Wellcome Film Project

The Pharmacology of the Autonomic Nervous System

University of London Audio-Visual Centre, 1971.

Made by Bryan Robinson PhD, Department of Pharmacology, Guy's Hospital Medical School, and John Metcalfe, Audio-Visual Centre, University of London.

Colour
Duration: 00:20:56:16

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<**Opening titles**>

<**Unnamed narrator over animated diagrams showing pathways of autonomic nervous system, some listing effects of stimulation of the parasympathetic and sympathetic nerves**>

The autonomic nervous system is responsible for the control of the cardiovascular system and of the digestive system. It also controls the secretion of many glands, particularly the salivary and sweat glands and the adrenal medulla. The autonomic nervous system can be divided into two parts – the parasympathetic and the sympathetic.

Anatomically, the parasympathetic nerves arise from the brain stem of the sacral segments of the spinal cord. They have long pre-ganglionic fibres and short post-ganglionic fibres. The connecting synapses, or ganglia, lie close to, or in, the organ innervated. Stimulation of these nerves causes bradycardia, glandular secretions, increased peristalsis and bronchiolar constriction.

The sympathetic nerves leave the spinal cord in the ventral roots from the first thoracic to the second lumbar segments. They have short pre-ganglionic and long

post-ganglionic fibres. Stimulation of the sympathetic nerves produces effects which include tachycardia with increased force of contraction of the heart, bronchiolar dilatation and vasoconstriction in the skin and splanchnic areas.

The transmitter of all ganglia in the autonomic nervous system is acetylcholine. The transmitter of the adrenal medulla, which is a modified ganglion, is also acetylcholine. But the transmitter at post-ganglionic nerve endings varies. In the post-ganglionic nerves it is acetylcholine at all nerve endings. At the sympathetic nerve endings it is usually noradrenaline, though at some sites it may be adrenaline or even acetylcholine.

<**Unnamed narrator over film showing surgical experiment on anaesthetised cat to show the effect of drugs on the autonomic nervous system**>

An anaesthetised cat will be used to demonstrate the effect of drugs on the autonomic nervous system. The cat, of course, remains unconscious throughout the experiment and consequently feels no pain. After stage 1 anaesthesia has been induced using first ethyl chloride and then ether, a glass cannula is inserted into the trachea. Through this more ether will be given and, if necessary, we can attach a pump to the cannula to give positive pressure artificial respiration.

At this stage of surgical anaesthesia, a cannula is inserted into the femoral vein in the hind leg so that chloralose may be administered. Chloralose is a combination of chloral hydrate and glucose and after it has been given it is quite common to see the cat licking. Now, the supply of ether via the trachea cannula may be stopped. A cannula inserted in the femoral artery of the opposite hind leg will allow us to measure the cat's blood pressure which is under control of the autonomic nervous system. Both sympathetic and parasympathetic control cardiac output which is reflected in systolic blood pressure. The sympathetic also controls arteriolar tone and thus peripheral resistance on which diastolic pressure principally depends.

This cannula is connected via a pressure transducer to a hot wire pen recorder and systolic and diastolic blood pressure are recorded in millimetres of mercury. Impulses from this pen recorder are also fed into a meter to enable heart rate to be monitored.

A Doppler probe detects ultrasound reflected from blood cells moving in the femoral artery and this can be used to give an auditory indication of heart rate. The nictitating membrane of the eye gives a useful indication of activity in the sympathetic system. Pre- or post-ganglionic stimulation of the nerves supplying the nictitating membrane will cause it to contract. In order to demonstrate the site of action of a drug affecting the sympathetic system, we can artificially stimulate the nerves supplying the nictitating membrane and monitor the resulting contractions on the pen recorder. Here, the nictitating membrane has been connected to a strain gauge which, in turn, will be connected to the pen recorder. And here, the lower trace is recording a contraction of the membrane.

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Two electrodes are attached to the nerves supplying the nictitating membrane. One electrode is attached at a pre-ganglionic site, the other at a post-ganglionic site. Stimulation of the nerve via either of these electrodes produces a contraction of the nictitating membrane. This contraction is recorded on the pen recorder.

Later in the experiment it will be possible to use this arrangement of electrodes to determine whether a drug affecting the sympathetic nerves is acting at a pre- or a post-ganglionic site.

<**Intertitle**>

Sympathetic transmission

<**Unnamed narrator over animated diagrams showing the effects of stimulation on the sympathetic nerves following injection by noradrenaline and adrenaline**>

We can mimic the effects of stimulation of sympathetic nerves by injecting noradrenaline and adrenaline. Sympathetic transmission following nerve stimulation produces a variety of effects. The most important of these in relation to blood pressure are an increase in the rate and force of contraction of the heart and constriction of the visceral arterioles. These effects are produced by noradrenaline released from the sympathetic nerve endings and by noradrenaline and adrenaline released from the adrenal medulla.

Schematically, the sympathetic nerve ending is composed of mitochondria and many vesicles containing noradrenaline. When the nerve is stimulated, the vesicles stream towards the terminal membrane and release their contents into the junctional gap. This noradrenaline activates the receptors on the postjunctional membrane to produce its effects. Most of the noradrenaline released is taken back into the nerve; this process of re-uptake limits the action of noradrenaline and provides a source of noradrenaline for subsequent release.

<**Unnamed narrator over further scenes from earlier film of experimental surgical procedure on anaesthetised cat, showing the effect of drugs on the sympathetic nervous system**>

To study the effect on the sympathetic nervous system, various drugs will be injected into the femoral vein through this cannula. A saline solution is used to flush the drugs into the circulatory system. The apparatus and the cannula are filled with saline and the first drug, adrenaline, is ready to be injected.

In the cat, adrenaline produces a marked increase in both systolic and diastolic blood pressure and in heart rate. This is usually followed by a small fall in mean blood pressure. In man, heart rate increases but diastolic blood pressure falls so that mean blood pressure is little affected. Noradrenaline, on the other hand, produces a rise in blood pressure and a rise in heart rate in the cat, although in man one would see a reflex fall in heart rate due to the rise in mean blood pressure.

The different effects that these drugs produce in man compared with those produced in the cat are related to the different proportions of skeletal muscle in the two animals. So far we have shown only the naturally occurring transmitters, but the synthetic compound isoprenaline can also be used to mimic some of the effects of sympathetic nerve simulation.

In the cat, isoprenaline produces a fall in blood pressure and a marked increase in heart rate. In man, the heart rate will also increase but mean blood pressure will be little affected. How can these different reactions be explained?

<**Unnamed narrator over animated diagrams showing function of alpha- and beta-receptors at the sympathetic nerve ending**>

It appears that there are two types of receptors at the sympathetic nerve ending which may be stimulated by the transmitter substances, they're called alpha- and beta-receptors. Stimulation of alpha-receptors produces vasoconstriction in the splanchnic and skin areas but does not affect heart rate. Stimulation of beta-receptors stimulates a response in the rate and force of contraction of the heart and a dilatation of blood vessels in skeletal muscle and in the coronary circulation.

Adrenaline stimulates both alpha- and beta-receptors, thus it causes increased heart rate, vasoconstriction in skin and splanchnic areas, and vasodilatation in skeletal muscle. Noradrenaline stimulates mainly alpha-receptors. This produces vasoconstriction with a consequent rise in blood pressure and little direct effect on the heart. Isoprenaline stimulates only the beta-receptors, causing an increase in heart rate and peripheral vasodilatation with a subsequent fall in blood pressure.

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<**Unnamed narrator over animated diagrams showing stimulation of the parasympathetic nerves**>

Parasympathetic transmission. Stimulation of the parasympathetic nerves produces a different series of effects. When a parasympathetic nerve is stimulated, acetylcholine is released at the nerve ending. The transmitter substance in the parasympathetic system is released in the same way as in the sympathetic system. The principle effect of parasympathetic stimulation is the slowing of the heart.

Choline esterase present in the membrane hydrolyzes the acetylcholine to choline and acetate, represented by the white particles. This limits the spread and action of the acetylcholine.

<**Unnamed narrator over further scenes from earlier film of experimental surgical procedure on anaesthetised cat, interspersed with animated diagrams explaining the muscarinic effect**>

In the living animal, the effect of stimulating the parasympathetic nervous system can be mimicked by injecting acetylcholine. Stimulation of the parasympathetic system lowers blood pressure and slows the heart rate. This action of acetylcholine is known as the muscarinic effect because the drug muscarine also produces this effect.

The muscarinic effects of acetylcholine can be blocked by atropine. Atropine will act as the effector organ, blocking the acetylcholine. If we give atropine and follow it with acetylcholine, the pen recorder shows that the acetylcholine no longer lowers the blood pressure, nor does it slow the heart rate; this is because atropine, here shown in green, occupies the receptor sites of the acetylcholine, so blocking its normal action.

In the demonstration of the muscarinic effect, the injection of 1 microgram of acetylcholine produced a fall in blood pressure. After atropine this same dosage has no effect but if it is increased to 250 micrograms of acetylcholine it produces not a fall but a dramatic rise in blood pressure. Why is this? Besides acting on parasympathetic nerve endings, acetylcholine is the transmitter at all ganglia so one would expect a large dose of acetylcholine to stimulate the whole of the autonomic nervous system. But atropine, as we have just seen, blocks the effect in the

parasympathetic system so that only the sympathetic system is stimulated, producing tachycardia, vasoconstriction and release of noradrenaline and adrenaline from the adrenal medulla. This action of acetylcholine on ganglia is known as the nicotinic action because nicotine produces a similar effect.

<**Intertitle**>

Drugs which interfere with transmission at ganglia

<**Unnamed narrator over animated diagram showing effects of ganglion-blocking agents, interspersed with further scenes from the earlier film showing surgical experiment on anaesthetised cat**>

The nicotinic action of acetylcholine can be blocked by ganglion-blocking agents such as hexamethonium. This classic effect of hexamethonium on ganglia can be demonstrated by pre- and post-ganglionic stimulation of the nerves supplying the nictitating membrane.

Post-ganglionic stimulation produces the normal contraction. But pre-ganglionic stimulation produces no effect. Hexamethonium is poorly absorbed from the intestine, which limits its clinical usefulness. More useful are mecamylamine and pempidine which are readily absorbed. But ganglion-blocking agents interfere with all autonomic functions, both sympathetic and parasympathetic, producing unwelcome side effects in the treatment of high blood pressure such as reduced gut motility, loss of accommodation, reduced glandular secretions and impotence. More precise control of blood pressure can be obtained by interfering with the transmission only in sympathetic nerves, for example, the action of the transmitter released at the nerve ending can be blocked.

You will recall that there are two types of receptors at the nerve ending – alpha- and beta-receptors. Stimulation of alpha-receptors produces vasoconstriction. Stimulation of beta-receptors produces increase of heart rate and vasodilatation. Adrenaline normally stimulates both alpha- and beta-receptors.

But if adrenaline is injected after the administration of an alpha-blocking drug such as phentolamine, then only the beta effects of adrenaline are seen producing a fall in blood pressure. This is known as the adrenaline reversal phenomenon. At this stage, the injection of a beta-blocking drug such as propranolol will antagonise the remaining beta actions of adrenaline thus following both phentolamine and propranolol; adrenaline has no effect.

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Both phentolamine and propranolol are post-junctional receptor blockers. Phentolamine is used in the control of peripheral vascular disease and propranolol is used to prevent sympathetic over-activity of the heart.

It's possible to interfere with sympathetic nerve transmission in yet another way by giving drugs such as alphamethyldopa and guanethidine which act directly on nerve fibres. To understand the action of these drugs it is necessary to understand the synthesis of noradrenaline and its liberation at the sympathetic nerve endings.

Noradrenaline is synthesised from tyrosine obtained from the blood stream. Tyrosine is converted to dihydroxyphenylalanine or dopa, then to dopamine and finally to noradrenaline. At present, the precise mode of action of alphamethyldopa is not known but there is good evidence that this drug is substituted for dopa in the synthetic pathway to produce the fourth transmitter, alphamethylnoradrenaline. This is released from the nerve endings along with a diminished amount of noradrenaline. But this combination is less effective in stimulating receptor sites.

Thus after giving alphamethyldopa, there is vasodilatation and a useful lowering of blood pressure. A similar result is produced by guanethidine which is shown here preventing the release of noradrenaline from the nerve ending. The reduced amount of noradrenaline now finds its way to the receptor sites and the result is a reduction of vasoconstriction and a lowering of blood pressure. Some time after the administration of guanethidine, the amount of noradrenaline within the vesicles is

also depleted, reducing still further the amount of noradrenaline present at the nerve ending. Like alphamethyldopa, drugs of the guanethidine type are useful in the treatment of hypertension.

<**Intertitle**>

Summary

<**Unnamed narrator over animated diagram summing up main points of the programme**>

To summarise, transmission in the autonomic nervous system can be blocked at a number of sites. Some drugs affect ganglionic transmission. Specific effects result from drugs which affect only the nerve endings of either the parasympathetic or the sympathetic nerve pathways. Atropine blocks the effects of acetylcholine released from parasympathetic post-ganglionic nerve endings. Phentolamine will antagonise the actions of adrenaline and noradrenaline at alpha-receptor sites, while propranolol will antagonise the actions of adrenaline and noradrenaline at beta sites. Drugs such as alphamethyldopa and guanethidine affect the synthesis and release of the transmitter substance noradrenaline.

<**End credits**>