and nicotinic drugs according to their main effects.

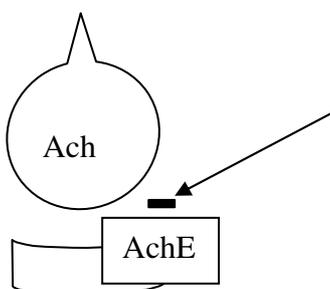
Pilocarpine is a directly acting muscarinic agonist and used for the treatment of glaucoma (a disease with enhanced pressure of fluid in the eyeball). Pilocarpine constricts the pupil and the ciliary muscle in the eye, the latter of which promotes the outflow of intraocular fluid through the canal of Schlemm. Because of the small pupil diameter, this effect of pilocarpine is called: miotic effect.

Bethanecol is a muscarinic agonist with a small nicotinic receptor stimulating effect. As a peroral drug, it is used to stimulate the detrusor muscle of the bladder, and relieves difficulty in urination.

Carbachol is a direct agonist of both muscarinic and nicotinic receptors. It is useful only as an eye drop.

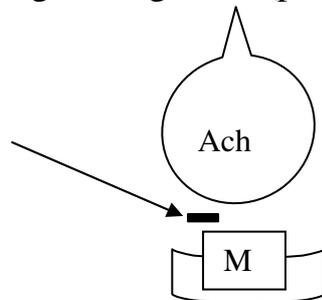
Adverse effects of cholinergic agonists are practically muscarinic types: bronchoconstriction, bradycardia, increased gastric acid secretion, sweating, difficulty in visual accommodation, increased salivation.

2.2.1.2. Indirectly acting parasympathetic agonists



Indirectly acting drugs –logically- do not directly act on the receptor. They inhibit the acetylcholine esterase enzyme (AChE) and thus, these drugs do not mimic but increase and prolong the effect of endogenous acetylcholine. AChE-inhibitors can be reversible and irreversible inhibitors. Reversible inhibitors are *physostigmine* or *neostigmine* while irreversible inhibitors are poisonous insecticides (e.g. malathion) in the agriculture. Reversible inhibitors are used to treat paralytic ileus, myasthenia gravis, the latter of which is not an autonomic disease (a disease of the neuromuscular junction). Irreversible inhibitors are topical eyedrops only for the treatment of severe glaucoma (e.g. ecotiophate). Despite the local administration, they may cause toxic effects. Symptoms of toxicity (sweating, salivation, cramps in GIT, CNS effects, involuntary skeletal muscle movements) are treated with atropine. A causative treatment within 12 hours is possible: AChE reactivators (oxims) may split down the poisonous inhibitor from the AChE enzyme.

2.2.1.3. Cholinergic antagonists (parasympatholytic drugs)



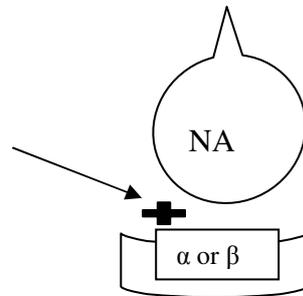
Cholinergic antagonists are only muscarinic receptor blockers. Nicotinic receptor blockers are ganglionic blocking drugs or neuromuscular blockers (skeletal muscle relaxants) depending on the location of the nicotinic type acetylcholine receptors. The prototype of muscarinic antagonists is *atropine*. Because of lipid solubility, atropine enters the brain and produces hallucinations in high doses. Cholinergic antagonists are contraindicated (addition is prohibited) in glaucoma and hypertrophy of the prostate. Atropine is combined with antiinflammatory drugs for the treatment of GIT and urinary disorders. Muscarinic 1-subtype receptor is selectively blocked by *pirenzepine* in the stomach; *ipratropium* decreases the production of bronchial mucus in asthma bronchiale.

2.2.2. Adrenergic agonists and antagonists

Adrenaline is an agonist of α and β adrenergic receptors. Noradrenaline is mainly an α -stimulant, the synthetic isoproterenol excites only β receptors. α_1 stimulants cause vasoconstriction, α_2 agonists decrease the sympathetic tone by a negative feed-back on the synthesis of the neurotransmitter, noradrenaline. β_1 agonists excite the heart (positive chrono-, dromo-, inotropic effects). Selective

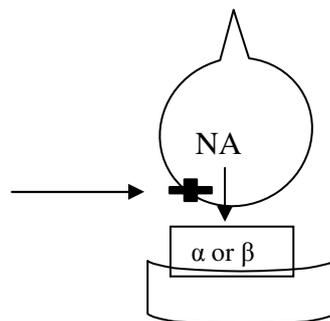
β_2 agonists relax bronchial, vascular, uterine smooth muscles. Antagonists of α adrenergic receptors cause vasodilation and decrease the peripheral vascular resistance; β receptor blockers decrease the minute volume in the heart.

2.2.2.1. Directly acting sympathetic agonists



Direct sympathetic agonists (sympathomimetics) bind to the postganglionic postsynaptic adrenergic receptors. Non-selective drugs are either local nasal decongestants (*methazolines*) or systemic hypertensive drugs (*methoxamine*). *Adrenaline* is used in anaphylactic shock (systemic parenteral); it is combined with local anaesthetics in dentistry. Noradrenaline is effective in vasodilating shock; *isoproterenol* is an emergency treatment in asystole of the heart. Selective agonists of adrenergic receptors (and indication): *phenylephrine* (α_1 , vasodilating shock), *clonidine* and *guanfacin* (α_2 , hypertension), *dobutamine* (β_1 , acute heart failure), *fenoterol* and *salmeterol* (β_2 , asthma bronchiale and premature labour).

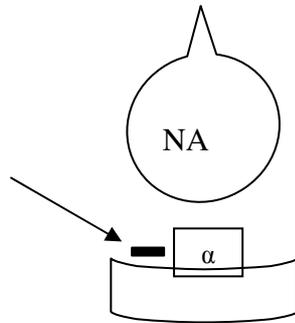
2.2.2.2. Indirectly acting sympathetic agonists



Indirectly acting sympathetic agonists do not bind to adrenergic receptors. These drugs release noradrenaline from the axon terminal, such as *amphetamine*, *ephedrine* and *tyramine*. *Tyramine* is not a drug but a sympathomimetic amino acid in foods (cheese, wine). Large amounts of chianti wine or camembert contain so much tyramine that MAO enzyme can not completely metabolize the amino acid, especially in depressive patients who are treated with MAO inhibitors. In these cases tyramine may result in hypertensive crisis ('cheese reaction'). Because of the effect on the brain, amphetamine is considered mainly

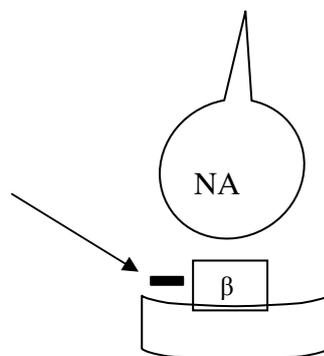
as a narcotic (its congener is 'ecstasy'). *Ephedrine* is a bronchodilator in pulmonology.

2.2.2.3. Adrenergic α receptor blocking drugs



Representatives of α adrenergic receptor blockers are the ergot alkaloids, more precisely, the dihydro derivatives of ergot alkaloids. They are non-selective drugs (inhibit both α_1 and α_2 receptors) similar to *phentolamine* and *phenoxybenzamine*. α_1 selective blocking drugs, *prazosine* or *doxazosine*, are indicated for the treatment of hypertension and hypertrophy of the prostate.

2.2.2.4. Adrenergic β receptor blocking drugs

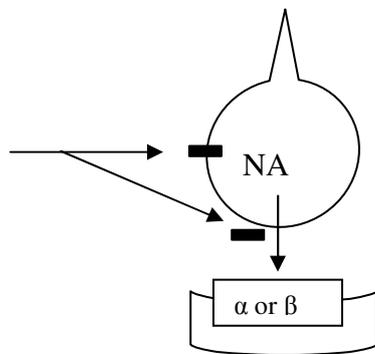


A β receptor blockers produce negative cardiac effects (negative chrono-, dromo-, inotropic effects). Accordingly, tachycardia and hypertension ('minute volume' hypertension) are the main indications. β receptor blocking drugs are also used in angina pectoris (decrease the oxygen demand of the heart) and in certain types of cardiac arrhythmias (mainly supraventricular). Non-selective blockers are (β_1 and β_2 blockers): *propranolol*, *pindolol*, *oxprenolol*. Pindolol and oxprenolol have intrinsic sympathomimetic activity (ISA). ISA positive drugs enhance the resting work but they decrease the frequency and contractility of the heart upon sympathetic stimulation. The advantage of the selective blockers (only β_1 receptor block: *metoprolol*, *bisoprolol*) is that

bronchoconstriction and vasoconstriction do not occur with these drugs because β_2 receptors are not blocked. It should be stated, however, that selectivity is relative and, in large doses, β_1 blockers may also exert β_2 block and, consequently, these drugs may cause difficulties in respiratory diseases or ischaemia in e.g. Raynaud's disease.

β blockers improve life expectancy in chronic (but not in acute!) heart failure. The drugs, mainly the non-selective ones, inhibit glycogenolysis and thus, antidiabetic therapy should be adjusted to the patients' need when β -blockers are used together with antidiabetic drugs. Beta blockers may cause atrioventricular block in the heart –as an adverse effect- in patients with an underlying heart block.

2.2.2.5. Adrenergic neuronal blocking drugs



Adrenergic neuronal blocking drugs do not act on postsynaptic receptors. These drugs act in the presynaptic (axonal) part of the sympathetic postganglionic fiber, and decrease the synthesis and/or release of noradrenaline. In a broad sense, the agonists of α_2 receptors are also belong to this group of drugs. Antagonists of tyrosine hydroxylase by *methyrosine* or that of dopa decarboxylase by methyl dopa decrease the store of intraaxonal neurotransmitter. *Reserpine* inhibits vesicular storage and depletes noradrenaline (intraaxonal MAO degrades the amine outside the vesicle). Adrenergic neuronal blocking drugs are used- although there are much better drugs today- in the treatment of hypertension resistant to other drugs. *Bretylium* inhibits the propagation of axonal electrical impulses along the sympathetic fibers and, the drug is used as a 'chemical defibrillator' in the postoperative room following heart surgery.

