Introduction to Autonomic Pharmacology

Dr.A.A. Nekooeian
Full Professor
Department of Pharmacology
Medical School
Shiraz University of Medical Sciences
Email: nekooian@yahoo.com

Reference: Katzung BG and Trevor AG.Basic and Clinical Pharmacology, McGraw-Hill, 13th edition, 2015

Learning objectives:

- Name the neurotranmitters of sympathetic and parasympathetic nervous system

- Name the receptors of sympathetic and parasympathetic nervous system

- Describe the effects of stimulation of sympathetic and parasympathetic nervous system receptors

- Describe the reflex control of cardiovascular system

The nervous system is conventionally divided into the central nervous system (CNS; the brain and spinal cord) and the peripheral nervous system (PNS; neuronal tissues outside the CNS). The motor (efferent) portion of the nervous system can be divided into two major subdivisions: autonomic and somatic. The autonomic nervous system (ANS) is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as cardiac output, blood flow distribution, and digestion, which are necessary for life. The somatic subdivision is largely concerned with consciously controlled functions such as movement, respiration, and posture.

Nervous connection in the ANS

A nervous connection in the ANS from the CNS to the periphery (to an organ) is composed of 3 components (figure 1). These components include a preganglionic neuron (fiber), ganglia, and postganglionic neurons. The preganglionic neurons originate from the CNS (brain and spinal cord), and end up in autonomic gangalia. The gangalia are the places that pre- and post ganglionic fibers do synapse. The post ganglionic fibers originate from the ganglia and end up in innervated organs. However, the autonomic inneravation of adrenal medulla does not follow this general rule. Here, there is no postganglionic neuron, and sympathetic preganglionic fiber synapse with Chromaffin cells, which upon stimulation release epinephrine (80%) and norepinephrine (20%).

Autonomic nervous system

The ANS lends itself to division on anatomic grounds into two major portions: the sympathetic (thoracolumbar) division and the parasympathetic (craniosacral) division.

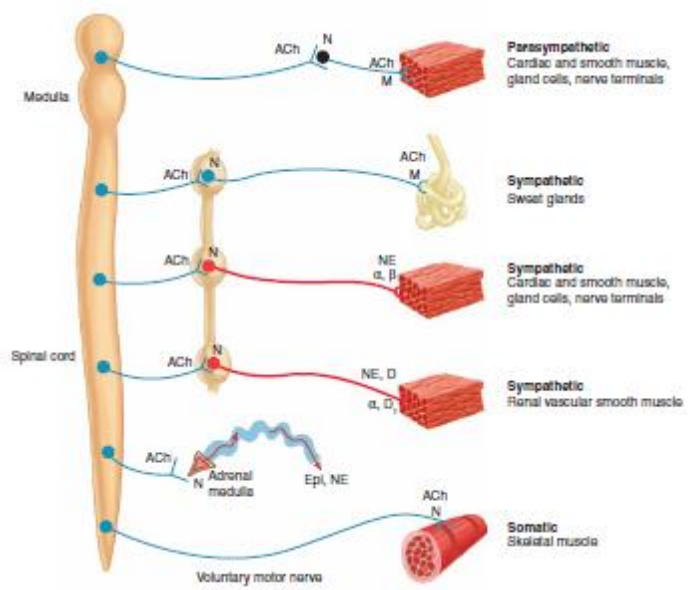

Figure 1.

Parasympathetic (cholinergic) nervous system

The parasympathetic preganglionic fibers originate from the CNS through the cranial nerves (the third, seventh, ninth, and tenth) and sacral spinal nerve roots (the third and fourth). Majority of parasympathetic preganglionic fibers terminate on ganglion cells distributed diffusely or in networks in the walls of the innervated organs. However, some preganglionic parasympathetic fibers terminate in parasympathetic ganglia located outside the organs innervated: the ciliary, pterygopalatine, submandibular, otic, and several pelvic ganglia. The neurotransmitter for the parasympathetic nervous system is acetylcholine, which is released by both pre- and postganglionic neurons.

Synthesis, storage, and release of cholinergic neurotransmitter

The neurotransmitter of parasympathetic nervous system is acetycholine, which is released by both parasympathetic pre- and postganglionic neurons (figure 1). Moreover, sympathetic postganglionic nerves innervating thermoregulatory sweat glands, and somatic motor nerves innervating skeletal muscles release acetylcholine.

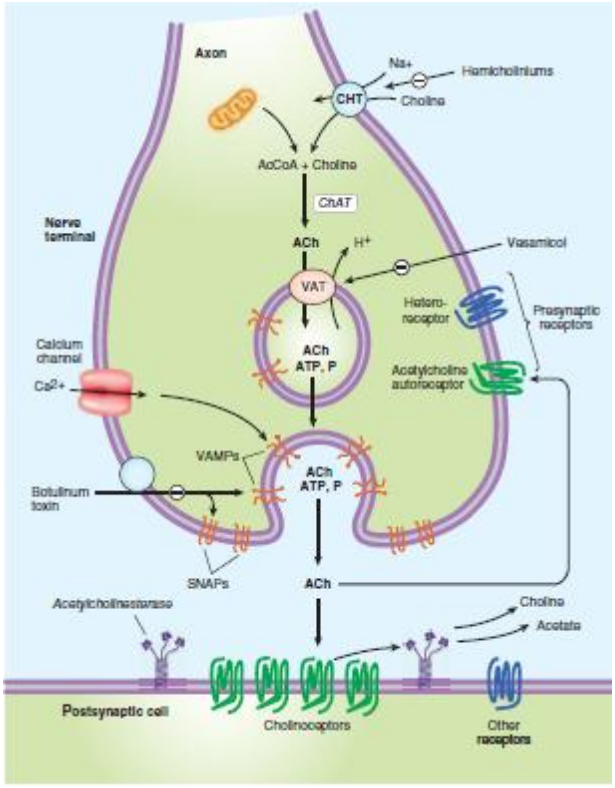

Figure 2

The terminals and varicosities of cholinergic neurons contain large numbers of small membrane-bound vesicles concentrated near the synaptic portion of the cell membrane as well as a smaller number of large dense-cored vesicles located farther from the synaptic membrane (figure 2). The large vesicles contain a high concentration of peptide cotransmitters, whereas the smaller clear vesicles contain most of the acetylcholine. Vesicles are initially synthesized in the neuron cell body and carried to the terminal by axonal transport. They may also be recycled several times within the terminal. Vesicles are provided with vesicle-associated membrane proteins (VAMPs), which serve to align them with release sites on the inner neuronal cell membrane and participate in triggering the release of transmitter. The release site on the inner surface of the nerve terminal membrane contains synaptosomal nerve-associated proteins (SNAPs), which interact with VAMPs. VAMPs and SNAPs are collectively called fusion proteins. Acetylcholine is

synthesized in the cytoplasm from acetyl-CoA and choline through the catalytic action of the enzyme choline acetyltransferase (ChAT). Acetyl-CoA is synthesized in mitochondria, which are present in large numbers in the nerve ending. Choline is transported from the extracellular fluid into the neuron terminal by a sodium-dependent membrane choline transporter (CHT). This symporter can be blocked by a group of research drugs called hemicholiniums. Once synthesized, acetylcholine is transported from the cytoplasm into the vesicles by a vesicle-associated transporter (VAT) that is driven by proton efflux. This antiporter can be blocked by the research drug vesamicol. Acetylcholine synthesis is a rapid process capable of supporting a very high rate of transmitter release. Storage of acetylcholine is accomplished by the packaging of "quanta" of acetylcholine molecules (usually 1000 to 50,000 molecules in each vesicle). Most of the vesicular acetylcholine (ACh) is bound to negatively-charged vesicular proteoglycan (VPG). Vesicles are concentrated on the inner surface of the nerve terminal facing the synapse through the interaction of so-called SNARE proteins on the vesicle (a subgroup of VAMPs called v-SNAREs, especially synaptobrevin) and on the inside of the terminal cell membrane (SNAPs called t-SNAREs, especially syntaxin and SNAP-25). Physiologic release of transmitter from the vesicles is dependent on extracellular calcium, and occurs when an action potential reaches the terminal and triggers sufficient influx of calcium ions via N-type calcium channels. Calcium interacts with the VAMP synaptotagmin on the vesicle membrane and triggers fusion of the vesicle membrane with the terminal membrane and opening of a pore into the synapse. The opening of the pore and inrush of cations results in release of the acetylcholine from the proteoglycan and exocytotic expulsion into the synaptic cleft. One depolarization of a somatic motor nerve may release several hundred quanta into the synaptic cleft. One depolarization of an autonomic postganglionic nerve varicosity or terminal probably releases less, and releases it over

a larger area. In addition to acetylcholine, several co-transmitters are released at the same time. The acetylcholine vesicle release process is blocked by botulinum toxin through the enzymatic removal of two amino acids from one or more of the fusion proteins. After release from the presynaptic terminal, acetylcholine molecules may bind to and activate an acetylcholine receptor (cholinoceptor). Eventually (and usually very rapidly), all of the acetylcholine released diffuses within range of an acetylcholinesterase (AChE) molecule. AChE very efficiently splits acetylcholine into choline and acetate, which have no significant transmitter effect, and thereby terminates the action of the transmitter. Most cholinergic synapses are richly supplied with acetylcholinesterase; the half-life of acetylcholine molecules in the synapse is therefore very short (a fraction of a second).

Parasympathetic (cholinergic) receptors

Cholinergic receptors are divided into main groups of nicotinic and muscarinic receptors. The nicotinic receptors are further divided into neuronal nicotinic and muscular nicotinic receptors. There are 5 subtypes of muscarinic receptors (M1, M2, M3, M4, M5), of which the first 3 are of clinical significance.

Locations and functions of nicotinic receptor

Neuronal nicotinic receptors have been located on the cell body of autonomic (both sympathetic and parasympathetic) nervous system, Chromaffin's cells of adrenal medulla, and postganglionic parasympathetic nerve terminal. In autonomic ganglia, the stimulation of nicotinic receptors leads to excitation and depolarization of postganglionic nerves in both branch of autonomic nervous system. In Chromaffin's cells, the activation of nicotinic receptor leads to the release of

epinephrine and norpeinephrine. In postganglionic parasympathetic nerve terminal, stimulation of nicotinic receptors results in the enhanced release of acetylycholine from the nerve terminal. These receptors mediate acetylcholine positive feedback effect on its own release. The nicotinic receptors are also located on the neuromuscular endplate. The stimulation of these receptors results in depolarization, excitation and contraction of skeletal muscle.

Locations and functions of muscarinic receptor

The M1 receptors are located on postganglionic parasympathetic nerve terminals, and its activation results in the deccreased release of acetylcholine from the nerve terminal. These receptors mediate acetylcholine positive feedback effect on its own release. The M2 receptors are mainly distributed in the heart, and it stimulation leads to decrease of heart rate, atrioventricular conduction, and atrial contraction. The ventricles do not have significant number of M2 receptors, therefore, stimulation of these receptors do not affect ventricular contractility to a significant extent. The M3 receptors have a wider distribution in the body organs. In the eye M3 receptors have been located on circular muscle of iris and ciliary muscle. Stimulation of the receptor causes contraction of both muscles. The contraction of the first muscle results in miosis, and that of the second one lead to accommodation.

The M3 receptors are also located on vascular endothelial cells, and their stimulation leads to the release of nitric oxide from such cells. Nitric oxide causes vaodilation. Stimulation of M3 receptors on pregnant uterine smooth muscle causes contraction. In gastrointestinal tract, M3 receptors are found on GI wall smooth muscle, GI sphincter, and GI epithelium. The stimulation of M3 receptors in GI cause wall smooth muscle contraction and increased peristaltic activity, relaxation of GI sphincters, and increased release of GI secretions. The salivary and gastric

glands are strongly stimulated; the pancreas and small intestinal glands are stimulated less so. The stimulation of M3 receptors on bronchiolar smooth muscle and bronchiolar glands results in the muscle contraction and increased glands' secretion. In urinary system, stimulation of M3 receptors on bladder wall smooth muscle and bladder sphincter results in the wall contraction and sphincter relaxation. These two action help voiding. Also, stimulation of M3 receptors on thermoregulatory sweat gland results in increased sweating.

Sympathetic (adrenergic) nervous system

Sympathetic nervous system originates from spinal nerves (from thoracic 1 to lumbar 3).

Most sympathetic preganglionic fibers are short and terminate in ganglia located in the paravertebral chains that lie on either side of the spinal column. The remaining sympathetic preganglionic fibers are somewhat longer and terminate in prevertebral ganglia, which lie in front of the vertebrae, usually on the ventral surface of the aorta. From the ganglia, postganglionic sympathetic fibers run to the tissues innervated.

Synthesis, storage, and release of adrenergic neurotransmitters

Sympathetic nervous system has 4 neurotransmitter including acetylcholine, norpeinephrine, epinephrine and dopamine. All preganglionic fibers of sympathetic nervous system release acetylcholine. Majority of sympathetic postganglionic fibers release norepinephrine. However, in adrenal medulla there is no post ganglionic fibers, and Chromaffin's cell release epinephrine (80%) and norpeinephrine (20%). Also, sympathetic postganglionic fiber to thermoregulatory sweat gland and renal vasculature release acetylcholine and dopamine, respectively (figure 1).

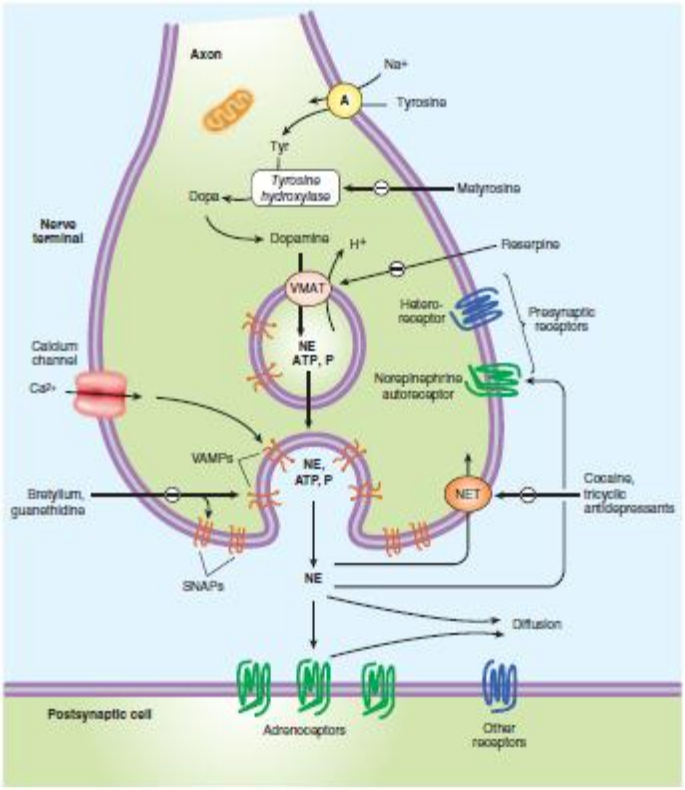

Figure 3

Adrenergic neurons transport a precursor amino acid (tyrosine) into the nerve ending, then synthesize the catecholamine transmitter, and store it in membrane-bound vesicles (figure 3). In most sympathetic postganglionic neurons, norepinephrine is the final product. In the adrenal medulla, some norepinephrine is further converted to epinephrine. In dopaminergic neurons, synthesis terminates with dopamine. Several processes in these nerve terminals are potential sites of drug action. One of these, the conversion of tyrosine to dopa by tyrosine hydroxylase, is the rate-limiting step in catecholamine transmitter synthesis. It can be inhibited by the tyrosine analog metyrosine. A high-affinity antiporter for catecholamines located in the wall of the storage vesicle (vesicular monoamine transporter, VMAT) can be inhibited by the reserpine alkaloids. Reserpine causes depletion of transmitter stores. Another transporter (norepinephrine

transporter, NET) carries norepinephrine and similar molecules back into the cell cytoplasm from the synaptic cleft. NET is also commonly called uptake 1 or reuptake 1 and is partially responsible for the termination of synaptic activity. NET can be inhibited by cocaine and certain antidepressant drugs, resulting in an increase of transmitter activity in the synaptic cleft. Release of the vesicular transmitter store from noradrenergic nerve endings is similar to the calcium-dependent process previously described for cholinergic terminals. Termination of noradrenergic transmission results from two processes: reuptake into the nerve terminal by NET and simple diffusion away from the receptor site (with eventual metabolism in the plasma or liver). Norepinephrine and epinephrine can be metabolized by several enzymes including monoamine oxidase and catecholamine-o-methyl transferase.

Sympathetic (adrenergic) receptors

Sympathetic receptors are divided into two main groups of alpha and beta receptors. Two subtypes of alpha receptors ($\alpha 1$ and $\alpha 2$) and 3 subtypes of beta receptors ($\beta 1$, $\beta 2$, and $\beta 3$) have been characterized.

Location and effects of alpha1-receptor activation

Alpha1 receptors are widely expressed in vascular beds (skin, splanchnic and skeletal muscle), and their activation leads to arterial and venous vasoconstriction. In the eye, the radial pupillary dilator (radial) muscle of the iris contains $\alpha 1$ receptors; activation of which causes contraction of the muscle contraction and mydriasis. Moreover, GI sphincter express alpha1 receptors, which their stimulation leads to contraction of the sphincters. Also, urinary bladder sphincter and prostate smooth muscle contain alpha1 receptors. The activation of these receptor leads to

contraction of the sphincter and the smooth muscle. Alpha1 receptors are also expressed in pregnant uterus, and their stimulation leads to uterine contraction. Stimulation of alpha1 receptors on apocrine (stress) sweat glands results in increase stress sweating. The human liver express alpha1 receptors, which their stimulation results in increased glycogenolysis and gluconeogenesis.

Location and effects of alpha2-receptor activation

Postganglionic sympathetic nerve terminals express alpha2 receptors. Stimulation of these receptors decreases the release of norepinephrine from such nerve terminals. These receptors mediate the negative feedback effects of norepinehrine on its own release. Alpha2 receptors are present in the vasculature, and their activation leads to vasoconstriction. However, the role of alpha2 receptors in producing this effect is much less than that of alpha1 receptors. Moreover, alpha2 receptors are also present on GI wall smooth muscle, and their activation results in the relaxation of GI wall smooth muscle. Central nervous system has α2 receptors, which their activation leads to inhibition of sympathetic tone and reduced blood pressure. Stimulation of Alpha2 receptors in the eye increases the outflow of aqueous humor from the eye.

Location and effects of beta1 receptor activation

Stimulation of β1 receptors in the heart increases heart rate, cardiac (atrial and ventricular) contractility, atrioventricular conduction, and cardiac output. Also, stimulation of β1 receptors on juxtaglumerular cells in the kidney results in increased release of rennin.

Location and effects of beta2 receptor activation

Beta2 receptors have been located in SA node, and atrial and ventricular muscle. The stimulation of these receptors also leads to increased heart rate, and atrial and ventricular contractility. However, the contribution of β2 to these effects is much less than that of β1 receptors. Similar to α1 receptors in the liver, stimulation of β2 cause increased glycogenolysis and gluconeogenesis. The contribution of β2 receptors to these effects is much more than that of α1 receptors. Beta receptors are also present in skeletal muscle vessels, and their activation leads to vasodilation. In GI wall smooth muscle, activation of β2 receptors causes relaxation of GI wall. Bronchiolar, bladder, uterine smooth muscle also express β2 receptors, which relaxes these muscle upon stimulation. Stimulation of β2 receptor in the eye ciliary muscle causes the relaxation of the muscle. Fat cells express β3, which upon stimulation causes lipolysis.

Integration of Cardiovascular Function

Autonomic reflexes are particularly important in understanding cardiovascular responses to autonomic drugs. The primary controlled variable in cardiovascular function is mean arterial pressure. Changes in any variable contributing to mean arterial pressure (eg, a drug-induced increase in peripheral vascular resistance) evoke powerful homeostatic secondary responses that tend to compensate for the directly evoked change. The homeostatic response may be sufficient to reduce the change in mean arterial pressure and to reverse the drug's effects on heart rate. A slow infusion of norepinephrine provides a useful example. This agent produces direct effects on both vascular and cardiac muscle. It is a powerful vasoconstrictor and, by increasing peripheral vascular resistance, increases mean arterial pressure. In the absence of reflex control—in a patient who has had a heart transplant, for example—the drug's effect on the heart is also

stimulatory; that is, it increases heart rate and contractile force. However, in a subject with intact reflexes, the negative feedback response to increased mean arterial pressure causes decreased sympathetic outflow to the heart and a powerful increase in parasympathetic (vagus nerve) discharge at the cardiac pacemaker. This response is mediated by increased firing by the baroreceptor nerves of the carotid sinus and the aortic arch. Increased baroreceptor activity causes the changes mentioned in central sympathetic and vagal outflow. As a result, the *net* effect of ordinary pressor doses of norepinephrine in a normal subject is to produce a marked increase in peripheral vascular resistance, an increase in mean arterial pressure, and a consistent *slowing* of heart rate. Bradycardia, the reflex compensatory response elicited by this agent, is the *exact opposite* of the drug's direct action; yet it is completely predictable if the integration of cardiovascular function by the ANS is understood.

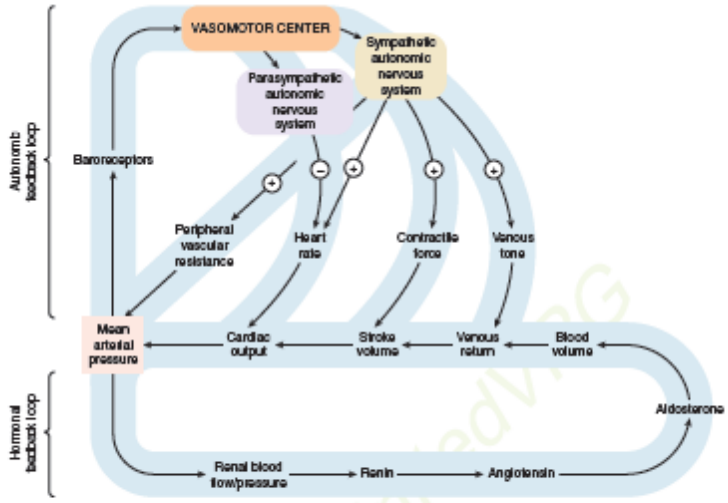

FIGURE 6–7 Autonomic and hormonal control of cardiovascular function. Note that two feedback loops are present: the autonomic nervous system loop and the hormonal loop. The sympathetic nervous system directly influences four major variables: peripheral vascular resistance, heart rate, force, and venous tone. It also directly modulates renin production (not shown). The parasympathetic nervous system directly influences heart rate. In addition to its role in stimulating aldosterone secretion, angiotensin II directly increases peripheral vascular resistance and facilitates sympathetic effects (not shown). The net feedback effect of each loop is to compensate for changes in arterial blood pressure. Thus, decreased blood pressure due to blood loss would evoke increased sympathetic outflow and renin release. Conversely, elevated pressure due to the administration of a vasoconstrictor drug would cause reduced sympathetic outflow, reduced renin release, and increased parasympathetic (vagal) outflow.

Sample question:

Which of the following effects occur upon activation of parasympathetic nervous system?
A) Bronchodilation
B) Decreased intestinal motility
C) Increased thermoregulatory sweating
D) Increased heart rate