

ACTIONS OF THE AUTONOMIC NERVOUS SYSTEM

Certain drugs exert their effects by binding to cholinergic and adrenergic receptors to increase or decrease the activity of effectors normally controlled by the ANS. Drugs that are **agonists**, binds to a specific receptor and activates it, while an **antagonist** binds to a receptor and prevents it from being activated, or inhibits it.

Another drug mechanism that can affect the autonomic nervous system involves inhibition of enzymes that break down the normally secreted neurotransmitters. For example, acetylcholinesterase inhibitors cause an excessive amount of acetylcholine to build up in the synaptic cleft (because it is not broken down by the enzyme called acetylcholinesterase). This excessive acetylcholine causes more parasympathetic symptoms than sympathetic symptoms because acetylcholine is used in both the first and second synapses of the two neuron pathway to body target tissues. Acetylcholinesterase inhibitors do affect the sympathetic nervous system in the first synapse but not the second synapse where norepinephrine is released. Therefore if a person is exposed to an acetylcholinesterase inhibitor they will have symptoms like bradycardia, diarrhea, bronchoconstriction and constriction of the pupils. Interestingly, they will have a lot of general body sweating as well even though that is a sympathetic response. But, that is because general sweating is the one exception in the sympathetic nervous system that has acetylcholine in the second synapse between neuron and target organ. Sweating is the one exception that acts just like the parasympathetic nervous system in its organization of the neurotransmitters and target receptors.

In the following section, some other drugs will be presented. Having an understanding of the ANS and its particular receptors located on effectors and the drugs that activate or block these receptors will assist your understanding of the actions of this system.

Eyes

The eye has multiple autonomic functions controlled by several autonomic receptors. Among these are the intrinsic muscles of the eye (those controlling the size of the pupil and the shape of the lens) and the secretory epithelium (produces aqueous humor) of the ciliary body.

Circular and radial muscles of the iris, named sphincter pupillae and dilator pupillae respectively, control how much light enters the eye. Outer iris smooth muscles - the dilator pupillae muscles express alpha 1 receptors, cause mydriasis when they contract and are controlled by sympathetic fibers. The inner, sphincter pupillae muscles are innervated by the parasympathetic division, express M3 receptors, and cause miosis when they contract.

Ophthalmologists often need to enlarge the diameter of the pupil in order to more easily examine the retina.

Phenylephrine is an alpha 1 agonist and **atropine** is a muscarinic antagonist. Both are mydriatics and are administered as eye drops to reduce systemic effects.

The function of the lens is to focus an image on the retina. Depending on whether light rays are coming from an object seen up close (more bending of light required) or far away (less bending required), the lens changes shape to allow for this clear focus. The lens of the eye is an elastic bi-convex structure made of crystalline protein. The lens in a more spherical shape (more convex) will cause more bending of light which is necessary to see things close up. The lens in a

more flattened state (less convex) will cause less bending of light. A flatter lens is necessary to see things far away. Regulation of the ciliary muscles helps determine the convexity of the lens. Ciliary muscles are innervated by both parasympathetic and sympathetic fibers. Activation of beta 2 receptors expressed on ciliary muscles causes a flatter lens for far vision, while muscarinic receptors mediate a more convex lens for near vision. One of the side effects of atropine eye drops used to cause mydriasis is blurred vision because it impairs the lens' ability to accommodate for near vision (**cycloplegia**).

Contraction of the ciliary muscle also puts tension on the trabecular network. This action opens up its pores and facilitates outflow of aqueous humor into the canal of Schlemm and back into systemic circulation. For this reason, eye drops that are muscarinic agonists, such as **pilocarpine**, can be used to treat elevated intraocular pressure (glaucoma), lowering intraocular pressure by increasing the outflow of aqueous humor. Stimulation of beta 1 receptors on the ciliary body epithelium increases the production of aqueous humor. Therefore, beta 1 antagonists such as **betaxolol** are also often used to treat glaucoma, since they reduce the production of aqueous humor.

Blood Vessels

Arterioles of the body mostly express alpha 1 receptors on their smooth muscle cells. Activating these receptors results in an increase in intracellular calcium causing smooth muscle contraction. This contraction narrows the diameter of the arteriole lumen thus reducing blood flow. Since arterioles express primarily alpha 1 receptors, you might imagine that an increase in sympathetic nerve firing would result in vasoconstriction of most arterioles. Arterioles of certain organs including skeletal muscle and cardiac muscle express beta 2 receptors in addition to alpha 1 receptors. Beta 2 receptors are activated primarily by circulating epinephrine and their stimulation causes relaxation of smooth muscle and vasodilation. The degree of vasodilation is dependent on the density of alpha 1 vs. beta 2 receptors expressed on arterioles in a particular tissue as well as on the concentration of epinephrine in the blood. During a "fright, flight, or fight" response, vasodilation of certain arterioles supplying skeletal tissue is essential. Ample oxygen and nutrients are critical when running away from ferocious bears or scary dating situations.

Since alpha 1 receptors are so important in regulating the size of arterioles, activating or blocking them can greatly influence blood pressure. **Prazosin** is an alpha 1 antagonist used to treat high blood pressure. It can also be used to treat Raynaud's disease which results from excessive vasoconstriction particularly in the fingers, cutting off the blood supply leading to cold fingers and in severe cases gangrene.

While it is true that there are some blood vessels (very few) that have parasympathetic cholinergic innervation that will cause vasodilation, the vast majority of blood vessels have no parasympathetic innervation.

Sweat Glands

Sweat glands are exclusively innervated by the sympathetic division. Postganglionic neurons of the sympathetic division that innervate glands responsible for generalized sweating secrete ACH. This is the exception to the rule since postganglionic sympathetic neurons usually secrete norepinephrine. After its release from the postganglionic cell, ACH crosses the neuroeffector junction and binds to muscarinic receptors expressed on sweat glands for generalized sweating. Localized sweat glands are activated by stress and are those located in the palms, soles, genitalia, and armpits and express alpha 1 receptors. **Terazosin** is another alpha 1 antagonist that is sometimes used to treat excessive sweating (hyperhidrosis).

Heart

Activation of the sympathetic division and release of catecholamines from the adrenal medulla leads to increased heart rate and force of contraction. This stimulatory effect is due to a high concentration of beta 1 receptors in the myocardium and cells in the SA node. Selective beta 1 antagonists like **atenolol** are often used to treat high blood pressure by decreasing heart rate and force of contraction.

Parasympathetic stimulation or administration of a muscarinic agonist has an opposing effect on the heart, decreasing heart rate. Injectable **atropine**, a muscarinic antagonist, is often used with other drugs in emergency medicine to start

the heart back up after cardiac arrest. This action blocks parasympathetic activity which normally slows the heart rate.

Lungs

Activation of muscarinic receptors located in the smooth muscle lining the bronchiole tree results in constriction of air passageways, while activation of beta 2 receptors by circulating epinephrine causes smooth muscle relaxation and dilation of the bronchioles (Note: beta 2 receptors are not innervated by postganglionic fibers and therefore respond to circulating epinephrine secreted by the adrenal medulla). Pharmacological treatment aimed at opening up the airways focuses on blocking parasympathetic actions or augmenting actions of the sympathetic division. A muscarinic antagonist such as **ipratropium**, or a beta 2 agonist like **albuterol** can be administered via an inhaler and cause bronchodilation. This relaxation of the smooth muscle in air passageways is very important in the treatment of asthma and chronic obstructive pulmonary disease (COPD) when ventilation of the lungs is compromised.

Stomach and Intestines

Activity of the enteric nervous system can be modified by activity of the ANS. The gastrointestinal tract is dually innervated by both divisions, but regulation is not equal. Recall that the parasympathetic division is most active under "rest and digest" conditions. Parasympathetic fibers leading to the gastrointestinal tract are much more extensive and have a much greater influence on digestion compared to the sympathetic division. The parasympathetic division increases the secretions from glands, promotes mixing of food with digestive enzymes and bile, and propels material down the digestive tract. Many muscarinic receptors and fewer adrenergic (alpha 1 and beta 2) receptors are located in the smooth muscle of the digestive tract wall. Activation of the muscarinic receptors and blocking of adrenergic receptors leads to increased motility and relaxation of sphincters which augments material propulsion.

Postoperative ileus is a condition which sometimes results after surgery in which there is a disruption in the normal peristaltic activity of the GI tract. To re-establish normal gut motility, a muscarinic agonist such as **bethanechol** may be given to offer a "jump start."

For a summarized list of the effects of autonomic nervous activity, receptors in specific tissues, and drugs used to modify ANS activity, please review the tables below. You can also download a [colored .pdf version of the table](#) below.

A Table of Actions for the Sympathetic and Parasympathetic Divisions
Various Drugs Used to Modify the Actions of the ANS



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