

Section Two: Chapter 10: The Peripheral Nervous System

The central nervous system (**CNS**) is connected to the peripheral nervous system (**PNS**) by many nerves. As mentioned previously, the CNS in simplistic terms is the brain and the spinal cord. Think of the brain as a top and centrally located organ with the spinal cord traveling down into the rest of the body.

This central portion of the nervous system must communicate with the outer regions of the body, and in this way the PNS can be viewed as an extension of the CNS radiating out and then coming back in, connected by elongated neurons and ganglion.

The PNS can be divided into two parts, the **Somatic Nervous System** (SNS) and the **Autonomic Nervous System** (ANS). The SNS is responsible for movement of the body (**soma** = body), and its effector tissue is skeletal muscle. The ANS is responsible for what are called the **automated** responses in the body (e.g., heart rate, blood pressure) and the effector tissues are cardiac muscle, smooth muscle and glands.

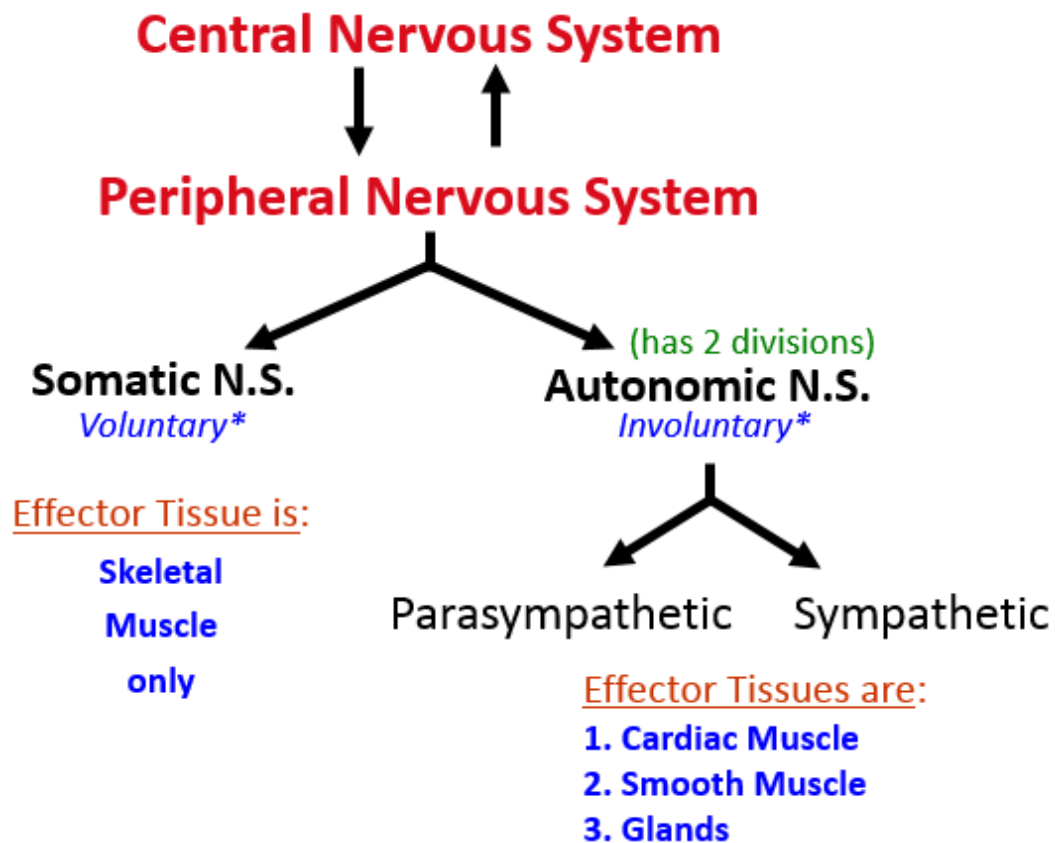


Figure 10.1 The Central Nervous System (CNS) and the Peripheral Nervous System (PNS) are in constant communication with each other. As seen in the flow chart above there are two more systems embedded in the PNS: The Somatic Nervous System (SNS) and the Autonomic Nervous System (ANS), and each has separate effector tissue. The SNS only controls skeletal muscle. The ANS has two divisions: The Parasympathetic and the Sympathetic and they control cardiac muscle, smooth muscle and glands.

**There are important exceptions relating to the control for each system: The somatic nervous system has reflexes which are involuntary, and the Autonomic Nervous System can be controlled by biofeedback mechanisms which are voluntary.*

The Somatic Nervous System (SNS)

The somatic nervous system is for the control of the **skeletal muscle** of the body, so essentially this means it controls **body movement**. For the most part this is **voluntary**, that is, it is under conscious control, you ‘think’ about it first (**Fig. 10.2**). In fact, the main region of the central nervous system that sends signals out to the SNS is located in the frontal lobe (the precentral gyrus). As we know from earlier, this is located in the cerebrum, which is the seat of the conscious mind.

The exception to the voluntary control of these actions are **somatic reflexes** – these are automated. By definition, a reflex is a rapid, automated, stereotyped response to a stimulus, usually to get the body out of danger. For example, think of how you might put your hand on something hot without realizing, but before you even perceive the hotness, you have automatically pulled your hand away from the potentially dangerous stimulus. Examples of somatic reflexes are the monosynaptic ‘patellar’ reflex and the polysynaptic ‘withdrawal’ reflex which occur without conscious control.

The Control of Skeletal Muscle

Many different areas of the brain relay their inputs to the **primary motor cortex**, and the information it receives aids in the planning of body movement that is facilitated by the contraction of skeletal muscle. Principally, the efferent (outward) commands move down the brain centers to stimulate **spinal cord neurons**, which then continue outward to the **neuromuscular junction** (NMJ) and act to stimulate and contract **skeletal muscle**.

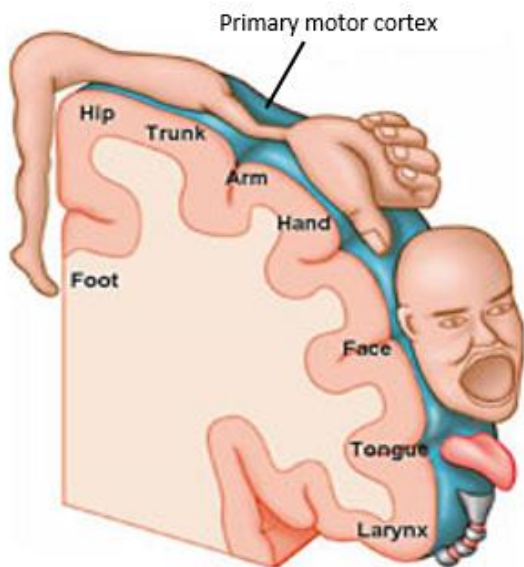


Figure 10.3. This is the homunculus or the ‘little person’ within the primary motor cortex, which is located on the precentral gyrus. This is the region of the brain that coordinated skeletal muscle action.

CNS (Brain/Spinal Cord)

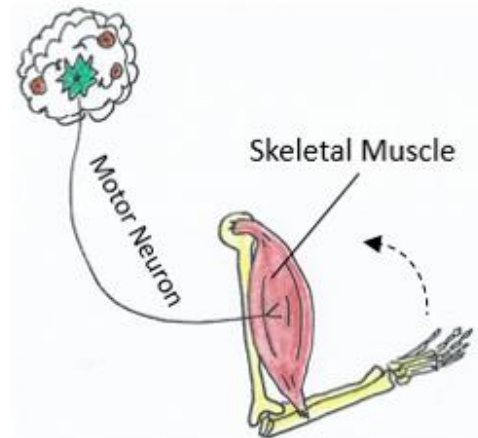


Figure 10.2 The somatic nervous system involves one somatic motor neuron that travels from the CNS to innervate skeletal muscle to control voluntary movements.

We will go into some details of the pathway for signaling (see **Figure 10.5** below), and take a quick look at the neuromuscular junction (see **Figure 10.6** below).

The Primary Motor Cortex

The primary motor cortex is in the frontal lobe, specifically it is located on the **precentral gyrus**. Like the somatosensory cortex in postcentral gyrus, this gyrus is also arranged as a **homunculus** (see **Fig. 10.3**) which literally means “little person”. It is a distorted representation of a small human being in the brain based on the proportions of the neurological real estate occupied in the brain by various body parts. Note the large area of the motor cortex that is occupied by the **hands, face and tongue**. This is due to their complexity of actions. These muscles perform nimble, fine, and nuanced movements - just think of the array of facial expression, the dexterity of the fingers, the complexity of the tongue actions when speaking. All of these body parts have significantly more cortical space because these actions require significantly more neural circuitry than say

the foot or the trachea. Large gluteal muscles are powerful but they perform more rudimentary movements and thus occupy proportionately less space on the motor cortex. Therefore, this the region of the brain (and others) is analogous to a topographical "map" of the human body in terms of neural processing requirements.

The Efferent Descending Pathways

The motor output from the **motor cortex** descends into the **brain stem** and to the **spinal cord** to control the musculature through **somatic motor neurons**. Neurons located in the primary motor cortex (called **Betz cells**) are neurons in the primary motor cortex that synapse with lower motor neurons in the brain stem (midbrain and medulla oblongata), and in the spinal cord.

There are two descending pathways for the voluntary (conscious) movements of skeletal muscle which moves the body: The **corticobulbar tract** and the **corticospinal tract** (see **Fig. 10.4** below). These are named for their **origin** in the cortex and their **targets**, being the brain stem (= "bulbar" in reference to the bulb-like enlargement of the brain stem), and the top of the spinal cord (spinal).

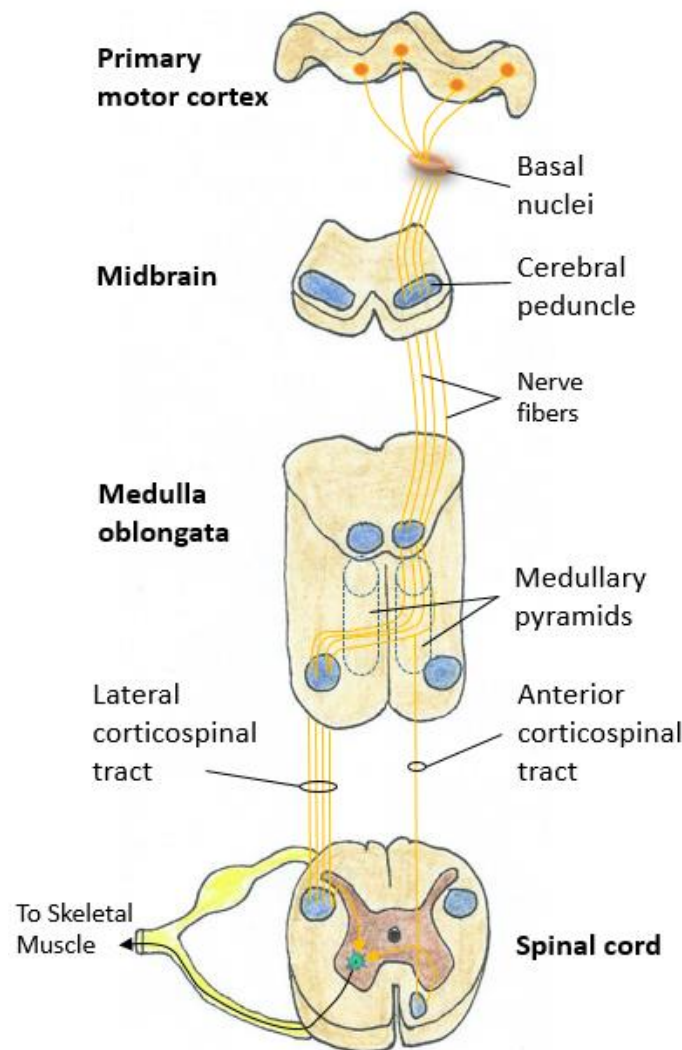


Figure 10.4 From the primary motor cortex in the cerebrum, the signals for skeletal muscle action start. They descend to the basal nuclei, midbrain and medulla before reaching the cranial motor nuclei in the ventral horn of the spinal cord spinal. From there, somatic motor neurons (the lower motor neuron) projects into the periphery reaching the skeletal muscle to stimulate contraction and body movement.

The Sequence of Events for Signaling Skeletal Muscle

Motor signals from the primary motor cortex in the cerebrum is sent down via the axons to stimulate motor neurons in either the **cranial motor nuclei** in the **ventral horn** of the spinal cord. The axons of the corticobulbar tract are ipsilateral (same side of body), but the decussation (crossing over) occurs in the brain stem and the axons of the corticospinal tract are mostly contralateral (opposite side of body). Thus, the right hemisphere of the cerebrum controls muscles on the left side of the body, and vice versa.

The **corticospinal tract** descends from the cortex to the caudate nucleus and putamen of the **basal nuclei** as a bundle called the **internal capsule**. The tract continues down to the midbrain via the **cerebral peduncles**, through the pons and into the **pyramids** of the medulla oblongata. Here is where **pyramidal decussation** occurs with the majority the fibers in the corticospinal tract crossing over to the opposite side of the brain. This is where the two tracts separate into lateral (the bulk) and anterior corticospinal tract's for control over different domains of the musculature. Examine **Figure 10.4** above to see the flow of information.

Somatic Nervous System Mode of Action

Compared to the ANS, the SNS is very simple in terms of its arrangement (see **Fig. 10.5**). We can view it as one motor neuron from the CNS which goes out into the periphery and innervates (has an effect on) one type of tissue, skeletal muscle.

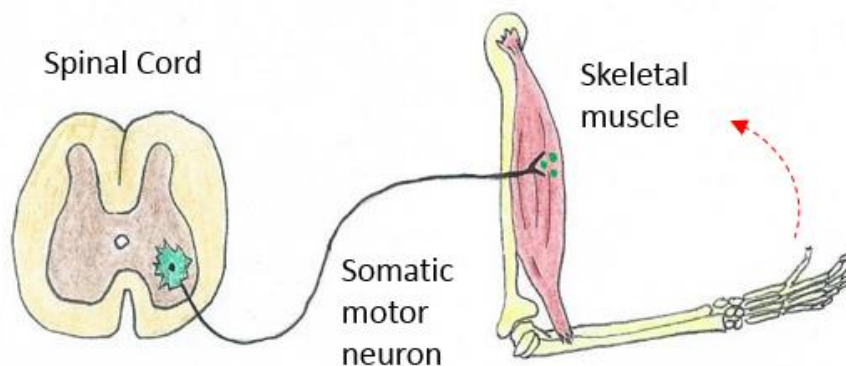


Figure 10.5 The nerve fiber from the somatic motor neuron in the ventral horn of the spinal cord reaches out to innervate skeletal muscle in the periphery. The somatic motor neuron releases the neurotransmitter acetylcholine (ACh) at the site of communication between the neuron and the muscle, called the neuromuscular junction. The stimulation of skeletal muscle by somatic motor neurons always causes contraction. It is the lack of stimulation that causes the relaxation of skeletal muscle.

Concise Description of Skeletal Muscle Contraction

At the junction between the neurons synaptic end bulb and the muscle cell, called the **neuromuscular junction (NMJ)**, the **somatic motor neuron** releases the neurotransmitter **acetylcholine (ACh)**. This diffuses across the NMJ and binds to **nicotinic receptors** that are on the plasma membrane (sarcolemma) of the skeletal muscle cell. Recall from the neurophysiology section that nicotinic receptors are always **excitatory!** This means they laws elevate the membrane potential when they are activated. As we shall see in much more detail in the section on skeletal muscle physiology, muscle cells (fibers) have action potentials to. When skeletal muscle has an action potential, it **contracts** and **generates force**.

Neuromuscular Junction for Skeletal Muscle

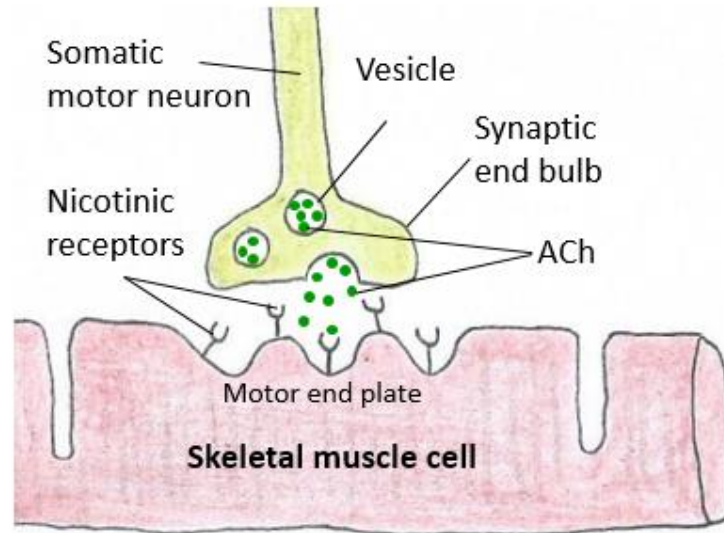


Figure 10.6 This is the neuromuscular junction (NMJ) of skeletal muscle and shows the somatic motor neuron releasing acetylcholine (ACh) from vesicles in the synaptic end bulb. The ACh diffuses across to the motor end plate of the skeletal muscle cell and binds to nicotinic receptors densely located there.

Body Movement

Skeletal muscles are attached to bones and they span over moving joints, therefore, contraction of skeletal muscle causes body movement. In the body skeletal muscles are arranged in antagonistic groups so that if the contraction of one muscle group has one action (flexion), then contraction of the antagonist group will produce the opposite action (extension).

Myasthenia Gravis: This is a disease of the **neuromuscular junction (NMJ)** that has already been discussed as it related to neurotransmitter interactions with their receptors. Specifically it is concerned with the **nicotinic receptors** for ACh that become damaged and therefore less or non-responsive to the signals from the SNS. The prefix 'myo' means muscle, 'asthenia' means weakness and 'gravis' means grave or serious.

The SNS in Summary:

- The # of Neurons: 1 motor neuron.
- Effector Tissue: Skeletal Muscle.
- Neurotransmitter: ACh.
- Receptors: Nicotinic.
- Action: Excites tissue, causing contraction.
- Control: Voluntary (except for reflexes).

The Autonomic Nervous System (ANS)

The autonomic nervous system is another component of the peripheral nervous system. As the name indicates, it predominantly involves automatic or involuntary regulation of the body. The autonomic nervous system (ANS) actually has **three** divisions or branches: the **parasympathetic**, the **sympathetic**, and the ***enteric** nervous system.

***Note:** The enteric nervous system (ENS) or intrinsic nervous system is an amazing division and is a virtually autonomous branch of the ANS. In fact, there are at least the same number of neurons in this system as there are in the spinal cord, from 100 to 600 million. To give you an idea of how complex and advanced this system is.

The ENS is composed of a great number of neural circuits that control motor functions, local blood flow, mucosal transport and secretions, in addition to immune and endocrine function of the gastrointestinal tract (**Fig. 10.7**). This division is capable of operating independently of the brain and spinal cord. Though it does rely on innervation from the vagus, it can operate without it.

For this course we will focus on the two divisions of the ANS the **parasympathetic** (rest and digest) and the **sympathetic** (fight or flight), that are predominately 'antagonistic' with one another, although there are important exceptions to that.

Autonomic Nervous System Mode of Action

The Autonomic Nervous System (ANS) has a more complex arrangement than the SNS. It involves **two motor neurons**, one from the CNS to an autonomic ganglion and the second motor neuron from the ganglion to the effector tissue. A ganglion is a cluster of nerve cell bodies outside of the CNS (or in the PNS). There are two divisions to the ANS, the **Parasympathetic** and the **Sympathetic** (see **Fig. 10.8**).

The ANS is a control system that acts largely unconsciously and regulates bodily a broad range of bodily functions. It regulates **involuntary** physiological processes including heart activity, air flow in the lungs, the activity of smooth muscle in organs and vessels, influencing blood pressure, digestion, exocrine and endocrine glands, and sexual arousal, among other bodily processes. The ANS continuously monitors various conditions within these different systems and implements changes depending on the circumstance. There are three categories of effector tissue in the ANS, they are: Cardiac muscle; smooth muscle and, glandular tissues. Both the Parasympathetic and the Sympathetic divisions act on the same effector tissue.

The Enteric Innervation of the GI Tract

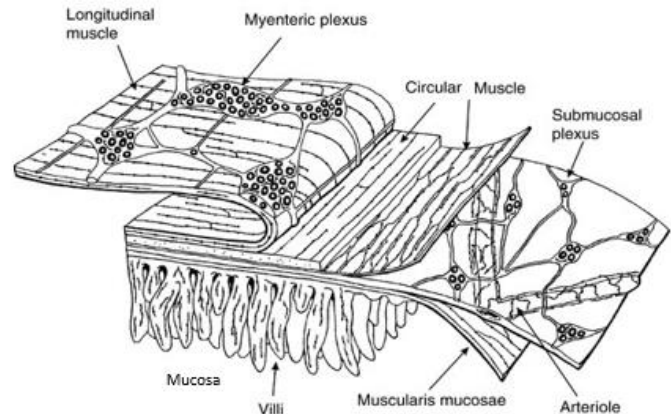


Figure 10.7 Shows the widespread, intricate and comprehensive neural circuits and networks that are involved in the enteric nervous system. It is this system that allows for the significant autonomy of the gastrointestinal tract.

Arrangement of the Autonomic Nervous System and How it Functions

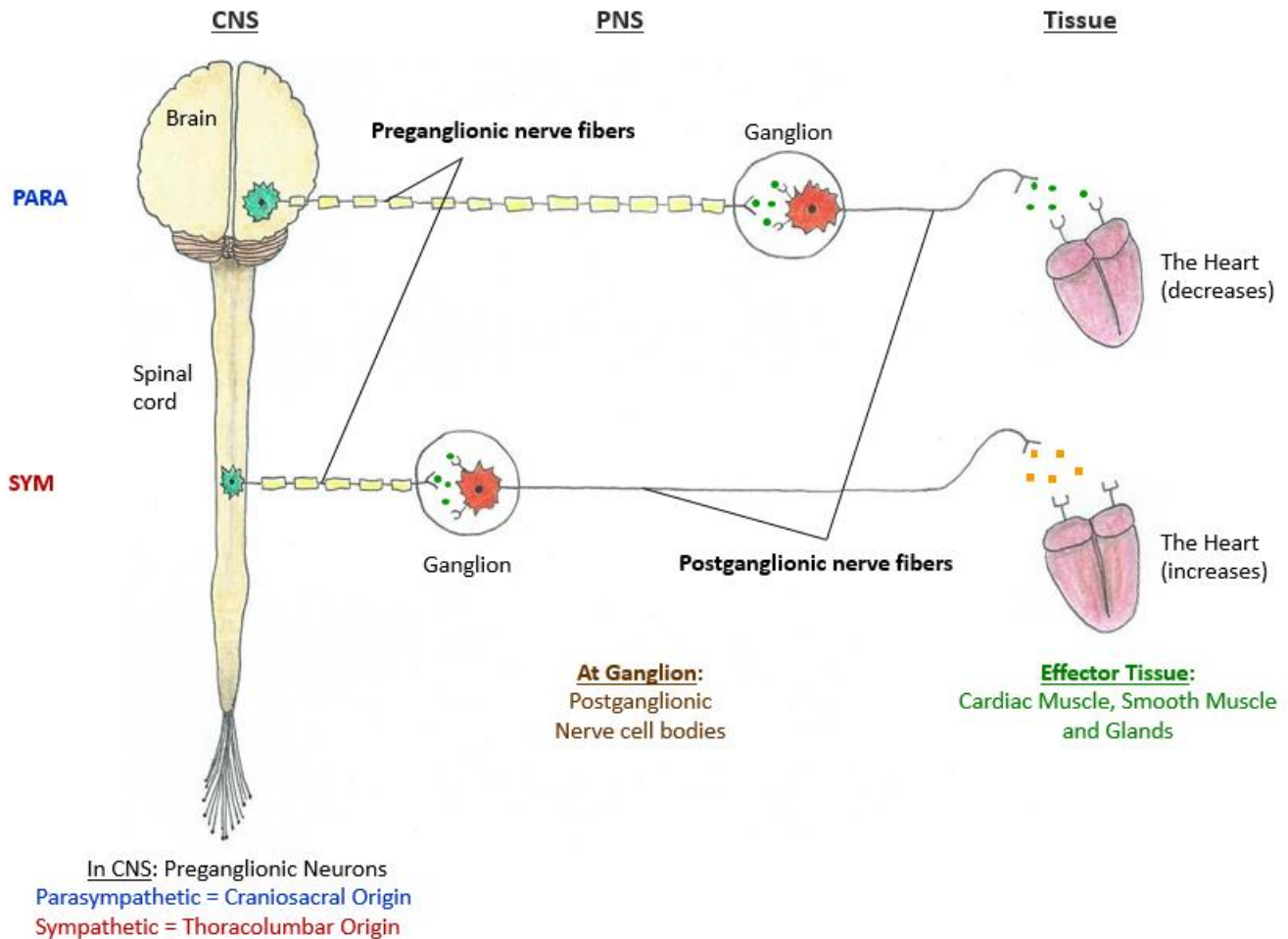


Figure 10.8 Shows the arrangement of both the parasympathetic and sympathetic divisions of the ANS in terms of their origins in the CNS and the order of the preganglionic and postganglionic neurons. It also shows the relative distances of their ganglia from the CNS to effector tissue, and the actions on an effector tissue, the heart.

The Arrangements of the Parasympathetic and Sympathetic Divisions

When we talk about the **origins** of each division, this means the location of the **preganglionic** nerve cell body in the central nervous system. The **parasympathetic** division has its origins in the **craniosacral** regions, which means the brain and sacral regions. From there, the outward direction into the periphery goes to the ganglion, which is defined as a cluster of nerve cell bodies outside of the CNS. The **parasympathetic ganglion** is located relatively far away from the CNS and much closer to the effector tissue. The parasympathetic **postganglionic** neuron leaves the ganglion and the axon travels to the effector tissue. Note in **Figure 10.8** above, that parasympathetic preganglionic nerve fiber (axon) is very long and the postganglionic nerve fiber is very short, sometimes even in the effector tissue.

The **sympathetic** division has its origins in the **thoracolumbar** regions, which means the thoracic and lumbar regions of the spinal cord. The **sympathetic ganglion** is located very close to the CNS (sympathetic ganglionic chain) and relatively far away from the effector tissue. The sympathetic **postganglionic** neuron's axon leaves the ganglion and travels to the effector tissue. Again, as seen in **Figure 10.8** above, the sympathetic preganglionic nerve fiber is very short and the postganglionic nerve fiber is very long.

The ANS is interesting and unique in how it functions in a sequential two-neuron efferent (outgoing) pathway. The preganglionic neuron must go to a ganglion to synapse with the postganglionic neuron. And in both divisions the chemical signal and receptors at the ganglion are identical. This really acts like a relay station, and the area where the two division are remarkably different are at the postganglionic neuron at the effector tissue. A good example of effector tissue is shown in **Figure 10.8** above with the heart: The parasympathetic division slows down the heart and the sympathetic division speeds it up! Both divisions have virtually the same effector tissues, which means they act on the same tissues in the body but they often have antagonistic or opposite effects. There are three categories of effector tissue in the ANS, they are shown in **Figure 10.9** below.

The Three Types of Effectors Tissue for the ANS

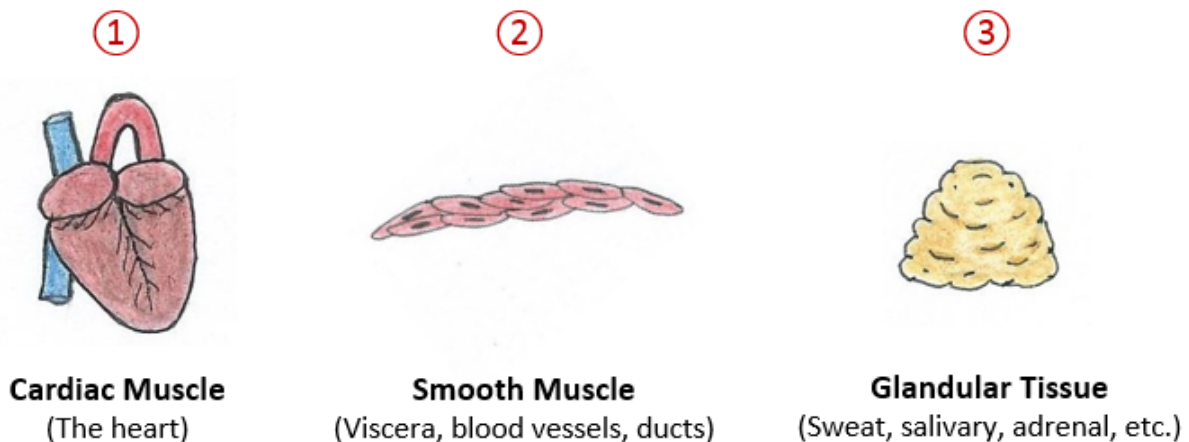


Figure 10.9 Both the Parasympathetic and the Sympathetic divisions of the ANS act on the same effector tissue. The three types of effector tissue are: ① Cardiac Muscle, which is the heart; ② Smooth Muscle which is found in internal viscera (organs) such as the stomach, lungs, etc., the walls of blood and lymphatic vessels and in ducts for transportation in the body; and ③ Glandular Tissue, such as sweat, tears, salivary, adrenal, etc.

The Parasympathetic Division

In general the Parasympathetic (Para) division can initially be described by the phrases “Rest and Digest” or “Feed and Breed”. This simply means that this portion of the ANS is for housekeeping activities, putting things back in place, storing needed things for later and eliminating waste. For example, after lunch, when you sit down to read, the Parasympathetic division is at work. Your heart rate is lowered, your gastrointestinal tract activity is increased, elevated in its mobility and secretions. The diameter of your bronchioles (airways) are small, as you don’t need more air when you are sitting resting and reading. The diameter of your pupils is also small and constricted because this enables your eyes to fine focus for reading the pages directly in front of you (near focus).

The main relay of the parasympathetic effect is the vagus nerve, cranial nerve X (read ‘ten’), which is often cited for carrying out about 75% of the effects that the parasympathetic division is responsible for. Through the vagus nerve it decreases heart rate, blood pressure and alertness, as well as helping with calmness, relaxation, and digestion. The vagus nerve is also involved with the processes of salivation, lacrimation (crying), urination, defecation and sexual arousal (SLUDS).

Now for more details of the parasympathetic division.

Of the two motor neurons, the first one is called the **preganglionic neuron**, as it is going to the ganglion and synapses with the second neuron called the **postganglionic neuron**, the one leaving the ganglion. At the ganglion for the parasympathetic division, the preganglionic neuron releases the neurotransmitter **ACh** and this diffuses across the synaptic cleft to bind to **nicotinic receptors** on the plasma membrane of the postsynaptic neuron. The effect is to excite the postsynaptic neuron to send a signal to the effector tissue from the second neuron. See these details in **Fig. 10.10**. If this sounds familiar, it is because it is the same chemical arrangement as the neuromuscular junction of the somatic nervous system.

The postganglionic neuron is the one that goes to the effector tissue, cardiac, smooth muscle or glands. Within the parasympathetic division, the postganglionic neuron releases **ACh** again, it diffuses across and binds to **muscarinic receptors** on the plasma membrane of the **effector tissue**. When muscarinic receptors are stimulated, they often cause inhibition, thus we see the reduction of the heart rate, the reduction of bronchiole diameter, etc.

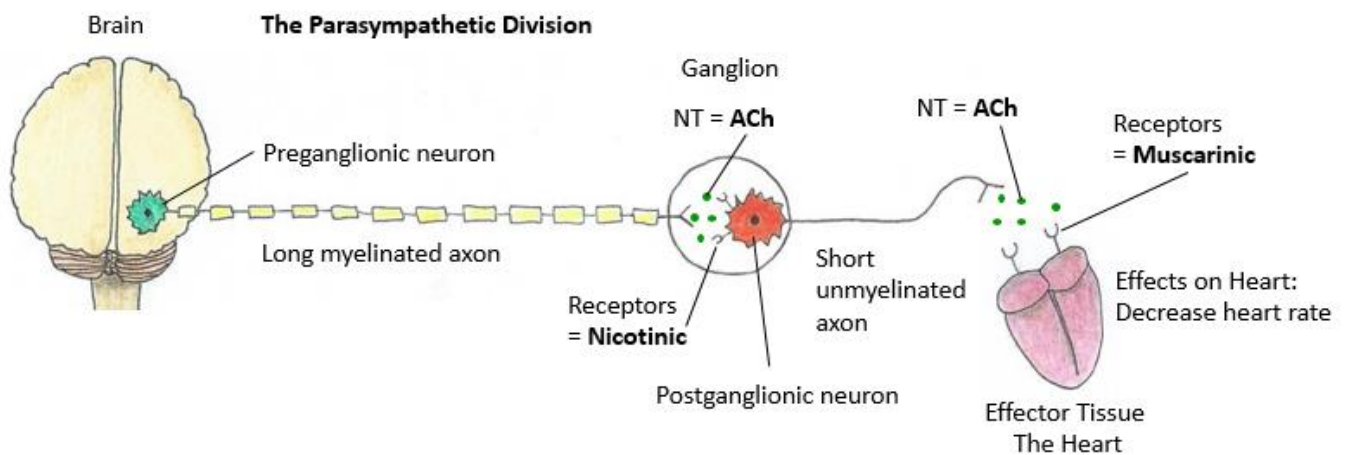


Figure 10.10 The parasympathetic division of the ANS has a very long preganglionic nerve fiber from the CNS to its ganglion. At the ganglion the preganglionic neuron release ACh, which bind to nicotinic receptors on the postganglionic nerve cell body. This neuron then sends a signal along its short unmyelinated nerve fiber to its effector tissue (in the case the heart), where it again releases ACh, but the receptors on the effector tissue are muscarinic and this is what determines how the effector tissue will respond.

Responses of the ANS Effector Tissues

Can you recall what the three effector tissues of the ANS are? Yes..., the heart, smooth muscle and glands!



Please note, **skeletal muscle is NOT an effector tissue of the ANS**, though it is tempting to associate it with the sympathetic division of the ANS, for example when running away from that monster, skeletal muscle is the effector tissue of the Somatic Nervous System, not the ANS! The sympathetic division does increase the blood flow to skeletal muscle and therefore assists in supplying

it with what it needs to function, but it does not control skeletal muscle itself.

The Sympathetic Division

In general the **Sympathetic** (Sym) division can initially be described by the phrases “**Fight or Flight**”. This implies that this portion of the ANS is for **emergency** situations, for putting up your dukes and fighting, or running away – either way **it requires a lot of energy**. If we stay with the example above, after lunch, let’s say instead just as you sit down to read, a hungry monster of some kind enters the room. Immediately the Sympathetic division springs into work. Your heart rate skyrockets (to pump more blood to body to get you out of danger), your gastrointestinal tract activity comes to a halt, and the diameter of your bronchioles (airways) become larger as you need much more air to either fight or run away. The diameter of your pupils also become larger to enable distant focus of your eyes, so you can see an open window or some other escape route.

The preganglionic neuron the both divisions (parasympathetic and sympathetic) function in exactly the same way, so we have already covered that above, but just quickly, the sympathetic **preganglionic neuron** releases **ACh** onto **nicotinic receptors** on the postsynaptic neuron. The postganglionic neuron of the sympathetic division goes to the same effector tissue as the parasympathetic division (cardiac, smooth muscle or glands). However, the sympathetic postganglionic neurons release norepinephrine (**NE**) and this diffuses across and binds to either α or β receptors on the plasma membrane of the effector tissue. These α and β receptors will have various effects, depending on what tissue they are on. For the heart as an example, overall, what will be seen is an increase in heart activity (therefore blood delivery to tissues in need). See these details in **Fig. 10.11**. The effects on other tissues of the body will fall into a pattern, one that helps respond to emergency situations, including increase in bronchiole diameter, pupil diameter, sweat production, etc.

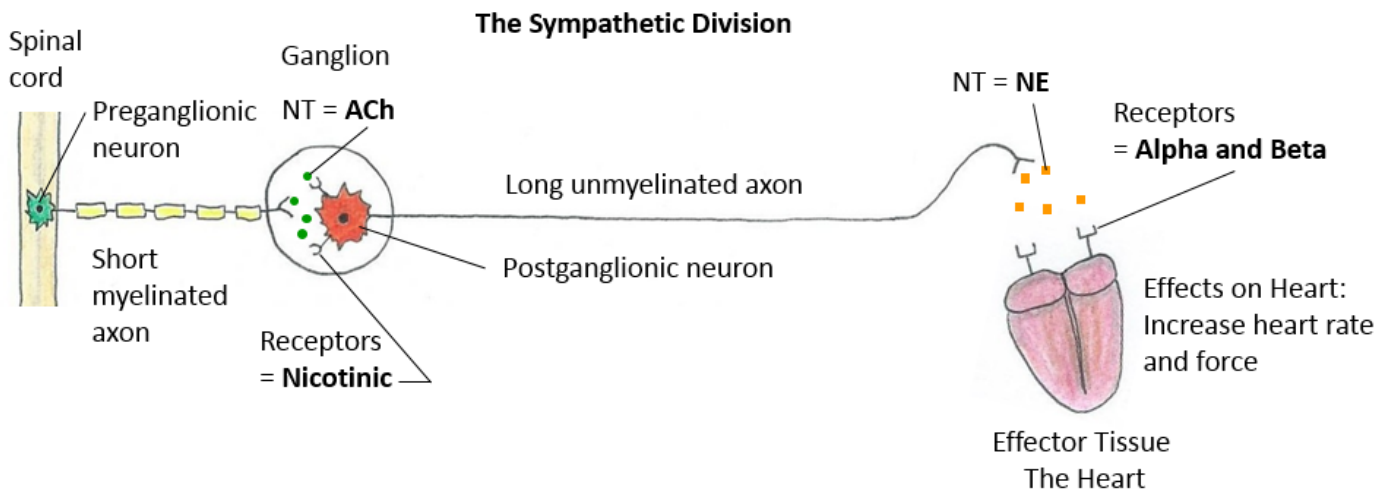


Figure 10.11 The sympathetic division of the ANS has a very short preganglionic nerve fiber from the CNS to its ganglion. At the ganglion the preganglionic neuron release ACh, which bind to nicotinic receptors on the postganglionic nerve cell body. This neuron then sends a signal along its long unmyelinated nerve fiber to its effector tissue (in the case the heart), where it releases NE and the receptors on the effector tissue are alpha and beta, and this is what determines how the effector tissue will respond.

Adrenergic and Cholinergic Neurons and Receptors

It is vital to understand that it is the **receptors** on the tissue that determines how it responds to the **neurotransmitter**. And the neuron is described by the type of neurotransmitter it releases. Therefore, we need to now be thorough about the neurotransmitter ACh and NE (and E) and the receptors they bind: **1)** ACh nicotinic and muscarinic, and **2)** NE and E bind to alpha (α) and beta (β) receptors.

Neurons of the Autonomic Nervous System (ANS)

When discussing the types of neurons certain terms are used based on the neurotransmitter they release. As such, a neuron that releases the neurotransmitter **acetylcholine (ACh)** is called a “**cholinergic**” neuron. Neurons that release norepinephrine (NE) or epinephrine (E) are termed “**adrenergic**” neurons, since NE used to be called *noradrenaline*, that’s where the term adrenergic comes from.

ACh has excitatory actions at the neuromuscular junction, at autonomic ganglion, at certain glandular tissues and in the CNS. It has inhibitory actions at certain smooth muscles and at cardiac muscle. NE and N are largely excitatory though opposing effects can result from stimulating **alpha (α)** or **beta (β)** receptors.

Receptors of the ANS (both divisions)

In our studies of physiology, ACh binds to two types of receptors, **nicotinic** and **muscarinic**, therefore these are called **cholinergic receptors**. Both NE and E bind to alpha (α) and beta (β) receptors, therefore these receptors are called **adrenergic receptors**.

The Parasympathetic Division of the ANS

The parasympathetic (parasympathetic) division of the ANS has cholinergic neurons and cholinergic receptors. All neurons in the parasympathetic division release the neurotransmitter ACh. There are two general types of receptors for this division and they are muscarinic and nicotinic.

At the ganglion of the parasympathetic (and the sympathetic) divisions, the receptor is **nicotinic**! Therefore, when the **preganglionic** parasympathetic neuron releases ACh, the receptors on the **postganglionic** neuron are nicotinic.

Cholinergic Receptors

There are two types of cholinergic receptors, **nicotinic** and **muscarinic** receptors. These were named after the **nicotine** used to stimulate the nicotinic receptors, and the **muscarine**, which is a component found in certain mushrooms, used to stimulate the muscarinic receptors. These cholinergic receptors are on the surface of cells that are stimulated by the neurotransmitter acetylcholine or **ACh**.

Nicotinic Receptors

The **nicotinic** receptor is a key player in neuronal communication. When **ACh** binds to **nicotinic receptors** on a plasma membrane, it opens cationic transmembrane ion channels, most predominantly Na^+ channels. The influx of the positively charged Na^+ causes the cell to **depolarize**. This results in an **excitation** of the cell, and in postsynaptic neurons this is called an excitatory postsynaptic potential (**EPSP**). Therefore, we can state that **nicotinic receptors are always excitatory**. This means that when nicotinic receptors are stimulated, they will always cause excitation of the target cell.

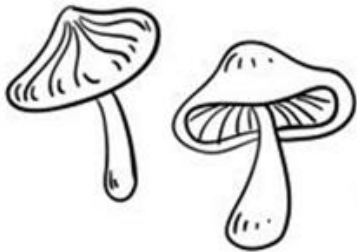
The rapid nature of the synaptic transmission mediated by nicotinic receptors is consistent with its role at the neuromuscular junction (NMJ) for **skeletal muscle** in the somatic nervous system (SNS), and at the **ganglion** of the Autonomic Nervous System (ANS).



Note: Nicotinic receptors are involved in skeletal muscle contraction and are affected by substances such as **curare** (used on those poison-tipped arrows) that cause muscle paralysis by blocking these nicotinic receptors. Medications such as **succinylcholine** are nicotinic antagonists that block these receptors and induce paralysis necessary for certain medical procedures.

Muscarinic Receptors

The activation of **muscarinic** receptors on effector tissue cells can be either **excitatory** or **inhibitory** but is always slow in onset and long in duration. This is because the muscarinic receptors activate **G proteins** which either inhibits or stimulates second messenger systems. This type of response takes longer, whether it is excitatory or inhibitory. The G protein activation underlies all actions of muscarinic receptors, thus accounting for their slow onset. There are five (5) subtypes of muscarinic receptors located on various target tissues across the body (seen in **Figure 10.12** below).



At Effector Tissue for Parasympathetic

At the **effector tissue** for the **parasympathetic** division there are basically only **muscarinic receptors**. The name 'muscarinic' comes from how they were initially characterized as being more sensitive to muscarine (a type of mushroom) than to nicotine (from tobacco). The parasympathetic postganglionic neuron releases ACh, and the receptor on the effector tissue is muscarinic. Muscarinic receptors are important mediators of behavior in the CNS, for example, they have a role in modulating motor control circuits in the **basal ganglia** for body movement. Their participation in learning and memory are evident as muscarinic antagonists are amnesic agents, and the deterioration of the cholinergic innervation of the neocortex is associated with memory loss in Alzheimer's disease.

Now let's look at the signal transduction pathways that occur via muscarinic receptors.

Biochemistry of Muscarinic Receptor

The biochemical responses to stimulation of muscarinic receptors are associated with the GTP-binding protein or the **G protein**. The activation of a G protein allows for the dissociation of the **α subunit** to interact with effector systems to mediate specific responses in essentially one of the two ways briefly described below. The rate of hydrolysis of the **GTP** dictates the length of time the G protein (pro^-) remains activated. So, if a G pro^- is activated, one of these responses is possible:

#1 It results in the hydrolysis of **phosphatidylinositol 4, 5-bisphosphate (PIP₂)** which yields two second messengers; **inositol trisphosphate (IP₃)** and **diacylglycerol (DAG)**. The **IP₃** diffuses to the **smooth endoplasmic reticulum*** (ER) where it binds with IP₃ receptors on the ER to release the **Ca²⁺** from that intracellular storage into the cytoplasm. The DAG, together with the **Ca²⁺** just released from the ER activates the **Protein Kinase C**. Recall that protein kinases stick phosphates on proteins. Therefore, the PKC is now able to phosphorylate target proteins and this is an aspect of the cell's responses.

**Results in smooth muscle contraction.*

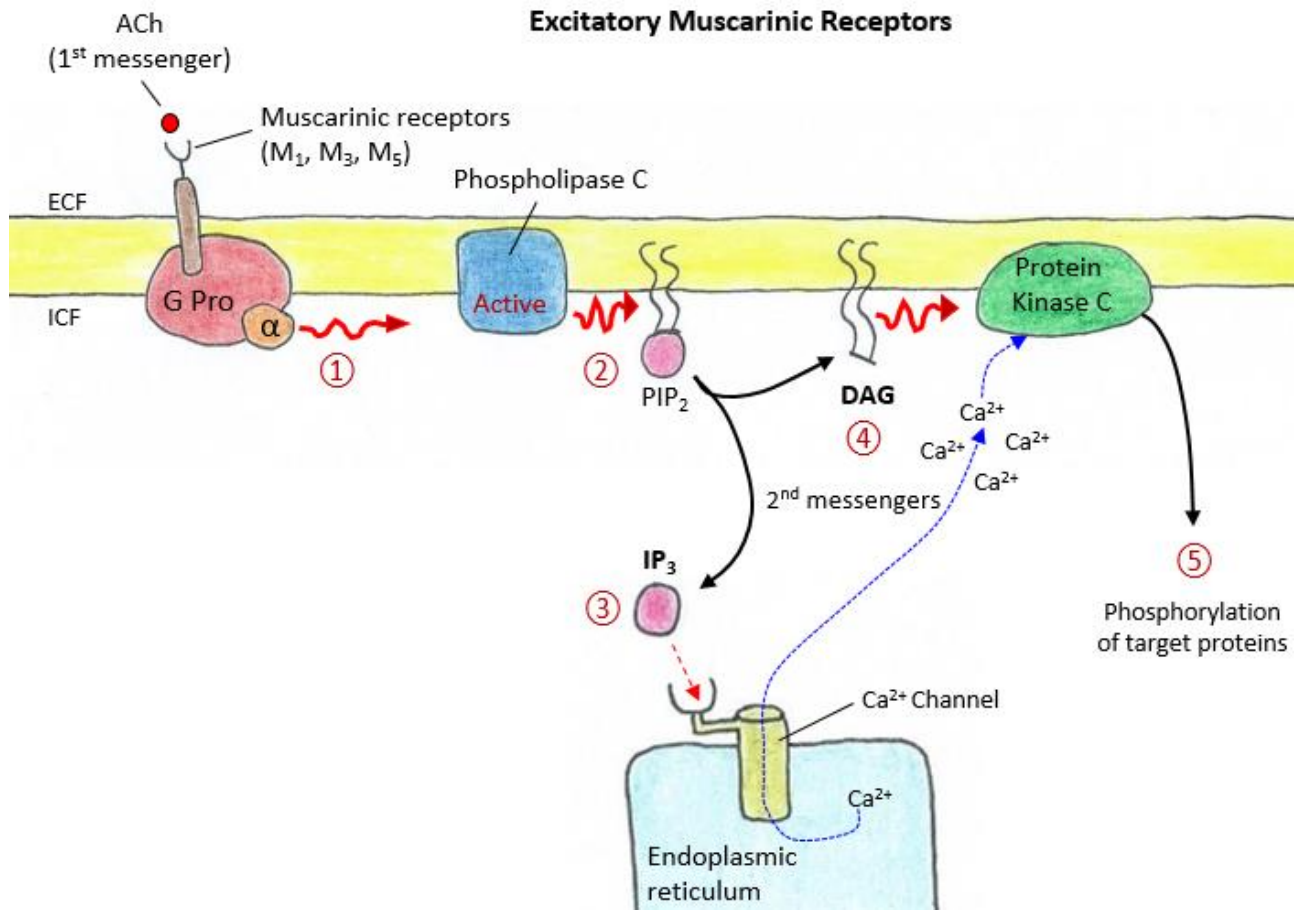


Figure 10.12 This shows how the binding of ACh to excitatory muscarinic receptors (M₁, M₃ and M₅) ① activates a G protein, which ② activates phospholipase C that hydrolyzes phosphatidylinositol 4, 5-bisphosphate (PIP₂) into two second messengers; ③ inositol trisphosphate (IP₃) and ④ diacylglycerol (DAG). The IP₃ diffuses to the endoplasmic reticulum (ER) where it binds with receptors to release Ca²⁺ from the ER, while the DAG activates Protein Kinase C (PKC) and along with Ca²⁺ as another second messenger, ⑤ stimulates the PKC's phosphorylation of target proteins.

Excitatory Muscarinic Receptors (response #1 above and in Fig. 10.12)

The odd-numbered receptors (M₁, M₃, and M₅) work through **G protein** activation of **phospholipase C**, which initiates the **inositol trisphosphate (IP₃)** mediated release of calcium from the endoplasmic reticulum and to **diacylglycerol (DAG)**-mediated activation of **protein kinase C**. As a consequence, depending on cell type, other cellular effectors may become activated, thus this is considered excitatory as detailed in **Figure 10.12** above. Stimulation of post-synaptic muscarinic receptors may not directly lead to action potentials, but commonly enhances the neuron's response to excitatory input - this is called **neuromodulation**.

- In smooth muscle, muscarinic receptor (M₃) activation of the phosphatidylinositol turnover response leads to elevation in cellular calcium and **contraction**.
- In glandular tissue, M₃ receptor-mediated phosphatidylinositol turnover leads to **hormone secretion**.
- In brain, activation of post-synaptic M₁ or M₃ receptors often mediates "slow" neuronal excitability.

#2 The response results in the **inhibition of Adenylate Cyclase**. The reduced cAMP production leads to reduced activation of **cAMP-dependent protein kinase**, reduced heart rate, and reduced force of contraction. **This response is opposite to adrenergic receptor stimulation.*

Imagine if the response in **Figure 10.13** below were inhibited, this is common in smooth muscle. On the other hand, the pathway in the figure below is how the inhibitory muscarinic receptors work in other excitable tissue such as neurons and cardiac muscle. By **indirectly opening K⁺ channels**, causing hyperpolarization, reducing the membrane excitability and decreasing the activity and responsiveness of the tissue.

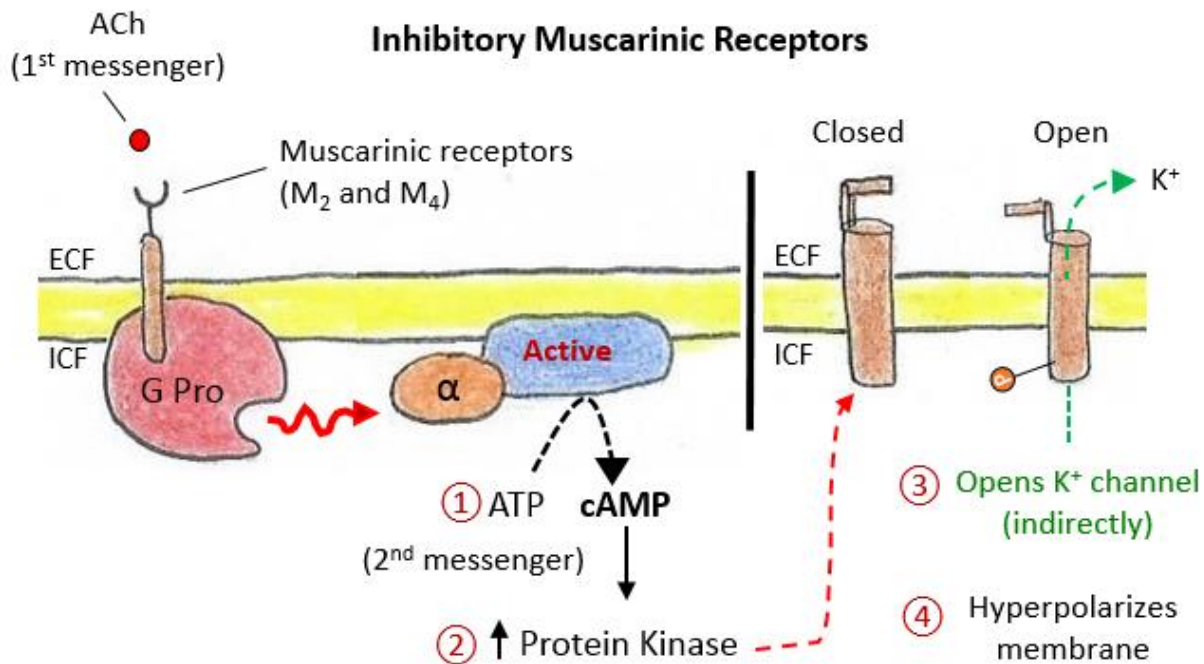


Figure 10.13 For the inhibitory muscarinic receptors (M₂ and M₄), the neurotransmitter ACh binds to a muscarinic receptors linked to a G protein, that is coupled to K⁺ channels. This leads to decreases the resting membrane potential (RMP) in myocardial and other cell, which leads to hyperpolarization and inhibition of the plasma membrane of excitable cells.

Inhibitory Muscarinic Receptors (response #2 above and in Fig. 10.13)

The even-numbered muscarinic receptors (M₂ and M₄) activate G proteins that **inhibit adenylyl cyclase**.

- The M₂ and M₄ receptors activate G protein-coupled K⁺ channels, this leads to decreases the resting membrane potential (RMP) in myocardial and other cell, which leads to **hyperpolarization** and **inhibition** of the plasma membrane of excitable cells.
- In nervous tissue, M₂ and M₄ receptors can inhibit neuronal firing and inhibit neurotransmitter release.
- The M₂ receptor inhibits adenylyl cyclase in smooth muscle and, as a consequence, **opposes the effects of adrenergic innervation**.
- In **cardiac tissue**, M₂ receptors activate G protein-coupled K⁺ channels to hyperpolarize the muscle, contributing to the slowing of the heart rate.

Parasympathetic Blockers

A substance that binds to a receptor and prevents the normal action or effect from occurring is a **blocker** or **antagonist** of the natural ligand. For example, if a substance blocks ACh from acting on either its receptor types, the substance can be called a **parasympathetic blocker**, or a **parasympathetic antagonist**, or an **anticholinergic**.

Since the muscarinic receptors are on the effector tissue, let's focus on these. So what would happen if muscarinic receptors were blocked? Just recall what happens when they are stimulated and the action would be the opposite. Therefore blocking muscarinic receptors would cause an increase in heart rate and contractility. It would cause dilation of the bronchioles of the lungs and increased air flow. There would be less production of secretions in the body, such as saliva, bronchial secretions, digestive secretions and tears.

Atropine is a parasympathetic antagonist (also termed a parasympatholytic). It can be derived from plants, such as belladonna (see at right) and is used as a drug to counteract too much parasympathetic activity, for example, from overstimulation of the vagus nerve, or even from the effects of pesticides and chemical warfare nerve agents like **organophosphates**, which poison the body.



Atropine can be used to alleviate bradycardia (low heart rate) and to reduce salivation and bronchial secretions before surgery. Atropine also relaxes and dilates pupillary muscles in the eye, widening before an eye exam. It's also used to treat eye conditions such as amblyopia (lazy eyes) and cycloplegia (paralysis of the ciliary muscle of the eye). It would also be an antidote for an overdose of cholinergic drugs or mushroom poisoning.

Ipratropium is another parasympathetic blocker but is inhaled in order that the lungs are more specifically effected. Blocking parasympathetic receptors in the bronchioles cause them to dilate and decrease production of secretions like mucus. Which can be useful for those with COPD, dealing with excessive pulmonary mucous.

Parasympathetic Agonist

An **agonist** is a substance that binds to a receptor and activates the receptor to produce a biological response. **Pilocarpine** is a parasympathomimetic (activates the parasympathetic division of ANS) drug, that is, it mimics or enhances the effect of parasympathetic nerve stimulation, and therefore acts as an agonist. Pilocarpine acts to facilitate the release of the neurotransmitter **acetylcholine** (ACh) from the vagus nerve, resulting in a **decrease in heart rate**. This drug can also be used to treat glaucoma (excessive pressure in the eye) by dilating vessels that drain fluid from the eye.

Other things that Stimulate Parasympathetic Activity

For the vast majority of time, the body should be in the **parasympathetic state**. This is the state of being calm and relaxed, which is incredibly beneficial for many reasons. The parasympathetic state allows the body to take care of business, enabling tissue to grow and repair, processing and storing nutrients. There is a lot of activity required and it take a bit of time.

The Sympathetic Division of the ANS

The sympathetic division of the ANS has **cholinergic** and **adrenergic neurons** and **receptors**. Important:

- At the **autonomic ganglion** for the sympathetic division, the neurotransmitter is **ACh** and the receptor, is **nicotinic!** This results in an **EPSP because** nicotinic receptors are always excitatory.
- At the **effector tissue** for the sympathetic division, the neurotransmitter is NE or E (*with exceptions) and there are 2 types of **adrenergic receptors**; they are **alpha (α)** and **beta (β)**. There are actually 9 subtypes of these receptors, but we will focus on α_1 and α_2 ; and β_1 , β_2 and β_3 .

At Effector Tissue for Sympathetic

At the effector tissue for the sympathetic division there are different subtypes of receptors, the two basic categories are alpha (α) and beta (β) receptors.

The Alpha (α) Receptors

The alpha (α) **receptors** are sympathetic **adrenergic** receptors and they have two subtypes: The α_1 **receptors** and the α_2 **receptors**.

Alpha 1

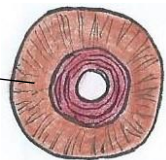
The α_1 **receptors** are located on postganglionic effector tissue, these α receptors are commonly found on **smooth muscle** within blood (and lymphatic) vessels. These α_1 receptors are also found in the reproductive and urinary tracts, in the intestinal walls along the GI tract, and within the cardiac system.

Prominent Actions of α_1 Receptors

When α_1 receptors on arteries, arterioles and veins are stimulated by norepinephrine (NE) or epinephrine (E), the **vascular smooth muscle (VSM)** in the walls of these blood vessels **contract** and **constrict**. This decreases local blood flow, and importantly, **increases blood pressure**. Constriction of large veins also **increases venous return** to the heart. These receptors determine both **arteriolar resistance** and **venous capacitance**, and thus are very important in regulating blood flow and blood pressure.

Activation of α_1 receptors is required for the normal contraction in the vas deferens in the male reproductive tract enabling sperm ejaculation, therefore, these receptors have a function in fertility.

Interestingly, α_1 receptors are involved in eye function, where they regulate **lacrimal gland** secretions, increase the vascular tone of ocular blood vessels, and cause **mydriasis**, which is a dilation of the pupil of the eye by contraction of the radial muscle of the pupil.



Alpha 2

The α_2 receptors are found both in the brain and in the periphery. In the brain stem they inhibit sympathetic discharge and in the periphery (including the heart) they are involved with presynaptic inhibition of sympathetic efferent neurotransmitter release (see **Figure 10.14** below). This diminished discharged can invoke vasodilation and vasoconstriction, depending on other receptors present. Stimulation of the α_2 -subtype in the iris of eye causes a noticeable ocular hypotensive response, the opposite of α_1 receptor stimulation, which was blocked by the selective α_2 -adrenoceptor antagonist **yohimbine** (see antagonists and agonist sections below).

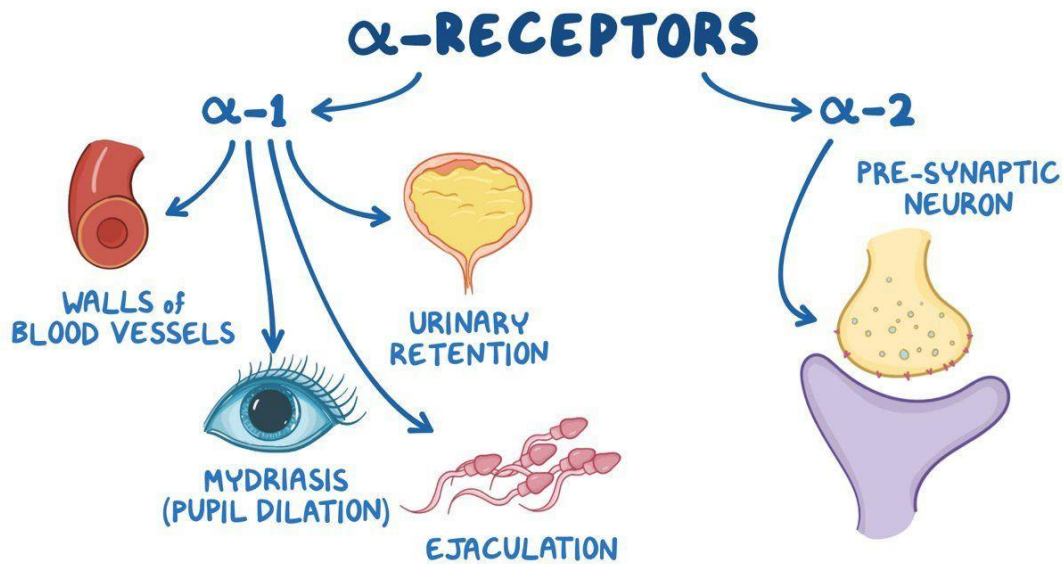


Figure 10.14 Shows a summary of the effector tissue that has α_1 and α_2 receptors and the basic action that occurs when these receptors are stimulated.

Beta Receptors

The beta (β) receptors are also sympathetic **adrenergic** receptors and they have three subtypes: The β_1 receptors, the β_2 receptors, and the β_3 receptors.

Beta 1

The β_1 receptors are principally found in the **heart**, but are also located in the **kidney** and on **fat cells (adipocytes)**. When β_1 receptors located in the heart are stimulated they causes an **increase in heart rate** and **increase the heart's force**, or strength of contraction (contractility).

Beta 2

The β_2 receptors are located in the **bronchioles of the lungs**. When stimulated, they increase the diameter of the bronchioles to let more air in and out during breathing, drastically increasing air flow in the lungs. They are on **arteries supplying skeletal muscles** and they dilate these vessels to increase blood flow to skeletal muscle. The β_2 receptors also promote glycogenolysis and gluconeogenesis in the liver, thus increase glucose availability.

Beta 3

The β_3 receptors are located in the small intestine, adipose tissue and vascular endothelium. They are on the cell surface of both white and brown adipocytes and are responsible for **lipolysis, thermogenesis**, they are also involved in glucose uptake, cardio-inhibition and **relaxation of intestinal smooth muscle** of the colon, esophagus In the urinary bladder it is thought to cause relaxation of the bladder and prevention of urination.

For all of these beta receptors, the binding of NE or E to a β receptor is linked to a G-protein, which acts through the G proteins alpha subunit, as we have seen earlier in the neurophysiology section regarding the **metabotropic effect**. Recall that the stimulation of the receptor linked to the G-protein triggers the activation of the enzyme adenylyl cyclase, which produces cAMP (from ATP) and this cAMP acts as a second messenger, initiating a cascade of variable events that are dependent on the tissue or organ.

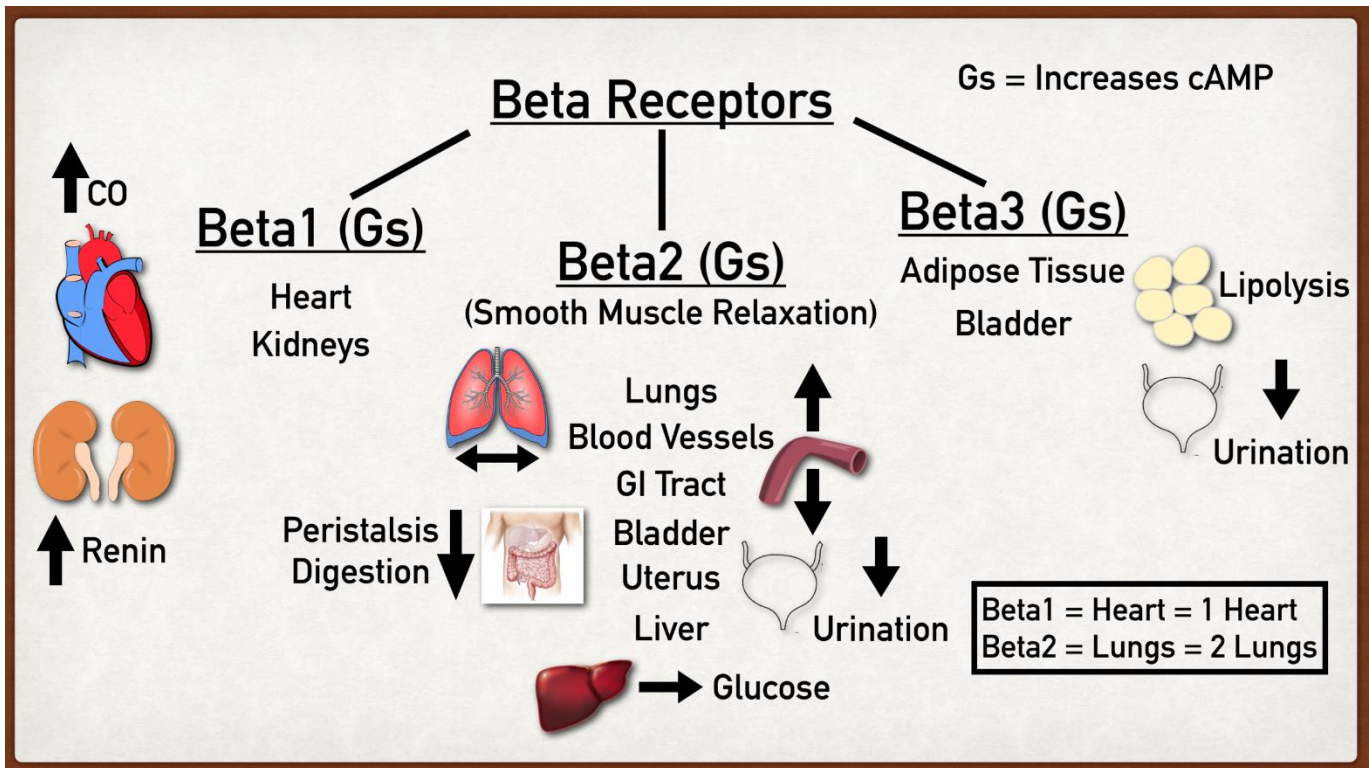


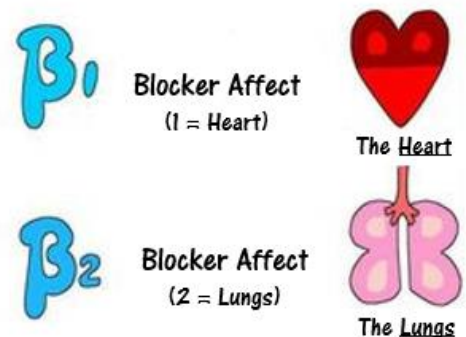
Figure 10.15 Shows a summary of the effector tissue that has β_1 , β_2 and β_3 receptors and the basic action that occurs when these receptors are stimulated.

Note: There are no α receptors in blood vessels supplying skeletal muscles - therefore blood vessels delivering blood to skeletal muscles **do not** constrict in response to **sympathetic innervation**, this is important to piece together, because it is brilliant! The last thing you'd want to do during a fight or flight response is reduce the blood supply to the legs that are going to run fast to get you out of danger! It makes perfect sense that the delivery of blood to skeletal muscle increases, that is why the heart is pumping harder to deliver blood to tissues that need it. Skeletal muscles lack α receptors and instead have β_2 receptors that dilate blood vessels and increase blood flow to skeletal muscle and the heart in times of stress or alarm. The α receptors on other systemic vessels enable them to constrict, thus elevating blood pressure and causing more blood to return to the heart, and that makes perfect sense too.

When epinephrine or adrenaline are administered, we expect α , β_1 and β_2 agonist effects; we expect an:

- Increase in blood pressure.
- Increased heart rate.
- Increased cardiac contractility.
- Dilation of the bronchioles in the lungs.
- Dilation of the vessels in the skeletal muscles.

Beta Blocker Actions



Sympathetic Blockers

A substance that binds to a receptor and prevents the normal action or effect from occurring is a **blocker** or **antagonist** of the natural ligand. For example, if a substance blocks NE from acting on either its receptor

types, the substance can be called a **sympathetic blocker**, or an **adrenergic antagonists**, or a **sympathetic antagonist**. These act to **reduce the effectiveness of** sympathetic stimulation. The receptor antagonists are divided into α -receptor antagonists and β -receptor antagonists.

a) Alpha blockers can be used to balance. They lower blood pressure by preventing norepinephrine (NE) also called adrenaline from contracting the vascular smooth muscle in the walls of smaller arteries and veins. As a result, the blood vessels remain relaxed and dilated, lowering blood pressure and enhancing blood flow.

The alpha-1 adrenergic receptor antagonists (also called alpha-blockers) are a **family of agents that bind to and inhibit type 1 alpha**-adrenergic receptors and thus inhibit smooth muscle contraction. These alpha blockers **widen the blood vessels by blocking both alpha 1 and alpha 2 receptors**. The blocking of alpha 1 (α_1) receptors causes the widening of the blood vessels by inhibiting the action of catecholamines that cause vasoconstriction.

The blocking of alpha 2 (α_2) receptors increases the release of norepinephrine, adrenergic, dopaminergic and serotonergic neurotransmitters and induce insulin secretion, decreasing blood sugar levels. A non-selective beta-adrenergic antagonist used to treat **mild to severe chronic heart failure, hypertension, and left ventricular dysfunction following myocardial infarction** in clinically stable patients.

Ma huang is a natural Chinese traditional medicine, like ephedrine and pseudoephedrine, and acts as an alpha and beta adrenergic agonists, and thus can increase blood pressure.

Yohimbine is from the bark of an evergreen tree (see left). It is an α_2 -adrenergic receptor antagonist, and may decrease the effects of alpha-1 blockers, it increases blood pressure.

Quercetin is a potent antioxidant flavonol plant pigment found mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits. It is a versatile antioxidant known to possess protective abilities against tissue injury induced by various drug toxicities.



b) Beta blockers are competitive antagonists that **block receptors** for the endogenous catecholamines epinephrine (E), also called adrenaline, and norepinephrine (NE), also called noradrenaline. The most commonly prescribed beta-blocker medications are **metoprolol succinate and metoprolol tartrate**. While both drugs are used to treat heart-related issues, their applications are very different. A beta 1 antagonist (beta-blockers) such as metoprolol (or other 'lol' ending drugs) decrease heart rate and contractility (force) which decreases blood pressure for a person with hypertension. The drug based medications prescribed to remedy ailments can be problematic. This is especially

true when the **etiopathology**, meaning the **cause** of the state, is completely unknown. This is only one good reason why natural remedies are a supreme idea. Natural beta blockers can be found in the following foods: Fish, garlic, berries, and vitamin B6 and the amino acid L-arginine are all natural sources of beta-blockers.



Sympathetic Agonists or Stimulants

Sympathomimetic drugs, such as **cocaine** and **methamphetamines** can precipitate severe hypertensive emergencies, since this division is for being in an emergency and fight or flight, then to overstimulate it can be dangerous. The sympathetic receptors can be over-stimulated by **cocaine**, **phencyclidine hydrochloride (PCP)**, and **lysergic acid diethylamide (LSD)**. Or overuse sympathomimetic drugs like pseudoephedrine or those used to drug people with 'attention deficit' disorders. Severe alcohol withdrawal can also induce sympathetic overdrive.

It is important to know that excessive stimulation of the sympathetic receptors can result in dangerously high blood pressure, **tachycardia** (elevated heart rate), **dysrhythmias** (erratic heart beat) and **hyperthermia** (below normal body temperature), any of these conditions could cause organ damage with the genuine potential for organism death.

A single receptor site can be stimulated, such as a beta 2 agonist medication like an **albuterol** inhaler that stimulates beta 2 receptors in the lungs then we can dilate the bronchioles in the patient with bronchospasm without causing excessive stimulation of the heart. **Isoprenaline** or **isoproterenol**, is a drug used for the **treatment of bradycardia** (slow heart rate), heart block, and sometime for asthma. It is a non-selective β adrenoceptor agonist that is the isopropylamine analog of epinephrine (adrenaline).



Postganglionic sympathetic receptors can be over-stimulated by the use of substances like **cocaine** and **methamphetamines**, or the excessive use or overdose of sympathomimetic medication like pseudoephedrine or those used to treat attention deficit disorders.

The Balance within the ANS Divisions

The body should usually spend most of its time being in the state of the **parasympathetic division** of the ANS. The parasympathetic engages in **anabolic activities**, such as **storing energy** in the body, organizing processes for **digestion, growth, repair, cleansing** and **elimination**. The catch phrases '*rest and digest*' and '*feed and breed*' are apt for the parasympathetic division as these are the activities it presides over. There is also more to it than that, because the storage and repair that occurs in the 'down' time when the body is at "rest" allows for the use of these resources and arrangements during an emergency. This calm restorative aspect of the ANS enables the **sympathetic division** to have many elements at its disposal, engaging in **catabolic activities** as it **uses up resources** and **elevates energy** and **alertness** in order to act quickly when responding to danger. Both are completely necessary but require balance.

As is shown, the **sympathetic division** is not bad or out of control, it is perfect for responding to **emergencies** or **excitement**. The key is that we are not meant to be in a state of emergency all the time, but rather only episodically. Therefore, it can become problematic for the human condition when an individual is in the sympathetic state too much of the time, especially when it is unnecessary. Being in a state of panic or believing you are in danger (whether it is real danger or perceived) is very taxing on the body, it uses up valuable resources and there is essentially **no growth** and **no repair** that can occur while in the sympathetic state. It is useful to understand the spectrum of the ANS responses and ensure that they respond appropriately and where possible are in alignment with the balance found in nature.

Here are some very good and effective suggestion for stimulating **parasympathetic activity**:

- Spend time in nature. Sitting, standing, walking, running, swimming, anything in nature.
- Practice proper deep abdominal breathing (from the diaphragm) – incredibly important.
- Take cold showers every morning, get a massage, and eat calming (low sugar) food.
- Engage in repetitive positive prayer or meditation.
- Play and interact with animals. Maybe even other people too, but they need to be enjoyable.
- Listen to and play complex, constructive sounds found in nature and good healthy music.
- Think of another example of an activity that would make you feel calm and happy.

Note how nice and relaxing it feels just to see pictures of nature and an adorable puppy dog.



Table 10.1 The Effects Parasympathetic and Sympathetic Stimulation and Receptors on Effector Tissue

Effector Tissue	Parasympathetic Neurotransmitter ACh Acting on muscarinic (M) receptors	Sympathetic Stimulation Neurotransmitters NE, E and ACh Acting on α and β receptors
Iris (Eye Muscles)	Pupil Constriction - M_3 (sphincter muscle)	Pupil Dilation - α_1 (radial muscle)
Ciliary Muscle	Contract - M_3 for Near focus	Relax - β_2 for Distant focus
Lacrimal Gland	Increase sections (tears) - M_3	-----
Sweat Glands	-----	Increase sections - M_3 [#] Muscarinic R
Scent Glands	-----	Increase sections - α_1
Arector Pili	-----	Contract hair muscle - α_1
Lung Bronchioles	Bronchial constriction - M_3	Bronchial dilation - β_2
Mucous Glands	-----	Increase secretion - β_2 Decrease secretion - α_1
Heart	Heart rate decreased - M_4 Force of beat decreased - M_4	Heart rate increase - β_1 and β_2 Force of beat increased - β_1
Coronary Arteries	Slight Vasodilation - M_3	Vasodilation - β_2 Vasoconstriction - α_1 and α_2
Visceral Blood Vessels	-----	Vasoconstriction - α_1 Vasodilation - β_2
Systemic Veins	-----	Vasoconstriction - α_1
Blood Vessels of Skeletal Muscle	-----	Vasodilation - β_2
Blood Vessels of Skin	Vasodilation (blushing) - M_3	Vasoconstriction - α_1 and α_2
Platelet cells	-----	Increased clotting - α_1
Salivary Glands	Increased Saliva - M_3 (watery increased)	Reduced Saliva - α_1 (mucus increased)
G. I. Tract Activity	Motility increased - M_3 Secretions increased	Motility reduced - α_1 , α_2 , β_1 and β_2 Secretions reduced - α_2 ,
Liver	Glycogen synthesis - M_3	Glycogen breakdown - α_1 and β_2
Pancreatic enzymes	-----	Decrease - α_1
Pancreatic insulin	-----	Decrease - α_2 Increase - β_2
Kidney	Increased urine output - M_3	Decreased urine output - α_1 and α_2
Bladder Wall	Contraction - M_3	-----
Internal Urethral Sphincter	Relaxation - M_3 (urine voided)	Contraction - α_1 (urine retained)
Adrenal Medulla	-----	*ACh onto Nicotinic receptors NE and E secreted into blood
Erectile tissue	Stimulation	-----
Glandular secretions	Stimulation	-----
Reproductive tract	-----	Stimulation - α_1
Uterus	-----	Labor contractions

[#]Muscarinic and *Nicotinic receptors

In **Table 10.1** above is a sampling of some specific effector tissues of the ANS and how the parasympathetic and sympathetic divisions differ in their effects on these tissues.

The ANS in Summary:

- The # of Neurons: 2 motor neuron.
- Effector Tissue: Three (3) main categories: Cardiac Muscle, Smooth Muscle and Glands.
- Neurotransmitter: ACh and NE.
- Receptors: For ACh there are: **a)** Nicotinic and Muscarinic; and NE there are: **b)** α and β
- Action: Parasympathetic usually clams things down and Sympathetic usually excites!
- Control: Involuntary (except biofeedback).

Review Questions for Chapter 10: The Peripheral Nervous System

1. Which of these characteristics best describe the somatic motor nervous system?
 - a) cell bodies are located in the lateral part of the spinal cord
 - b) effects can be excitatory or inhibitory
 - c) one neuron between CNS and skeletal muscle
 - d) receptor molecules can be nicotinic or muscarinic

2. The effector organs for the somatic motor nervous system are
 - a) cardiac muscle
 - b) smooth muscle
 - c) glands
 - d) skeletal muscle
 - e) all of these

3. Most postganglionic neurons of the sympathetic division are
 - a) adrenergic
 - b) dopaminergic
 - c) cholinergic
 - d) a and c
 - e) all of these

4. When acetylcholine binds to nicotinic receptors:
 - a) Na^+ ion channels open
 - b) G proteins are activated
 - c) K^+ channels open
 - d) Cl^- channels open

5. The membranes of all postganglionic neurons in autonomic ganglia and the membranes of skeletal muscle have:
 - a) adrenergic receptors
 - b) muscarinic receptors
 - c) nicotinic receptors
 - d) nothing in common

6. Effector cells that respond to acetylcholine released from postganglionic neurons have:
- adrenergic receptors
 - muscarinic receptors
 - nicotinic receptors
 - b and c
 - all of these
7. The **sympathetic** division of the ANS includes which of these descriptions?
1. it has long postganglionic fibers 2. increases heart rate 3. dilates bronchioles (air ways)
4. decreases pupil diameter 5. has short postganglionic fibers 6. decreases heart rate
- 2, 3 and 5
 - 1, 4, 2 and 3
 - 4, 6 and 5
 - 3, 2 and 1
 - 6, 3 and 5
8. In the ANS, the preganglionic neurons synapse with postganglionic neurons in the
- autonomic ganglia
 - brain stem
 - spinal cord
 - dorsal root ganglia
 - skeletal muscle cells
9. In the **parasympathetic** division of the ANS, which of these characteristics apply?
1. it speeds up heart rate 2. constricts bronchioles (air ways) 3. decreases pupil diameter
4. dilates bronchioles (air ways) 5. has short postganglionic fibers 6. increases watery saliva
- 6, 2, and 3
 - 1, 2 and 3
 - 4, 6 and 5
 - 5, 3, 2 and 1
 - 6, 3, 2 and 5
10. Stimulation of the **adrenal medulla** by sympathetic innervation predominantly causes release of
- acetylcholine
 - epinephrine
 - cortisol
 - norepinephrine
 - none of these

Answers in Appendix B