**Adrenoceptor Agonists: Noradrenaline, Adrenaline and Isoprenaline.**



**Noradrenaline** produces a marked increase in both systolic and diastolic blood pressure and a fall in heart rate. **Adrenaline** (at this dose) produces an increase in systolic blood pressure and a slight fall in diastolic blood pressure. Heart rate is increased. **Isoprenaline** produces a fall in both systolic and diastolic blood pressure and an increase in heart rate.

The differing effects of these adrenoceptor agonists can be explained in terms of their relative potencies on α and β adrenoceptors combined with the additional effect of central baroreceptor reflexes.

Noradrenaline has a greater potency for α- compared to β-adrenoceptors. It activates α-adrenoceptors in blood vessels to a greater degree than β-adrenoceptors, leading to a constriction of arteries and an increase in peripheral resistance to blood flow, causing a marked increase in blood pressure. As noradrenaline nevertheless acts on β-adrenoceptors, it might be expected that it would have increased heart rate. However, the large increase in blood pressure triggers baroreceptors in the carotid sinus which act to reduce heart rate via acetylcholine released via the vagus nerve.

Adrenaline has a similar potency on both α- and β-adrenoceptors. Activation of α-adrenoceptors cause vasoconstriction while β adrenoceptors cause vasodilation. By activating both type of adrenoceptor in blood vessels equally, little change in peripheral resistance occurs. Adrenaline acts on β-adrenoceptors on the heart to increase heart rate and contractile force. More blood is pumped into the arterial system increasing blood pressure but the increase is not large enough to trigger the baroreceptor reflex causing a reduction in heart rate.

Isoprenaline is selective for β-adrenoceptors. It therefore acts on blood vessels to produce vasodilation which produces a large reduction in peripheral resistance, and on the heart to increase heart rate and contractile force. The net effect is to produce a marked reduction in blood pressure.

**Adrenoceptor Agonists: α-adrenoceptor action of adrenaline**



Adding a 1 µg/kg dose of adrenaline produces an increase in heart rate and an increase in blood pressure. Systolic B.P. is increased more than diastolic B.P. (i.e. there is an increase in pulse pressure) This can be compared with a 5 µg/kg dose of, the α-adrenoceptor selective agonist, phenylephrine which also produces an increase in systolic and diastolic B.P. but no increase in pulse pressure. A baroreceptor reflex fall in heart can also be observed.

Adding a large dose (10 mg/kg) of the β-adrenoceptor antagonist propanalol produces a reduction in heart rate and blood pressure (because β-adrenoceptors on the heart are blocked).

Addition of a second 1 µg/kg dose of adrenaline now produces an effect similar to phenylephrine. Blood systolic and diastolic B.P. is increased by similar amounts (no increase in pulse pressure) and heart rate falls.

**Nicotinic ganglion blockers: hexamethonium.**



The above chart traces show cat blood pressure and heart. Addition of a 1 µg/kg dose of acetylcholine produces a fall in heart rate and blood pressure. Stimulation of the vagus nerve is then initiated which produces a sharp fall in heart rate and blood pressure with each stimulus.

Addition of a 10 mg/kg dose of hexamethonium causes a reduction in heart rate (HR) and a fall in arterial blood pressure (ABP). Hexamethonium also inhibits the fall in heart rate due to vagal stimulation.

However, the fall in heart rate and blood pressure produced by a second 1 µg/kg dose of acetylcholine is not inhibited.

The inhibition of the heart rate depressions produced by vagal stimulation indicates that hexamethonium blocks neurotransmission in the vagus nerve. It could, potentially, act either at the nicotinic ganglia or at the muscarinic cholinoceptors on the heart, or both. However, hexamethonium does not inhibit the fall in heart rate produced by acetylcholine (which directly acts on the muscarinic cholinceptors) indicating that it acts on nicotinic cholinoceptors on the ganglia.

Block of the nicotinic cholinoceptors in sympathetic ganglia also explains the observed reduction in blood pressure and heart rate.

**Calcium channel blockers: Verapamil**



**Acetylcholine: Effect on heart rate and blood pressure**



Addition of a 1 µg/kg dose of acetylcholine produces a large fall in heart rate and blood pressure.

Stimulation of the vagus nerve produces a sharp fall in heart rate and blood pressure with each stimulus.

Addition of 1 mg/kg of atropine produces an increase in resting blood pressure and heart rate and also inhibits the depressions in heart rate produced by vagal stimulation. The effects of atropine are prolonged.

Atropine also inhibits the effects of acetylcholine, since addition of a second 1 µg/kg dose of acetylcholine now produces only a very small fall in heart rate.

These results suggest that atropine acts as an antagonist on the muscarinic cholinoceptors on the heart forming part of the vagal nerve pathway which acts to slow the heart.

**Muscle relaxants: Tubocurarine**



The above chart shows blood pressure (ABP), heart rate (HR), nerve evoked, skeletal muscle (SKM) and nictitating membrane (NIC) contractions. The vagus nerve is also being stimulated to produce depressions in the heart rate.

Addition of a 500 µg/kg dose of tubocurarine (TC) produces a near complete inhibition of nerve evoked, skeletal muscle (SKM) contractions. The duration of action from drug addition to 50% recovery is 1000 seconds.

Nerve-evoked contractions of the nictitating membrane are also inhibited, as are the depressions in heart rate due to vagal stimulation. Blood pressure is also depressed by the addition of TC.

TC competitively antagonizes acetylcholine (Ach) at the nicotinic cholinceptors at the skeletal neuromuscular junction, inhibiting nerve-stimulated muscle contractions, leading to its clinical use as a muscle relaxant during surgical operations. However, TC also acts on a number of other receptors leading to effects on blood pressure, heart rate and the cat nictitating membrane.

TC also blocks nerve-stimulated contractions of the nictitating membrane, indicating that it blocks nicotinic cholinceptors on sympathetic ganglia. It also blocks the heart rate depressions evoked by vagal nerve stimulations, by blocking nicotinic cholinoceptors on parasympathetic ganglia. (Note that it might also inhibit vagally stimulated heart rate depressions by blocking muscarinic cholinoceptors on the heart but it can be shown that it does not, by adding a 1 µg/kg dose of Ach, before and after the addition of TC and observing that the depression in heart rate is not inhibited.

The depression in blood pressure is partially reverse by addition of a 10 mg/kg dose of the histamine H1 receptor antagonist mepyramine, indicating that TC either acts on H1 receptors or stimulates the release of histamine. The remaining reduction in blood pressure is likely to be due to TC’s nicotinic ganglion blocking effect.

**Muscle relaxants: Gallamine**



The above chart shows blood pressure (ABP), heart rate (HR), nerve evoked, skeletal muscle (SKM) and nictitating membrane (NIC) contractions. The vagus nerve is also being stimulated to produce depressions in the heart rate.

Addition of a 2 mg/kg dose of gallamine (GAL) produces a near complete inhibition of nerve evoked, skeletal muscle (SKM) contractions. The duration of action from drug addition to 50% recovery is 480 seconds. Nerve-evoked contractions of the nictitating membrane are also inhibited, as are the depressions in heart rate due to vagal stimulation. Resting heart rate is elevated and blood pressure , slightly elevated.

GAL competitively antagonizes acetylcholine (Ach) at the nicotinic cholinceptors at the skeletal neuromuscular junction, inhibiting nerve-stimulated muscle contractions. It also acts on a number of other receptors leading to effects on blood pressure, heart rate and the cat nictitating membrane.

GAL blocks the heart rate depressions evoked by vagal nerve stimulation, by blocking muscarinic cholinoceptors on the heart. This can be demonstrated by adding a 1 µg/kg dose of Ach, before and after the addition of GAL and observing that the depression in heart rate produced by Ach is inhibited.

**Muscle Relaxants: Atracurium**



The above chart shows blood pressure (ABP), heart rate (HR), nerve evoked, skeletal muscle (SKM) and nictitating membrane (NIC) contractions. The vagus nerve is also being stimulated to produce depressions in the heart rate.

Addition of a 500 µg/kg dose of atracurium (ATC) produces a near complete inhibition of nerve evoked, skeletal muscle (SKM) contractions. The duration of action from drug addition to 50% recovery is 180 seconds.

Nerve-evoked contractions of the nictitating membrane and vagal-stimulated depressions in heart rate are NOT inhibited. Blood pressure is unchanged.

ATC competitively antagonizes acetylcholine (Ach) at the nicotinic cholinceptors at the skeletal neuromuscular junction, inhibiting nerve-stimulated muscle contractions. At the dose used, ATC does not appear to act upon either muscarinic cholinoceptors or ganglionic nicotinic cholinoceptors.

**Muscle Relaxants: Vecuronium**



The above chart shows blood pressure (ABP), heart rate (HR), nerve evoked, skeletal muscle (SKM) and nictitating membrane (NIC) contractions. The vagus nerve is also being stimulated to produce depressions in the heart rate.

Addition of a 100 µg/kg dose of vecuronium (VEC) produces a near complete inhibition of nerve evoked, skeletal muscle (SKM) contractions. The duration of action from drug addition to 50% recovery is 212 seconds.

Nerve-evoked contractions of the nictitating membrane and vagal-stimulated depressions in heart rate are NOT inhibited. Blood pressure is unchanged.

VEC competitively antagonizes acetylcholine (Ach) at the nicotinic cholinceptors at the skeletal neuromuscular junction, inhibiting nerve-stimulated muscle contractions. At the dose used, ATC does not appear to act upon either muscarinic cholinoceptors or ganglionic nicotinic cholinoceptors.

**Anticholinesterases: Neostigmine**



The above chart shows blood pressure (ABP), heart rate (HR), nerve evoked, skeletal muscle (SKM) and nictitating membrane (NIC) contractions. The vagus nerve is also being stimulated to produce depressions in the heart rate.

Addition of a 1 mg/kg dose of tubocurarine (TC) produces a near complete inhibition of nerve evoked, skeletal muscle (SKM) contractions. Nerve-evoked contractions of the nictitating membrane are also inhibited, as are the depressions in heart rate due to vagal stimulation. Blood pressure is also depressed

Subsequently, addition of a 100 µg/kg dose of neostigmine produces a rapid reversal of the skeletal muscle contractions but no change in the block of nictitating membrane contractions, vagal-stimulated heart rate reductions or depression in blood pressure.

Neostigmine is an anticholinesterase which prevents the breakdown of acetylcholine (Ach) in the synaptic cleft at neuromuscular junctions by cholinesterases. It prolongs the lifetime of Ach in the synaptic cleft, increasing the amount available for binding with post-synaptic cholinoceptors, competing with and reversing the action of antagonists.

**Depolarising Muscle Relaxants: Suxamethonium**



Addition of a 200 µg/kg dose of suxamethonium produces a rapid block of nerve-stimulated skeletal muscle contraction. Unlike, non-depolarising muscle relaxants (e.g. tubucurarine, vecuronium) a 200 µg/kg dose of neostigmine does not reverse the block. Addition of a 2 mg/kg dose of atropine reverses the depression heart rate and blood pressure, caused by neostigmine.

Depolarising muscle relaxants are cholinergic agonists which act by activating cholinergic receptors causing prolonged muscle depolarization and receptor desensitization, leading to muscle paralysis. The reduction in heart rate and blood pressure can be reversed by adding an antagonist at muscarinic cholinoceptors (atropine). Adding a cholinesterase reversal agent, like neostigmine, does not reverse the block because providing additional acetylcholine only enhances desensitization.

Suxamethonium is used clinically as a muscle relaxant because it has a more rapid time course than non-depolarizing agents, as the chart below, comparing suxamethonium and vecuronium, shows.



Opioids: Morphine & Naloxone



**Purinergic Receptors: Adenosine**

