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The Autonomic Nervous System 25/07/05
Basic Anatomy and Physiology

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Many anaesthetic procedures and drugs used in anaesthetic practice have a direct influence on the autonomic nervous system. It is therefore essential that the anaesthetist should have a basic understanding of its structure and function.

Before reading the tutorial, see what you already know about this subject by answering the following questions:

1. What is the autonomic nervous system and what are its functions?
2. How do sympathetic nerves get from the CNS to the end organs?
3. How do parasympathetic nerves get from the CNS to end organs?
4. What are the transmitter substances in the autonomic nervous system?
5. What types of receptors are there in the autonomic nervous system?

What is the Autonomic Nervous System?

Many bodily functions proceed without any conscious supervision from our central nervous system (CNS). For example, we don't have to remember to digest our food after a meal, or sweat when too warm. These functions are controlled subconsciously, with a degree of automaticity, by a branch of the nervous system - The *Autonomic Nervous system* (ANS).

The ANS can thus be thought of as the regulatory system, that partly or wholly controls most of the body's organ systems and homeostatic mechanisms. In general, ANS effects are involuntary, relatively rapid, neuronal reflexes.

The afferent input to the reflex arc varies and can be from:

i) The Autonomic Nervous System - for example the tachycardia in response to hypotension, mediated by baroreceptors, or -

ii) The Central Nervous System – for example the "vaso-vagal response" to impending cannulation in a needle-phobic patient.

The efferent limb of neuronal autonomic reflexes consists of specific primary autonomic nerves that synapse in autonomic ganglia, with secondary or “postganglionic” fibres. These postganglionic fibres mediate the desired response at the effector organ.

The “effector limb” of the ANS is subdivided in to 2 separate divisions – the sympathetic, and parasympathetic nervous systems. These two divisions differ in both structure and function as will be seen later.

In general the sympathetic nervous system can be thought of as preparing the body for “fight or flight”. In the cardiovascular system, increased inotropic and chronotropic drive lead to increased cardiac output and blood flow is routed toward vital organs and skeletal muscle. There is an overall increase in CNS stimulation, and respiratory drive is increased. Visceral activity is decreased.

The parasympathetic nervous system in contrast, increases the activity of the abdominal viscera. The cardiovascular system is depressed - reducing heart rate and cardiac output, and routing blood flow toward visceral beds. The respiratory system and CNS are also depressed.

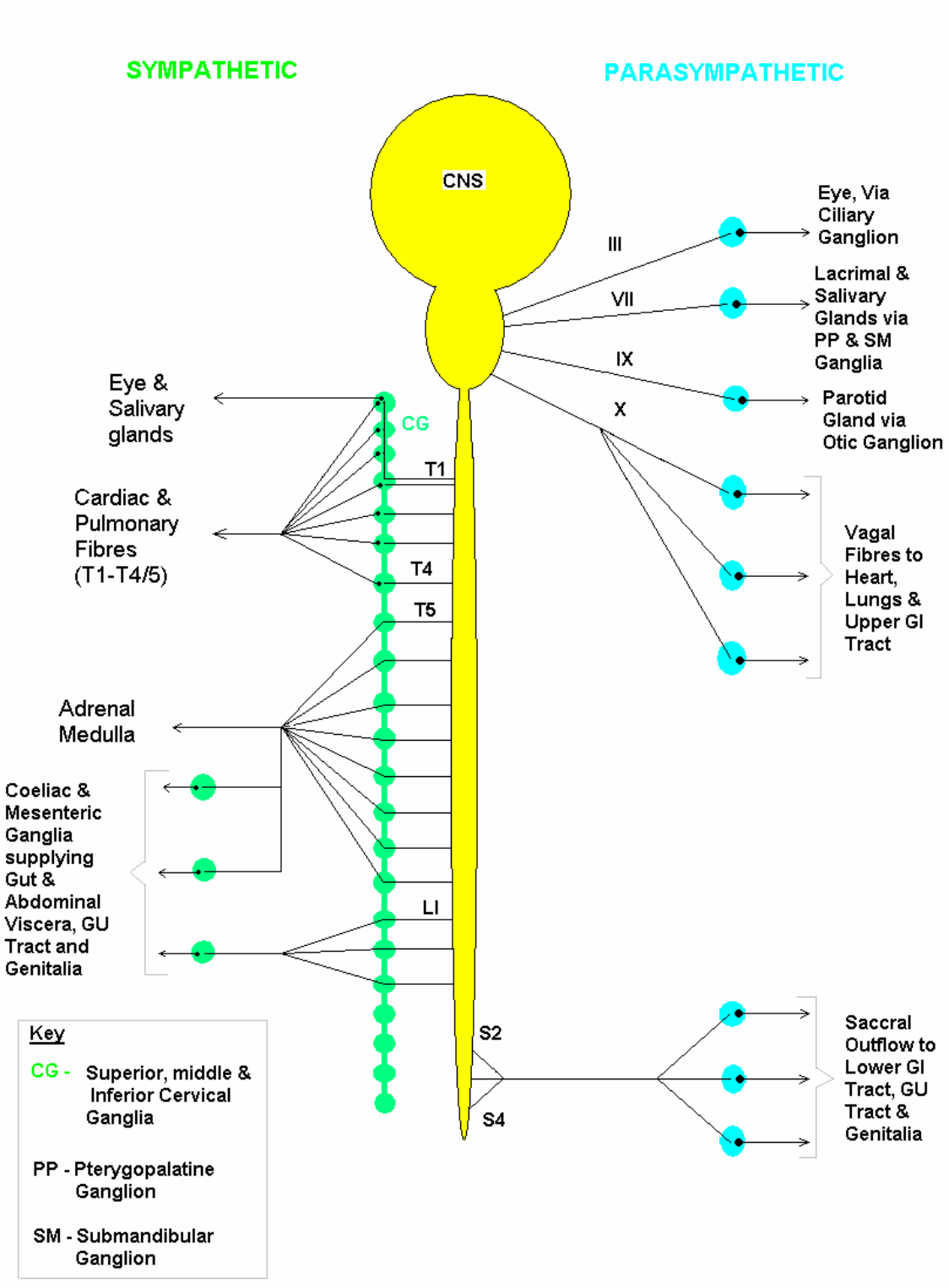
Structure of the Autonomic Nervous System

In addition to its close functional relationship to the central nervous system, the ANS shares a close anatomical proximity. In the sympathetic nervous system, the ganglia are fused to form the sympathetic chain, which lies adjacent to the spinal column throughout most of its length. Preganglionic sympathetic fibres have cell bodies in the intermedio-lateral horn of grey matter in the spinal cord between T1 & L2. These fibres emerge from the spinal cord in the primary ventral rami of the spinal nerves and pass to the sympathetic chain via the *white rami communicantes.* In the sympathetic chain the fibres will synapse, giving rise to unmyelinated post-ganglionic fibres that rejoin the spinal nerves via the *grey rami communicantes*. Some preganglionic fibres however ascend or descend to other levels of the sympathetic chain prior to synapsing. In general therefore, sympathetic preganglionic fibres are short, and postganglionic fibres tend to be longer.

Parasympathetic preganglionic fibres leave the CNS in both cranial and sacral nerves; the so-called “cranio-sacral outflow”. Cranial fibres arise from specific parasympathetic brainstem nuclei of cranial nerves III, VII, IX, and X. The fibres travel with the main body of the cranial nerves to ganglia that tend to be more distant from the CNS and close to the target organ. Consequently, in contrast to the sympathetic nervous system, preganglionic fibres tend to be long, whereas postganglionic fibres will be shorter.

Sacral preganglionic fibres emerge from the CNS via the ventral rami of nerves S2-S4 and form the pelvic splanchnic nerves, which pass to ganglia close to the effector organs.

The basic structure of the ANS is illustrated in the diagram below.



Basic Structure of the Autonomic Nervous System

One can imagine, that given the anatomical differences between the 2 divisions, anaesthetic interventions may have a greater or lesser effect on the sympathetic or parasympathetic nerves. A good example of this can be seen during spinal anaesthesia. A spinal block will temporarily halt input to the sympathetic afferents at the affected levels, leading to vasodilatation and loss of sweating in the affected dermatomes. If the block is allowed to spread to the levels supplying cardiac sympathetic fibres (T1-T4/5), there will be a loss of both inotropic and chronotropic drive to the heart and progressive hypotension. The parasympathetic supply to the heart coming from the vagus nerve will be unaffected by the spinal block, leading to unopposed parasympathetic stimulation and a bradycardia.

Physiology of the ANS

In order to understand the functions of the ANS, and the possible targets for pharmacological manipulation, it is necessary to have a basic knowledge of the neurotransmitters and receptors, which are integral to the ANS.

As with all neuronal systems, the effects of the ANS are mediated by the release of neurotransmitters. Preganglionic fibres of both the sympathetic and parasympathetic nervous systems secrete acetylcholine – thus nicotinic receptors (see below) predominate in the autonomic ganglia. Sympathetic postganglionic fibres are mostly adrenergic in nature – i.e. secreting noradrenaline and occasionally adrenaline. The effect of postganglionic nerve stimulation will depend upon the receptors present at the effector site – usually alpha and beta adrenoreceptors. The effects are terminated by noradrenaline re-uptake in to the nerve terminals.

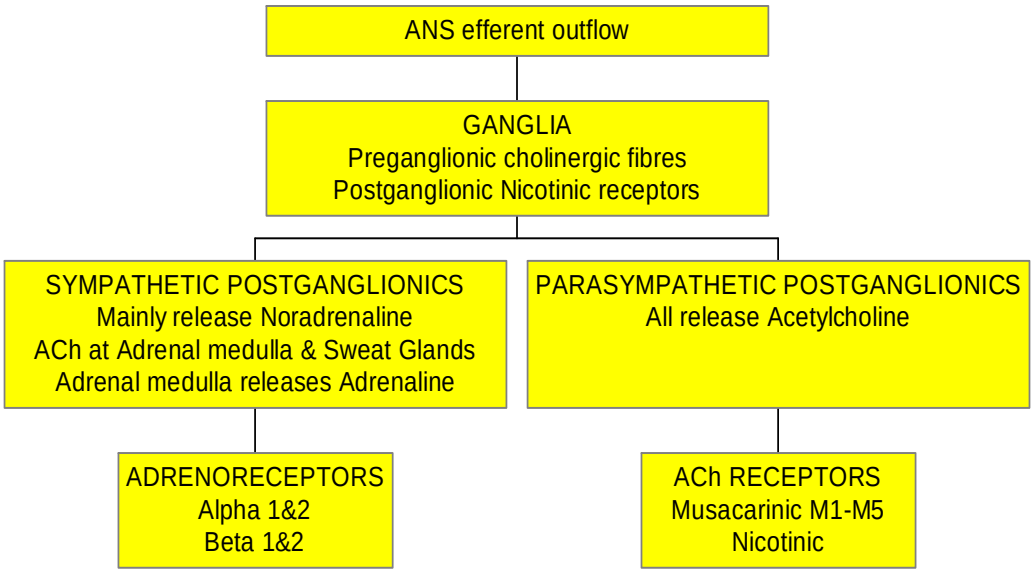
A special case within the sympathetic nervous system is the nerve to the adrenal medulla. This nerve does not synapse within the sympathetic chain and hence is strictly still “preganglionic” when it reaches the adrenal medulla and consequently secretes acetycholine. The adrenal medulla, which can be thought of as a modified autonomic ganglion, in turn secretes adrenaline in to the systemic circulation.

Parasympathetic postganglionic fibres release acetylcholine. Most effects are mediated via muscarinic receptors and actions are terminated as acetylcholine is hydrolysed by acetylcholinesterase within the synaptic cleft.

Neurotransmitters bind with specific receptors at target cells to produce their effects. Different receptor subtypes exist in each of the divisions of the ANS, and the intracellular response in the target cell and hence the target organ, is specific to the receptor type.

Within the sympathetic nervous system, effects are generally mediated by adrenoreceptors. In the parasympathetic system effects are mediated generally by muscarinic acetylcholine receptors. A further special case is that of sympathetic postganglionic fibres supplying sweat glands. These fibres secrete acetylcholine and exert their effects through muscarinic receptors.

ANS Neurotransmitters & Receptors



Adrenoreceptors

Adrenoreceptors are subdivided into alpha, and beta receptors. Each of these classes is further divided into subgroups – alpha 1&2, and beta 1&2.

Alpha Receptors

Alpha receptors are G-protein linked receptors. Alpha-1 receptors act via the G-protein subgroup Gz and phospholipase C to increase cytosolic calcium levels. This leads to mainly excitatory effects – such as smooth muscle contraction. Alpha-1 receptors are widespread in the peripheral vascular tree and stimulation causes vasoconstriction,

increased systemic vascular resistance and diversion of blood flow from the peripheries to the vital organs.

Within the ANS, alpha-2 receptors are largely presynaptic. They act via the G-protein subgroup Gi, inhibiting adenyl cyclase, reducing cytosolic cyclic AMP and calcium. They may also have a direct action – activating potassium channels and causing membrane hyperpolarization. The net effects of these responses are to downregulate, or at least reduce the sympathetic response. Alpha-2 receptors are also present in parts of the CNS – particularly the locus coerulus in floor of the forth ventricle. Their function appears to be linked to the thalamus, reticulospinal tracts and vasomotor centre – activation causing analgesia, drowsiness and hypotension.

Beta Receptors

Beta receptors are again G-protein linked receptors. Beta stimulation leads to increased activity of adenyl cyclase that in turn increases intracellular cyclic AMP.

Two major subgroups of beta receptors exist – beta-1 and beta-2. Traditional teaching tells us that beta-1 receptors are "cardiac", whereas beta-2 receptors are more widespread. This is probably an oversimplification, both types of beta receptor can be found in the heart and at many other sites. The beta receptor population is rather "fluid" in nature – receptors can be down or up regulated in terms of number and function. A good example of this is seen in cardiac failure, where reduced receptor density is observed in cardiac muscle.

Clinically, beta-1 stimulation leads to increased heart rate and positive inotropy. Renin release from the juxtaglomerular apparatus is stimulated leading to activation of the renin/angiotensin/aldosterone axis. Beta-2 stimulation causes relaxation of bronchial and uterine smooth muscle, vasodilatation in some vascular beds (eg skeletal muscle, pulmonary, coronary) and some degree of positive inotropy & chronotropy.

Acetylcholine Receptors

Acetylcholine receptors are named according to the agonist that they responded to in early experiments. Those activated by nicotine were named "Nicotinic" receptors, whereas those that responded to muscarine were named "Muscarinic".

Nicotinic receptors

Nicotinic receptors are ion channels, that when stimulated by acetylcholine, allow a flow of cations into the cell causing depolarization. They are found in all autonomic ganglia. Acetylcholine receptors at the motor end plate of the neuromuscular junction are historically nicotinic, but their structure differs slightly from those of the ANS.

Muscarinic receptors

Muscarinic receptors mediate the majority of effects caused by parasympathetic postganglionic fibres. Like adrenoreceptors, they are G-protein linked receptors and are further divided by structure and location into subtypes M1 – M5. M1 receptors are found on gastric parietal cells and stimulate acid secretion. M2 receptors are found in the heart

and have negatively chronotropic effects. M3 receptors promote smooth muscle contraction in the gut, and promote lacrimal secretion. M4 receptors cause adrenaline release from the adrenal medulla in response to sympathetic stimulation, and M5 receptors are thought to have CNS effects.

Summary

- The autonomic nervous system is instrumental in the control of most of the body's organ systems, via a series of neural reflexes
- The afferent limb of these reflexes can be from the ANS or CNS.
- The efferent limb will be mediated by the sympathetic or parasympathetic divisions, which are functionally and structurally distinct.
- The observed physiological effect will depend upon which neurotransmitter and receptor types are involved.
- Within the ANS there are many targets for pharmacological manipulation. These will be discussed in a further tutorial.