The Autonomic Nervous System - Basic Anatomy and Physiology

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INTRODUCTION
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 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 peripheral or central nervous system. The efferent limb is mediated by the sympathetic or parasympathetic divisions of the ANS, which are functionally and structurally distinct. The observed physiological effect of the ANS depends upon several neurotransmitter and receptor types and so there are many targets for pharmacological manipulation.

AFFERENT PATHWAYS
Although the ANS is predominantly an efferent system, transmitting impulses from the central nervous system (CNS) to peripheral organ systems, it receives afferent inputs (i.e. transmit information from the periphery to the CNS) into its reflex arcs from:

The ANS itself
These afferent neurones are concerned with the mediation of visceral sensation and the regulation of vasomotor and respiratory reflexes. Examples are the baroreceptors and chemoreceptors in the carotid sinus and aortic arch, which are important in the control of heart rate, blood pressure and respiratory activity. The afferent fibres are usually carried to the CNS by major autonomic nerves such as the vagus, splanchnic or pelvic nerves, although afferent pain fibres from blood vessels may be carried by somatic nerves.

Other parts of the CNS
An example is the ‘vaso-vagal response’ to impending cannulation in a needle-phobic patient.

EFFERENT PATHWAYS
The efferent limb of neuronal autonomic reflexes consists of specific primary autonomic nerves (preganglionic nerves) that synapse in autonomic ganglia, with secondary or postganglionic fibres. These postganglionic fibres mediate the desired response at the effector organ. The efferent limbs of these reflexes may also involve the somatic nervous system (e.g. coughing and vomiting). Simple reflexes are completed entirely within the organ concerned, whereas more complex reflexes are controlled by the higher autonomic centres in the CNS, principally the hypothalamus.

The effector limb of the ANS is subdivided into two separate divisions on the basis of anatomical and functional differences - the sympathetic and parasympathetic nervous systems. These two divisions differ in both structure and function.

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
Both the sympathetic and parasympathetic systems consist of myelinated preganglionic fibres that make synaptic connections with unmyelinated postganglionic fibres, and it is these which then innervate the effector organ. These synapses usually occur in clusters called ganglia. Most organs are innervated by fibres from both divisions of the ANS, and the influence is usually opposing, for example the vagus slows the heart, whilst the sympathetic nerves increase its rate and contractility. The effects on some organs, such as the salivary glands may be in parallel.

Sympathetic 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 intermediolateral column (lateral horn) of grey matter in the spinal cord between the first thoracic and second lumbar vertebrae (T1 to L2). These fibres emerge from the spinal cord and travel a short distance in the primary ventral rami of a mixed spinal nerve (anterior nerve root) and pass to the sympathetic ganglia via the white rami communicantes (Figure 1). The ganglia are mainly arranged in two paravertebral chains (the sympathetic ganglionic chains) which lie anterolateral to the vertebral bodies and extend from the cervical to the sacral region. In the sympathetic chain the fibres will synapse, giving rise to unmyelinated postganglionic fibres that rejoin the spinal nerves via the grey rami communicantes and are conveyed to the effector organ. Some preganglionic fibres however ascend or descend to other levels of the sympathetic chain prior to synapsing (5 in Figure 1). In general therefore, sympathetic preganglionic fibres are short, and postganglionic fibres tend to be longer.

The cranial nerves III, VII and IX affect the pupil and salivary gland secretion, whilst the vagus nerve (X) carries fibres to the heart, lungs, stomach, upper intestine and ureter. The sacral fibres form pelvic plexuses which innervate the distal colon, rectum, bladder and reproductive organs.

The basic structure of the ANS is illustrated in Figure 2.

**Parasympathetic nervous system**

Parasympathetic preganglionic fibres leave the CNS in both cranial and sacral nerves. Cranial fibres arise from specific parasympathetic brainstem motor nuclei of cranial nerves III (oculomotor nerve), VII (facial nerve), IX (glossopharyngeal nerve), and X (vagus nerve). The fibres travel with the main body of fibres within the cranial nerves to ganglia that tend to be distant from the CNS and close to the target organ. The ganglion cells may be either well organised (e.g. myenteric plexus of the intestine) or diffuse (e.g. bladder, blood vessels). In contrast to the sympathetic nervous system, the preganglionic fibres tend to be long, whereas the postganglionic fibres are shorter.

Sacral preganglionic fibres emerge from the CNS via the ventral rami of nerves S2 to S4 and form the pelvic splanchnic nerves, which pass to ganglia close to the effector organs.
in autonomic ganglia. Sympathetic postganglionic fibres are mostly adrenergic in nature – they secrete norepinephrine and occasionally epinephrine. Epinephrine and norepinephrine are both catecholamines, and are both synthesized from the essential amino acid phenylalanine by a series of steps, which includes the production of dopamine. The effect of postganglionic nerve stimulation depends upon the receptors present at the effector site – usually α- or β-adrenoreceptors. The effects are terminated by norepinephrine re-uptake into the presynaptic nerve ending where it is inactivated by the enzyme Monoamine Oxidase in mitochondria or metabolism locally by the enzyme Catechol-O-Methyl-Transferase.

A special case within the sympathetic nervous system is the nerve to the adrenal medulla. The adrenal medulla responds to nervous impulses in the sympathetic cholinergic preganglionic fibres by transforming the neural impulses into hormonal secretion. This nerve does not synapse within the sympathetic chain and hence is strictly still preganglionic when it reaches the adrenal medulla and consequently secretes acetylcholine as its neurotransmitter. The cells of the adrenal medulla can be thought of as a modified autonomic ganglion, but due to the presence of an additional enzyme the majority of norepinephrine is converted to epinephrine. In situations involving physical or psychological stress, much larger quantities are released.

Parasympathetic postganglionic fibres release acetylcholine. Most effects are mediated via muscarinic receptors and actions are terminated when 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 exception to this rule is the sympathetic postganglionic fibres supplying sweat glands. These fibres secrete acetylcholine and exert their effects via muscarinic receptors.

**ADRENORECEPTORS**

Adrenoreceptors are subdivided into α- and β-receptors. Each of these classes is further divided into subgroups – α₁, α₂, β₁, β₂ and β₃.

**α-receptors**

α-receptors are G-protein linked receptors. They act via the G-protein subgroup Gz and phospholipase C to increase cytoplasmic calcium concentration.

**β-receptors**

β-receptors act on the intracellular messenger protein Gq to increase cytoplasmic calcium concentration.

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**Table 1. Summary of the effects of the autonomic nervous system at different organs**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic stimulation</th>
<th>Parasympathetic stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>↑ heart rate β₁ (and β₂)</td>
<td>↓ heart rate</td>
</tr>
<tr>
<td></td>
<td>↑ force of contraction β₁ (and β₂)</td>
<td>↓ force of contraction</td>
</tr>
<tr>
<td></td>
<td>↓ conduction velocity</td>
<td>↑ conduction velocity</td>
</tr>
<tr>
<td>Arteries</td>
<td>constriction (α₁)</td>
<td>dilation</td>
</tr>
<tr>
<td></td>
<td>dilatation (β₂)</td>
<td></td>
</tr>
<tr>
<td>Veins</td>
<td>constriction (α₁)</td>
<td>dilation (β₂)</td>
</tr>
<tr>
<td>Lung</td>
<td>bronchial muscle relaxation (β₂)</td>
<td>bronchial muscle contraction</td>
</tr>
<tr>
<td></td>
<td>↓ motility (β₂)</td>
<td>↑ bronchial gland secretions</td>
</tr>
<tr>
<td></td>
<td>contraction of sphincters (α)</td>
<td>relaxation of sphincters</td>
</tr>
<tr>
<td>Liver</td>
<td>glycogenolysis (β₁, and α)</td>
<td>glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td>gluconeogenesis (β₂, and α)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lipolysis (β₂, and α)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>renin secretion (β₁)</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>detrusor relaxation (β₂)</td>
<td>detrusor contraction</td>
</tr>
<tr>
<td></td>
<td>contraction of sphincter (α)</td>
<td>relaxation of sphincter</td>
</tr>
<tr>
<td>Uterus</td>
<td>contraction of pregnant uterus (α)</td>
<td>relaxation of pregnant and non-pregnant uterus (β₂)</td>
</tr>
<tr>
<td></td>
<td>relaxation of pregnant uterus (α)</td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>dilates pupil (α)</td>
<td>constricts pupil</td>
</tr>
<tr>
<td></td>
<td>↑ lacrimal gland secretions</td>
<td></td>
</tr>
<tr>
<td>Submandibular and parotid glands</td>
<td>viscous salivary secretions (α)</td>
<td>watery salivary secretions</td>
</tr>
</tbody>
</table>

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levels. This predominantly leads to excitatory effects, such as smooth muscle contraction. $\alpha$-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. They can be further subdivided into $\alpha_1$, $\alpha_2$, and $\alpha_3$ based on receptor structure and agonist response but at the moment there is no clinical difference between them.

Within the ANS, $\alpha$-receptors are largely presynaptic. They act via the G-protein subgroup Gi, inhibiting adenylate cyclase, reducing cytoplasmic cyclic AMP and calcium levels. They may also have a direct action — the activation of potassium channels, causing membrane hyperpolarization. The net effects of these responses are to down-regulate, or at least reduce the sympathetic response. $\alpha$-receptors are also present in parts of the CNS — particularly the locus coeruleus in floor of the fourth ventricle. Their function appears to be linked to the thalamus, reticulospinal tracts and vasomotor centre, with activation causing analgesia, drowsiness and hypotension. $\alpha_3$-receptors can be also subdivided into four further subtypes.

$\beta$-receptors

$\beta$-receptors are again G-protein linked receptors; stimulation leads to increased activity of adenylate cyclase that in turn increases intracellular cyclic AMP. There are three major subgroups of $\beta$-receptors — $\beta_1$, $\beta_2$, and $\beta_3$, and recently a forth has been described, but as yet it is not certain of its exact function. $\beta_1$ and $\beta_2$-receptors predominate in the heart (about 85%), but the traditional view that $\beta_2$ are ‘cardiac’ and $\beta_1$ are peripheral is probably an over-simplification. 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, $\beta_1$-receptor 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. $\beta_2$-receptor stimulation causes relaxation of bronchial and uterine smooth muscle, vasodilatation in some vascular beds (e.g. skeletal muscle, pulmonary, coronary) and some degree of positive inotropy and chronotropy. $\beta_3$-receptors are found in adipose tissue and have a role in regulating metabolism, thermogenesis and body fat.

ACETYLCOLINE RECEPTORS

Acetylcholine receptors are named according to the agonist that they responded to experimentally. Those activated by nicotine are termed nicotinic receptors, whereas those that responded to muscarine are named muscarinic receptors.

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 controls non voluntary bodily functions in a reflex arc with afferent signals being processed either locally or in the brain stem. Its function and dysfunction are important to anaesthetists in that many of the drugs used in anaesthesia and intensive care are used to specifically modulate autonomic receptors in the control of the cardiorespiratory and neurologic systems. Other drugs have unwanted autonomic side-effects which need to be treated (such as using an anticholinergic when reversing neuromuscular blockade). We must take into account the autonomic dysfunction seen in such widespread scenarios as diabetes, Guillan-Barre syndrome and tricyclic antidepressant overdose and we must also be aware of the ‘normal’ dysautonomia seen with old age as this can exaggerate the effects of many anaesthetic agents and techniques.