THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) is the portion of the nervous system which innervates smooth muscle, cardiac muscle & glands, & controls the visceral functions of the body. It helps control arterial pressure, gastrointestinal tract (GIT) motility & secretion, urinary bladder emptying, sweating, body temperature, & many other activities, some of which are controlled almost entirely & some only partially by the ANS.

ANS operates largely unconsciously. So under normal conditions, you are not aware of GIT contractions, heart beat, blood vessel diameter change, pupil dilatation & constriction, etc. However, some visceral sensations do give rise to conscious recognition, such as hunger, nausea, & fullness of urinary bladder & rectum.

The ANS is activated by centers in the spinal cord, brainstem, hypothalamus, & parts of the cerebral cortex. The ANS often operates by means of visceral reflexes (i.e. sensory impulses initiated in visceral receptors are relayed via visceral afferent pathways to the central nervous system (CNS) & are integrated within it at different levels which in turn transmit reflex responses via efferent autonomic pathways to the visceral effectors to control their activities). Visceral reflexes can also be initiated by impulses passing through somatic afferent fibers. Simple reflexes, such as emptying of urinary bladder, are integrated in the spinal cord. More complex reflexes are integrated at higher levels (such as centers in the brainstem for control of blood pressure, heart rate, & respiration, & centers in the hypothalamus for temperature regulation & control of hunger & thirst). Also the hypothalamus sends signals which affect activities of the brainstem autonomic control centers; for instance stimulation in appropriate areas of the hypothalamus can activate the medullary cardiovascular control centers strongly enough to increase the arterial pressure to more than double normal. In addition, portions of the cerebral cortex can transmit impulses to lower centers in the hypothalamus & brainstem & influence the autonomic activities.

The ANS differs from the somatic motor system in the following ways:

1- Anatomically: In somatic motor system, each motor pathway from CNS to skeletal muscle is composed of a single neuron, whose axon is myelinated. In the autonomic nervous system, the pathway from CNS to the stimulated organ is made up of 2 neurons, preganglionic & postganglionic neurons (Fig. 1). Centrally located preganglionic neurons send out mostly myelinated axons (relatively slow conducting B fibers) that synapse on cell bodies of postganglionic neurons that are located in all cases outside the CNS. The axons of postganglionic neurons, mostly unmyelinated C fibers, end on visceral effectors.

2- Functionally: Somatic motor neurons have only an excitatory effect on skeletal muscle; there are no peripheral inhibitory actions exerted on skeletal muscle. In the ANS the postganglionic fibers cause excitation or inhibition of the innervated organ.

The ANS is divided into 2 major divisions, the sympathetic nervous system (SNS), & the parasympathetic nervous system (PNS) (this is an anatomic & functional division). The SNS & the PNS are continually active; impulses are transmitted at a low rate continuously through most of the nerve fibers of SNS & PNS. The basal rates of activity are known as sympathetic tone & parasympathetic tone, respectively.

Anatomic Organization of Sympathetic Nervous System

The preganglionic neurons have their cell bodies in the intermediolateral gray column of spinal cord segments (T1-L2) & their axons pass through the anterior nerve roots into the corresponding spinal nerves. Then soon leave the spinal nerves & pass through the white rami communicantes into the paravertebral sympathetic ganglion chain (a chain of ganglia that extend along either side of vertebral column from base of skull to the coccyx) (Figs. 2&3). Then the course of the fibers can be one of the following three:

1- They can synapse with postganglionic neurons in the ganglia that they enter.
2- They can pass up or down the chain to end in paravertebral ganglia at higher or lower levels than the point of entrance.
3- They can pass through the sympathetic chain without synapsing, then through one of the sympathetic nerves radiating outward from the chain & finally terminating in one of the prevertebral (collateral) ganglia such as the celiac ganglion.

So postganglionic neurons (Figs. 2&3) originate either in one of the sympathetic chain ganglia or in a prevertebral ganglion. Then postganglionic fibers travel to the various organs. Some
of the postganglionic fibers pass back from sympathetic chain through gray rami communicantes into the spinal nerves at all levels of spinal cord. These fibers extend to all parts of the body in branches of spinal nerves to supply smooth muscles in blood vessels’ wall, sweat glands & piloerector muscles connected with hair follicles in skin.

**Special nature of sympathetic nerve endings in the adrenal medullae:** Preganglionic nerve fibers pass all the way without synapsing from the spinal cord to the sympathetic chains, to splanchnic nerves to adrenal medullae, there they end directly on special cells that secrete epinephrine & norepinephrine directly into the blood stream. These cells are modified neuronal cells analogous to postganglionic neurons & even have rudimentary nerve fibers that secrete the hormones (Fig. 4).

**Anatomic Organization of Parasympathetic Nervous System**

PNS has a cranial outflow & a sacral one (Figs. 3&5). In the cranial outflow the preganglionic fibers leave the CNS through cranial nerves III, VII, IX, & X. In the sacral outflow the preganglionic neurons originate in the intermediate gray column of spinal cord segments S2 & S3 & occasionally S1 & S4. Their fibers leave the spinal cord through the anterior roots of the corresponding spinal nerves & then leave the spinal nerves & form the pelvic nerve on each side of spinal cord. The preganglionic fibers in both outflows end on short postganglionic neurons in peripheral ganglia located near or on the visceral structures (Figs. 3&5).

**Chemical Transmission at Autonomic Junctions**

Transmission at the synaptic junctions between pre- & postganglionic neurons & between the postganglionic neurons & the tissues is chemically mediated. The principal transmitter agents involved are acetylcholine & norepinephrine (noradrenaline) (Fig. 6).

Those neurons that secrete acetylcholine are said to be cholinergic, & those that secrete norepinephrine are said to be noradrenergic (the term adrenergic is also applied to these neurons). So on the basis of the chemical mediator released, the ANS is divided into cholinergic & noradrenergic divisions.

- **The neurons that are cholinergic are** (Fig. 6):
  1. All preganglionic neurons in SNS & PNS.
  2. All or almost all of the postganglionic neurons of PNS.
  3. Postganglionic sympathetic nerve fibers to the sweat glands & to few blood vessels in skeletal muscles which produce vasodilatation when stimulated.

- **The remaining postganglionic sympathetic neurons are noradrenergic.**

**Secretion of Acetylcholine & Norepinephrine by Postganglionic Nerve Endings:** A few of the postganglionic autonomic nerve endings, especially those of the parasympathetic nerves, are similar to but much smaller than those of the skeletal neuromuscular junction (Fig. 7a). However, some of the parasympathetic nerve fibers & almost all the sympathetic fibers merely touch the effector cells of the organs that they innervate as they pass by; in some instances, they terminate in connective tissue located adjacent to the cells that are to be stimulated. Where these filaments pass over or near the effector cells, they usually have bulbous enlargements called varicosities; it is in these varicosities that the transmitter vesicles of acetylcholine or norepinephrine are found. Also in the varicosities are large numbers of mitochondria to supply the ATP required to energize acetylcholine & norepinephrine synthesis (Fig. 7b).

When an action potential spreads over the terminal fibers, the depolarization process increases the permeability of the fiber membrane to Ca\(^{2+}\), allowing them to diffuse into the nerve terminals or nerve varicosities. There the Ca\(^{2+}\) interacts with those secretory vesicles that are adjacent to the membrane, causing them to fuse with the membrane & to empty their contents to the exterior. Thus, the transmitter substance is secreted.

**Acetylcholine (ACh):** It is synthesized in the terminal nerve endings of cholinergic fibers. Most of this synthesis occurs in the axoplasm outside the vesicles & then it is stored in the vesicles in the nerve endings. Once ACh has been secreted by the cholinergic nerve ending, it persists in the tissue for a few seconds; then most of it is split into an acetate ion & choline by the enzyme acetylcholinesterase present in the local connective tissue in the synaptic area. The basic chemical reactions of synthesis & catabolism of ACh are shown below:
Choline + Acetyl-CoA $\rightarrow$ ACh  
(choline acetyltransferase)  
Acetyl + Choline  
(acetylcholinesterase)

The choline that is formed is in turn transported actively back into the terminal nerve endings where it is used again for synthesis of new ACh.

There is usually no ACh in the circulation & the effects of localized cholinergic discharge are generally discrete & of short duration.

**Norepinephrine (NE):** Synthesis of NE begins in the axoplasm of the terminal nerve endings of noradrenergic nerve fibers, but is completed inside the vesicles. The basic steps are the following:

1. Tyrosine $\xrightarrow{\text{hydroxylation}}$ DOPA
2. DOPA $\xrightarrow{\text{decarboxylation}}$ Dopa min e
3. Transport of dopamine into vesicles.
4. Dopa min e $\xrightarrow{\text{hydroxylation}}$ NE
   In adrenal medulla, this reaction goes still one step further to transform 80% of the NE into epinephrine (E) & as follows:
5. NE $\xrightarrow{\text{methylation}}$ E

After secretion of NE by the terminal nerve endings, it is removed from the secretory site in 3 ways: 1-Reuptake into the noradrenergic nerve endings by an active transport process –accounting for the removal of 50-80% of secreted NE. 2-Diffusion away from the nerve endings into the surrounding body fluids & then into the blood –accounting for removal of most of the remainder of the NE. & 3-Destruction by enzymes to a slight extent. One of these enzymes is monoamine oxidase (MAO) which is widely distributed, being particularly plentiful in the nerve endings themselves, and another is catechol-O-methyl transferase (COMT) which is also widely distributed in all tissues particularly in liver, kidneys, and smooth muscles, but it is not found in nerve endings.

NE secreted directly into a tissue by noradrenergic nerve endings remains active for only a few seconds, demonstrating that its reuptake and diffusion away from the tissue are rapid. However, NE & E secreted into the blood by the adrenal medullae remain active until they diffuse into some tissue, where they are destroyed by COMT; this occurs mainly in the liver. Therefore, when secreted into the blood, both NE & E remain active for a longer time.

NE spreads farther & has a more prolonged action than ACh. E & some of the NE found in the plasma come from the adrenal medullae, but most of the NE diffuses into the blood stream from noradrenergic nerve endings.

**Receptors on the Effector Organs**

ACh, NE, & E stimulate the effector organs by first binding with highly specific receptors on the effector cells. The receptor is on the outside of the cell membrane, bound as a prosthetic group to a protein molecule that penetrates all the way through the cell membrane. When the transmitter binds with the receptor, this causes a conformational change in the structure of the protein molecule. The altered protein molecule excites or inhibits the cell, most often by: 1-Causing a change in the cell membrane permeability to one or more ions. Or 2- Activating or inactivating an enzyme (or other intracellular chemical) inside the cell. The enzyme often is attached to the other end of the receptor protein where it protrudes into the interior of the cell. For e.g. binding of E with its receptor on the outside of many cells increases the activity of the enzyme adenylcyclase on the inside of the cell, & this causes the formation of cyclic adenosine monophosphate (cAMP) which can initiate any one of many different intracellular actions.

The effects that occur, whether excitation or inhibition, by an autonomic transmitter substance in an organ is determined by the nature of the receptor protein in the cell membrane. In each organ,
the resulting effects are likely to be entirely different from those in other organs. So an autonomic
transmitter substance can cause inhibition in some organs or excitation in others.

**ACh Receptors (Cholinergic Receptors):** ACh activates 2 types of receptors (Fig. 6):
1. **Muscarinic receptors:** found in all effector cells stimulated by the postganglionic neurons of the
   PNS & in those stimulated by the postganglionic cholinergic neurons of the SNS.
2. **Nicotinic receptors:** found in the synapses between the preganglionic & postganglionic neurons
   of both the SNS & PNS. These receptors are also present at many nonautonomic nerve endings,
   for instance, in the membranes of skeletal muscle fibers at the neuromuscular junction (Fig. 1).

Both muscarinic & nicotinic ACh receptors are also found in large numbers in the brain.

**Adrenergic Receptors:** There are 2 major types of adrenergic receptors (Fig. 6):
1. **Alpha receptors:** divided into α1 and α2
2. **Beta receptors:** divided into β1, β2 and β3

- NE excites mainly α receptors, but excites the β receptors to a less extent as well. E excites
  both types of receptors approximately equally. Therefore the relative effects of NE & E on different
  effector organs are determined by the type of receptors in the organs. If they are all β receptors, E
  will be the more effective excitant.

- Table 1 gives the distribution of α and β receptors in some of the organs & systems controlled
  by the sympathetics. It can be noted that certain alpha functions are excitatory whereas others are
  inhibitory. The same is true for beta receptors.

### Table 1 Adrenergic receptors & function

<table>
<thead>
<tr>
<th>Alpha receptors</th>
<th>Beta receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction (α1, α2)</td>
<td>Vasodilatation (β2)</td>
</tr>
<tr>
<td>Contraction of radial muscle of iris (α1)</td>
<td>Cardioacceleration (β1)</td>
</tr>
<tr>
<td>Intestinal relaxation (α1, α2)</td>
<td>Increased myocardial Strength (β1)</td>
</tr>
<tr>
<td>Intestinal sphincter contraction (α1)</td>
<td>Intestinal relaxation (β2)</td>
</tr>
<tr>
<td>Pilomotor contraction (α1)</td>
<td>Uterus relaxation (β2)</td>
</tr>
<tr>
<td>Bladder sphincter contraction (α1)</td>
<td>Bronchodilatation (β2)</td>
</tr>
<tr>
<td></td>
<td>Calorigenesis (β2)</td>
</tr>
<tr>
<td></td>
<td>Glycogenolysis (β2)</td>
</tr>
<tr>
<td></td>
<td>Lipolysis (β1,β3)</td>
</tr>
<tr>
<td></td>
<td>Bladder wall relaxation (β2)</td>
</tr>
</tbody>
</table>

**Excitatory & Inhibitory Actions of Sympathetic & Parasympathetic Stimulation**

Table 2 shows the effects on different visceral functions of the body caused by stimulating
either the sympathetic nerves or the parasympathetic nerves. Sympathetic stimulation causes
excitatory effects in some organs but inhibitory effects in others; the parasympathetic stimulation
also causes excitation in some but inhibition in others. Many organs receive fibers from both the
SNS & PNS & the 2 systems occasionally act reciprocally to each other (e.g. when sympathetic
stimulation excites a particular organ, parasympathetic stimulation sometimes inhibits it). Most
organs are dominantly controlled by one or the other of the 2 systems.
<table>
<thead>
<tr>
<th>Organ</th>
<th>Effect of sympathetic stimulation</th>
<th>Effect of parasympathetic stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil</td>
<td>Dilatation (contraction of radial muscle of iris)</td>
<td>Constriction (contraction of circular muscle of iris).</td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Slight relaxation</td>
<td>Contraction (allows the lens to become more convex &amp; the eye can focus on near objects)</td>
</tr>
<tr>
<td><strong>GIT</strong></td>
<td>Decreased motility &amp; decreased tone &amp; contraction of sphincters</td>
<td>Increased motility &amp; tone &amp; relaxation of sphincters</td>
</tr>
<tr>
<td><strong>Heart:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>Increased rate &amp; increased force of contraction</td>
<td>Slowed rate &amp; decreased force of contraction (especially of atria)</td>
</tr>
<tr>
<td>Coronaries</td>
<td>Dilated(β₂) Constricted(α₁,α₂)</td>
<td>Dilated</td>
</tr>
<tr>
<td><strong>Systemic arterioles:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal viscera</td>
<td>Constricted</td>
<td>None, except dilatation of vessels in certain restricted areas, such as in the blush area of the face</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Constricted (α₁)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Dilated (β₂) Constricted</td>
<td></td>
</tr>
<tr>
<td><strong>Sweat glands</strong></td>
<td>Secretion of large quantities of sweat (cholinergic, except for a few adrenergic fibers to the palms &amp; soles)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Nasal, lacrimal, &amp; upper alimentary tract glands</strong></td>
<td>Formation of concentrated secretion, vasoconstriction of blood vessels supplying the glands &amp; in this way reduces their rates of secretion</td>
<td>Strongly stimulated resulting in profuse watery secretion</td>
</tr>
<tr>
<td><strong>Liver ducts, gall bladder, urinary bladder, bronchi</strong></td>
<td>Relaxation</td>
<td>Contraction</td>
</tr>
<tr>
<td><strong>Penis</strong></td>
<td>Ejaculation</td>
<td>Erection</td>
</tr>
<tr>
<td><strong>Adrenal medullae</strong></td>
<td>Secretion of epinephrine &amp; norepinephrine</td>
<td>None</td>
</tr>
<tr>
<td><strong>Metabolic effects</strong></td>
<td>Increased mental activity</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Increased blood glucose &amp; lipids.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased muscle strength.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased muscle &amp; liver glycogenolysis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Release of glucose from liver.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased basal metabolic rate.</td>
<td></td>
</tr>
</tbody>
</table>
Functions of the Adrenal Medullae

Stimulation of the sympathetic nerves to the adrenal medullae causes large quantities of epinephrine & norepinephrine to be released into the circulation, & carried to all tissues & have almost the same effects throughout the body as direct sympathetic stimulation, except that the effects last 5-10 times as long because these hormones are removed from the blood slowly. The only significant differences are caused by the beta effects of the epinephrine in the secretion, which mainly increase the rate of metabolism & cardiac output to a greater extent than is caused by direct sympathetic nerve stimulation, which releases only norepinephrine.

The value of adrenal medullae to the function of sympathetic nervous system is as follows: E & NE are almost always released by the adrenal medullae at the same time that the different organs are stimulated directly by generalized sympathetic activation. So the organs are stimulated in 2 ways at the same time; directly by sympathetic nerves & indirectly by the medullary hormones. These 2 means support each other & one mechanism substitutes for the other when the second is lost or destroyed. Another important value of adrenal medullae is the capability of E & NE to stimulate structures of the body that are not innervated by direct sympathetic fibers (e.g. metabolic rate is increased in every cell in the body especially by E, even though only a small proportion of all the cells in the body are innervated directly by sympathetic fibers).

The Function of Sympathetic Nervous System & the Characteristics of Sympathetic Discharge

In emergency or stressful situation or emotional states (fear or fright, severe pain, exercise, bleeding, etc.), the hypothalamus is stimulated by signals passing via afferents from sense organs & cerebral cortex (paths unknown), & signals are transmitted from hypothalamus downward through the reticular formation of brainstem & into the spinal cord to cause massive sympathetic discharge. The SNS discharges as one unit (mass discharge), to prepare the individual to cope with the emergency. Changes occur in most of the systems of the body (some are excitatory & some inhibitory), such as constriction of blood vessels of skin (limits bleeding from wounds & also directs blood to vital organs -heart & brain- & to skeletal muscles), pupillary dilatation (admits more light to the eyes), increased heart rate, increased blood pressure providing better perfusion to vital organs & to muscles, increased rate & depth of respiration, increased blood glucose & free fatty acids to supply more energy, increased mental activity & increased muscle strength. These changes increase the physical fitness to prepare the individual for “fight” or “flight”. So SNS is very important, without it body cannot cope with any emergency.

At other times, sympathetic activation occurs in isolated portions of the system & in response to reflexes & the effects is localized, e.g. in heat regulation the SNS controls sweating & blood flow in the skin without affecting other organs innervated by sympathetics.

Usually the SNS has widespread, diffuse & prolonged effects in the body; because:

1- Postganglionic fibers are long & each often has many branches, projecting to several visceral organs, thus most sympathetic responses have widespread effects on the body.

2- Neuronal reuptake of NE is incomplete & NE diffuses into the general circulation from the noradrenergic nerve endings & contributes to the prolonged & diffuse effects of sympathetic discharge.

3- Sympathetic preganglionic fibers also activate the adrenal medullae leading to the release of E & NE into the bloodstream. These hormones prolong & augment the effects of sympathetic discharge.
The Function of Parasympathetic Nervous System & the Characteristics of Parasympathetic Discharge

The parasympathetic effects are largely directed towards maintenance & conservation of bodily functions, for e.g. it slows heart rate, constricts the pupil, favours digestion & absorption of food by increasing GIT motility & gastric secretion & relaxing the pyloric sphincter. So the activity of PNS conserves energy, in contrast to SNS which mobilizes body energies. PNS is mainly activated in response to reflex activity & has localized & discrete effects. It has no diffuse effects on the body. So in contrast to the common mass discharge response of the SNS, control functions of the PNS are much more likely to be highly specific.

The localized discrete effects of parasympathetic discharge are due to:
1- Postganglionic neurons are short & control visceral effectors, locally, discretely.
2- ACh when released at the nerve endings is rapidly destroyed by acetylcholinesterase, present in high concentration in synaptic area, & if ACh reaches the circulation it is destroyed by pseudocholinesterase found in plasma. This limits the activity of the PNS.

Autonomic Pharmacology

The transmitter agents are synthesized, stored in nerve endings, and released at the nerve endings. They bind to receptors on the cells on which they act initiating their characteristic actions, and then they are removed by reuptake or metabolism. Each of these steps can be stimulated or inhibited by using different drugs & consequently influencing autonomic activity & thus affecting visceral function. For example, drugs which block adrenergic receptors, depress sympathetic activity e.g. propranolol which blocks β receptors. Drugs which stimulate adrenergic receptors augment sympathetic activity e.g. phenylephrine which stimulates α receptors. Drugs like atropine, which block muscarinic receptors, block cholinergic activity at effector organs. And drugs such as neostigmine inhibit acetylcholinesterase, so prevent rapid destruction of ACh liberated by the parasympathetic nerve endings, thus potentiating parasympathetic effect.
Fig. 1 Somatic motor pathway compared with autonomic pathway
Fig. 2 Sympathetic nervous system. Pre=preganglionic neuron; Post=postganglionic neuron; RC=ramus communicans
Fig. 3 Autonomic nervous system
Fig. 4 Sympathetic innervation of adrenal medulla

Fig. 5 Parasympathetic nervous system. Pre=preganglionic neuron; Post=postganglionic neuron
Fig. 6 Autonomic neurotransmitters and receptors

Fig. 7 Postganglionic autonomic nerve endings