

## THE AUTONOMIC NERVOUS SYSTEM

**James Ziogas and Fred Mitchelson**

*Department of Pharmacology, University of Melbourne, Parkville Victoria, 3010, Australia.*

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## 1. Introduction

Investigations of the autonomic nervous system have been at the centre of seminal discoveries including; neurochemical transmission, second messenger signaling, co-transmission, and the molecular identification of receptors that have often resulted in recognition by the Nobel Awards Committee (see [www.nobelprize.org](http://www.nobelprize.org)). These discoveries span the disciplines of anatomy, physiology, biochemistry and pharmacology and have led to the development of many therapeutic agents whose actions either directly or indirectly interfere with the operation of the autonomic nervous system. In this chapter we will review the organization and function of the autonomic nervous system and discuss the rational basis for the development of therapeutic agents that target specific aspects of autonomic nervous system function.

## 2. Anatomical and Functional Organization of the Efferent Peripheral Nervous Systems

### 2.1. Somatic and Autonomic Nerves

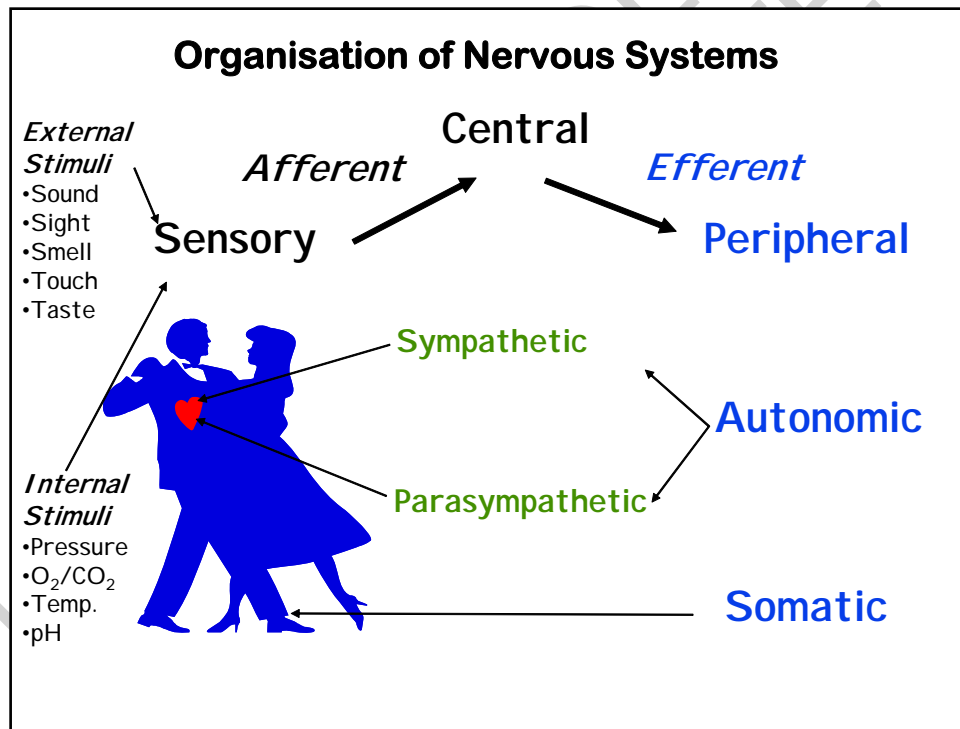


Figure 1. Organisation of the Nervous Systems.

Maintenance of a conscious state and an ability to respond to changes in our environment involves the coordinated activity of the central and peripheral nervous systems. The peripheral nervous system comprises afferent sensory neurones that transmit information about the environment to the central nervous system and efferent motor nerves that carry information to the target cells in the peripheral tissues (Figure 1). The somatic nervous system exclusively innervates striated muscle cells (skeletal muscle) and regulates their voluntary control while also receiving reflex inputs from the

muscle cells. The remaining visceral organs including smooth muscle, cardiac muscle, exocrine glands and endocrine glands are innervated by the autonomic nervous system. While some voluntary control can be exerted, it is the reflex control of the autonomic nerves that is critical to their role in maintaining a stable internal environment (homeostasis).

The sensory nervous system receives inputs from the internal and external environment that are processed in the central nervous system (brain and spinal cord) where they are integrated to regulate the outflow to the peripheral nervous system. The peripheral nervous system comprises the autonomic nerves that function outside voluntary control and the somatic motor nerves that control movement and posture.

In the somatic nervous system a single axon leaves the CNS and innervates the effector skeletal muscle cell which becomes active in response to stimulation and is termed the effector cell. In contrast in the autonomic nervous system, two neurones in series are required to connect the CNS to the visceral effector cell. These neurones synapse in specialized ganglia and the first neurone that leaves the CNS is the preganglionic neurone. The second neurone that innervates the visceral effector cells is the postganglionic neurone. On the basis of anatomical, functional and neuro-chemical criteria two divisions of the autonomic nervous system have been identified. Figure 2 depicts these features which will be detailed in the following section.

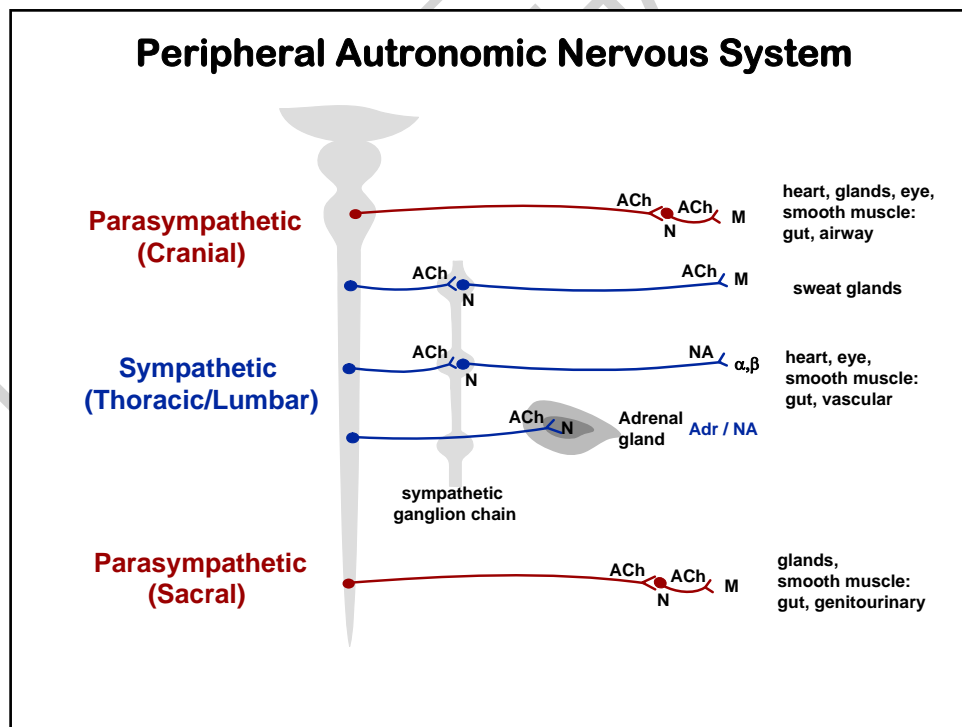


Figure 2 Representation of the anatomical, physiological and pharmacological characterisation of the efferent peripheral autonomic nervous system.

The origin of the preganglionic fibres determines the classification of the parasympathetic and sympathetic divisions of the autonomic nervous system. In all cases the preganglionic fibres release the neurotransmitter acetylcholine (ACh) that activates nicotinic (N) cholinergic receptors on the cell body of the postganglionic fibres. The short postganglionic fibres of the parasympathetic division all release ACh that activates muscarinic (M) cholinergic receptors on the target tissues. In contrast, the long postganglionic fibres of the sympathetic division mostly release noradrenaline (NA) that activates  $\alpha$ - or  $\beta$ -adrenoceptors depending on the target tissue. The exception to this is the nerves that target the sweat glands which are anatomically sympathetic, but release ACh from the long postganglionic fibres. Adrenaline (Adr) is released from the adrenal gland and mimics many of the actions of NA released from the postganglionic sympathetic fibres.

### **3. Sympathetic and Parasympathetic Divisions of the Autonomic Nervous System**

#### **3.1. Anatomical considerations**

The origin of the preganglionic fibers in the spinal cord defines the two divisions of the autonomic nervous system. Thus, the cell bodies of sympathetic preganglionic neurones are located in the inter-mediolateral column of the thoracic and lumbar regions of the spinal cord. Shortly after the dorsal and ventral roots fuse, the myelinated sympathetic preganglionic fibers leave the spinal nerve trunk to travel to the segmentally arranged paravertebral sympathetic ganglia chains that lie lateral to the spinal cord via the white rami communicantes. The preganglionic fibers synapse within the ganglia with the unmyelinated postganglionic sympathetic fibers that project to their target organs mainly via the gray rami communicantes and the segmental spinal nerves. Due to the proximity of the paravertebral ganglion chains to the spinal cord, preganglionic fibers are usually quite short and the postganglionic fibers are longer as they innervate many organs including the eye, the salivary glands, the sweat glands, the gut, the heart, smooth muscle of the blood vessels and the piloerector muscles of the skin hairs. Some preganglionic fibers pass through the paravertebral ganglia and join to form the splanchnic nerves, which pass to the celiac, hypogastric, superior, and inferior mesenteric ganglia where they synapse with the postganglionic neurone in prevertebral ganglia that lie near the various abdominal organs that they innervate. The exception is the preganglionic fibers that directly synapse with the chromaffin cells of the adrenal medulla. These chromaffin cells are homologous with sympathetic postganglionic neurones and share many of their physiological properties including the generation of action potentials and the secretion of catecholamines. In general, a single sympathetic preganglionic fiber branches and makes connections with a number of postganglionic neurones giving rise to the view that the system is designed such that a single preganglionic fiber can regulate widespread physiological activity. The widespread role of the sympathetic nervous system is reinforced by the release of adrenaline from the adrenal gland into the blood stream that allows sympathetic nervous system activation to influence tissues such as the bronchi that do not receive direct innervation.

The preganglionic autonomic nerves that originate in cranial and sacral segments of the spinal cord do not pass through the sympathetic ganglion chain and these form the parasympathetic division. In the cranial region, preganglionic nerves run to the ciliary ganglion where postganglionic fibers arise to innervate the iris and ciliary body of the

eye. The lacrimal glands receive parasympathetic motor input from the sphenopalatine ganglion, innervated by a branch of the facial nerve. The sublingual and submaxillary salivary glands receive postganglionic innervation from submaxillary ganglion cells innervated by the chorda tympani, another branch of the facial nerve while the parotid gland is innervated by postganglionic fibers from the otic ganglion, which receives preganglionic innervation from the glossopharyngeal nerve. The major parasympathetic motor output from the medulla oblongata is carried in the vagus nerve (10<sup>th</sup> cranial nerve) to thoracic organs such as the heart, trachea, bronchial smooth muscle and glands as well as to abdominal organs such as the stomach, jejunum, small intestine, pancreas, bile duct, gall bladder, spleen, and upper ureters. The vagus nerve also contains a majority of sensory neurons, constituting the afferent arm for autonomic reflex activity in these tissues. In the sacral region of the spinal cord, the parasympathetic motor neuronal system emerges to form part of the pelvic nerve tracts. These nerves innervate ganglia close to or within organs in the lower abdomen such as the distal colon, distal ureter, urinary bladder, prostate gland, penis and uterus. In all cases the parasympathetic ganglia are situated close to or within the end-organs so that the preganglionic fibers are generally quite long and the postganglionic fibers quite short. This organization of the nerves suggests that parasympathetic preganglionic nerves are targeted and influence only a specific organ.

### 3.2. Physiological considerations

Correlating with the anatomical separation are quite distinct functional consequences of the two divisions of the autonomic nervous system. Tables 1 and 2 list some of the actions of the sympathetic and parasympathetic divisions of the autonomic nervous system. These were elegantly described by the pharmacologist JH Burn as “ the sympathetic division prepares the animal for fight or flight. The heart increases in rate and in force of beat. The blood vessels constrict, in particular to the skin and viscera. The pupils of the eye dilate, the bronchioles dilate, the blood sugar rises and the hair is erected.” Thus, is the origin of the often used “fright or flight” term to described activation of the sympathetic nervous system. In contrast, for the parasympathetic division Burn wrote that it “is active in an old man sleeping after dinner. His heart rate is slow, his breathing noisy because of bronchial constriction, his pupils are small, drops of saliva may run out the corner of his mouth. A stethoscope applied to his abdomen will reveal much intestinal activity.” Thus, the parasympathetic nervous system is often referred to as being active during rest and repose.

Receptor	Agonist	Antagonist	Tissue	Response	2nd messenger system
$\alpha_1$	Phenylephrine	Prazosin	Blood vessels	Contraction	$G_{q/11}$ activation of IP3 and DAG $Ca^{2+}$
			Pupil radial muscle		
			Pilomotor muscle		
			Genitourinary smooth muscle		
			Heart	Increase force	
$\alpha_2$	Clonidine	Yohimbine	Nerve terminals Some blood vessels	Inhibit release Contraction	$G_i/G_o$ inhibition of cAMP

$\beta_1$	Dobutamine	Atenolol	Heart	Increase force and rate of contraction	Gs activation of cAMP
$\beta_2$	Salbutamol	Butoxamine	Bronchial muscle		
	Terbutaline		Skeletal muscle		
			blood vessels		
			Uterus		
			Skeletal muscle		
			Liver		
$\beta_3$	BRL 37344	n/a	Fat Cells	Lipolysis	Gs activation of cAMP

Table 1. Localization, action of adrenoceptor subtypes characterized by agonists, antagonists and biochemical mechanisms.

Receptor	Agonist	Antagonist	Tissue	Response	2nd messenger system
$M_1$	Acetylcholine	Atropine	CNS	Excitation	Activation of phospholipase C via $G_{q/11}$ leading to $IP_3$ and DAG production.
	Carbachol	Pirenzepine	Ganglia		Release of intracellular $Ca^{2+}$
	Muscarine				
$M_2$	Acetylcholine	Atropine	Heart	Decrease cardiac rate and force of contraction	Inhibition of adenylyl cyclase via $G_{i/o}$ leading to decrease in cAMP.
	Carbachol	Tripitramine			Activation of GIR $K^+$ channels.
	Muscarine	Otenzepad (AF-DX 116)			
$M_3$	Acetylcholine	Atropine	Exocrine glands	Secretion	Activation of phospholipase C via $G_{q/11}$ leading to $IP_3$ and DAG production.
	Carbachol Muscarine	Darifenacin	Smooth muscle	Contraction	Release of intracellular $Ca^{2+}$
			Vascular endothelium	Nitric oxide release (vasodilatation)	.
$M_4$	Acetylcholine	Atropine	Cholinergic neurons in urinary bladder.	Prejunctional autoinhibition of transmitter release.	Inhibition of adenylyl cyclase via $G_{i/o}$ leading to decrease in cAMP.
	Carbachol Muscarine	MT-3 toxin	CNS-	Inhibition of dopamine $D_1$ receptor function on	Activation of GIR $K^+$ channels.
			striatum		

				striatal GABAergic projection neurons	
M <sub>5</sub>	Acetylcholine	Atropine	CNS-ventral tegmental area	Activation of dopaminergic neurons projecting to Nu. Accumbens.	Activation of phospholipase C via G <sub>q/11</sub> leading to IP <sub>3</sub> and DAG production.
	Carbachol		Cerebral blood vessels.	Vasodilatation	Release of intracellular Ca <sup>2+</sup> .
	Muscarine				

Table 2. Localization, action of muscarinic receptor subtypes characterized by agonists, antagonists and biochemical mechanisms.

### 3.3. Pharmacological and Biochemical considerations

While the action potential was long recognized as a means by which information is transmitted along the axons it was the identification of the fact that nerves elicit responses in target tissues by releasing chemical transmitters that was able to fully explain the myriad of contrasting effects of the sympathetic and parasympathetic nerves. A productive era of research in the mid 20<sup>th</sup> century identified noradrenaline and acetylcholine as the principal neurotransmitters released in the peripheral autonomic and somatic nervous systems, and defined the essential steps required for chemical neurotransmission in all nerves in the body. These include the processes of synthesis, storage, release and inactivation of the transmitter as well as the need for activation of specific receptors on the target tissue in order to elicit a response. This work led to the award of the Nobel Prize to Julius Axelrod and colleagues in 1970.

Acetylcholine was identified as the neurotransmitter in all nerve fibers that left the CNS including the preganglionic nerves of both the sympathetic and parasympathetic divisions and the somatic motor nerves. Acetylcholine was also identified as the neurotransmitter in all postganglionic parasympathetic nerves. Noradrenaline was identified as the neurotransmitter from most postganglionic sympathetic nerves, the exception being the anatomically sympathetic fibers to the sweat glands that release acetylcholine from their postganglionic fibers. The receptors for these neurotransmitters vary at the different sites. Thus, acetylcholine released from preganglionic autonomic fibers activates nicotinic receptors on the cell bodies of the postganglionic fibers. In contrast, acetylcholine released from the postganglionic parasympathetic nerves activates muscarinic receptors on the target tissues. These receptors were named after the first compounds identified to mimic the actions of acetylcholine at the particular sites. The receptors for noradrenaline are the  $\alpha$ - and  $\beta$ -adrenoceptors that were named based on a comparison of the different actions of noradrenaline and the closely related circulating hormone adrenaline, which is released from the adrenal gland by activation of the preganglionic sympathetic fibers that originate in the lower lumbar segments. The release of noradrenaline from postganglionic sympathetic nerves provides a mechanism for the discrete regulation of specific organs, however activation of the splanchnic nerve results in the secretion of both adrenaline and noradrenaline from the adrenal medulla into the circulation. About 80% of the secretion is adrenaline and 20% is noradrenaline.

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### **Biographical Sketches**

**Fred Mitchelson** PhC (Vic. Coll. of Pharmacy), MSc (Melb), PhD (Lond). Previously Reader in Pharmacology, Department of Pharmacology, Victorian College of Pharmacy, Monash University (Australia), now occupies an honorary position as Principal Fellow, Department of Pharmacology, University of Melbourne. Research interests include muscarinic and nicotinic cholinceptors, allosteric mechanisms at muscarinic receptors, anticholinesterases and antidepressants.

**James Ziogas** BSc (Hons), PhD (Melb). Associate Professor in the Department of Pharmacology, University of Melbourne. Research interests include neurohumoral modulation of sympathetic neurotransmission, tissue rennin-angiotensin systems and angiotensin receptor signaling.