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## DRUGS AFFECTING THE AUTONOMIC NERVOUS SYSTEM

SUNALI MEHTA

The ans is part of the peripheral nervous system and regulates the involuntary activities such as heart rate, bp, respiration and digestive tract function.

The ans consists of two parts:

Sympathetic nervous system (sns)

Parasympathetic nervous system (psns)

1. sns: this is involved in the flight / fright/ fight response to stress or arousal. It stimulates the nervous system hence inc in heart rate and bp, dilation of the bronchioles hence inc the blood flow to the lungs hence an inc in supply of oxygen. The muscles are well supplied with blood vessels and there is a dec of blood supply to the digestive system.

2. psns: stimulation here is in the opposite way as compared to the sns. It is a state of rest and repose. Dec in heart rate and bp, less oxygen supplied to the lungs and the bronchioles are constricted. There is an inc blood flow to the digestive system with concurrent stimulation of peristalsis and inc secretion of digestive secretion such as saliva.

Drugs that stimulate the sns are called **sympathomimetics** i.e. they mimic the action of the neurotransmitters that are involved in the sns and produce an sns response.

Drugs that suppress the activity of the sns are called **sympatholytics** they block the sns response.

Mode of action of the ans drugs:

Neurophysiology:

1. a nerve cell (neuron) receives an input at the specialized end called the dendrites.
2. The message from the dendrites is passed down to the axon and from there to the terminal branches.
3. this stimulates the release of specialized chemicals called neurotransmitters which are released in a gap called the synaptic cleft or synapse
4. these then attach to the either the dendrites of another neuron or to a tissue such as a muscle or gland which are termed as effectors.

The binding of the nt at a specialized site on effector is termed as a receptor.

Receptors are selective and specific. There are two types of receptors that are associated with the ans i.e. adrenergic receptor and cholinergic receptor.

Adrenergic receptor:

The nt noradrenaline binds only to the adrenergic receptor. These receptors are found in the sns and the drugs that mimic the action of noradrenalin and bind to these receptors are called adrenergic drugs / adrenergic agonists. These drugs will result in increased heart rate, inc bp, inc brochodilation and dec digestive action. Conversely adrenergic antagonist are the ones that will bind to the receptor and will not allow the nt to bind as a result of which there will be dec heart rate, dec bp and dec brochodilation and an increased action of the digestive system.

Cholinergic receptors:

Nt acetylcholine binds to the cholinergic receptors. These are found in the psns and hence drugs that bind the cholinergic receptor and mimic the action of acetylcholine are called cholinergic agonists. That is there will be a dec in heart rate, dec in bp, dec in bronchodilation and inc activity of the digestive tract. Conversely cholinergic antagonist will lead to an inc in heart rate, inc bp, inc bronchodilation and dec in the GI tract activity.

Therefore:

Adrenergic agonist = cholinergic antagonists

Adrenergic antagonist = cholinergic agonists.

Removal of the nt from the synaptic cleft: is imp to avoid restimulation of the neurons by the nt.

There are two main mechanisms used for this:

1. Re – uptake of the released nt e.g. noradrenalin is taken up by the amine re – uptake pump.
2. Enzymatic breakdown of the nt: is achieved with the help of an enzyme e.g. acetylcholine esterase is an enzyme used in the breakdown of acetyl choline.

If the drug blocks the enzyme in the breakdown of the nt. The result of this is prolonged stimulation and hence further stimulation of the sns or the psns.

Key aspects of nt and how this relates to the drug action:

1. nt transmits a response between two neurons or between an neuron or a neuron to an effector. Drugs may mimic the action of the nt or affect the nt concentration
2. nt bind to specific receptors. The drug may bind to the receptor and either mimic the action of nt or block the receptor.
3. nt vary between the different nerve tracts. The key ones in the ans are noradrenalin and acetylcholine and depending on the shape of the drug it might bind to these receptors and this makes its action more specific.

4. since each nt is removed after release by a specific process the drug can alter this process.

#### Adrenergic Pharmacology:

Adrenergic agonists: inc heart rate, inc bp, bronchodilation, dec GI tract activity. They also stimulate the release of hormones like adrenalin and noradrenaline from the adrenal medulla.

Adrenergic antagonists: dec heart rate, dec bp, reduced bronchodilation and inc GI tract activity. They block the site of the receptor and hence reduce the sns reponse.

#### Drugs to know:

Adrenalin

Noradrenaline

Salbutamol

Ephedrine

Pseudoephedrine

Dopamine

Methylpoda

Clonidine

Adrenergic pharmacology refers to the drugs tht mediate their effect via the adrenergic receptors. These are found in the sns and also in the brain and cns.

There are different subsets of adrenergic receptors which allows the body to modify the stress response depending on the circumstances. This property of the

adrenergic receptors allows the drugs to be more selective in their mode of action.

The receptors are as follows:

Alpha1 receptors: are located in the blood vessels and effect both bp and tissue perfusion

Alpha2 receptors: located presynaptically

Beta1 receptors: found in heart muscle, adipose cells, sphincters and smooth muscle of the GI tract and renal arterioles.

Beta2 receptors: found in the smooth muscle of the bronchioles, skeletal muscle and blood vessels supplying the heart, brain, liver, uterus and mast cells.

For treatment of asthma this selective property of the adrenergic receptor is useful else it would lead to cardiovascular trouble if we concentrated on bronchodilation. For asthma the best would be to have a selective action on the beta2 receptor compared to having an action on the others. This will avoid harmful effects such as palpitations. E.g. of drugs used for asthma are Salbutamol and terbutaline.

Lot of the adrenergic drugs are not selective in that they can bind to both the type of receptors the alpha and the beta receptors e.g. adrenaline, ephedrine and pseudoephedrine.

Dopamine is a nt found in the CNS but is also found in the SNS and react with the beta 1 at low doses and alpha 1 at high doses. It structurally resembles the adrenaline and noradrenaline. Specific peripheral dopamine receptors are found in the blood vessels of the brain, heart, kidney and mesentery and is involved in vasodilation. It is used in restoring circulation and tissue perfusion in a cardiac shock.

### Adrenergic side effects:

These occur as a result of drug action on the adrenergic receptors at sites other than where the desired effect is wanted. E.g. drugs used to treat asthma can cause palpitations.

Some of the adrenergic agonist can cause the bbb and react with the adrenergic receptors in the brain and this can result in a fight / flight response leading to restlessness, insomnia, hyperactivity and anxiety.

### Presynaptic and postsynaptic receptors:

If the receptor are found after having crossed the synapse they are called postsynaptic receptors whereas if the receptor is present on the presynaptic terminal that is the place from where the nt is released is called a presynaptic receptor.

Alpha1, beta1 and beta2 are found postsynaptically.

Alpha 2 receptors are found presynaptically and these are found on all adrenergic nerve terminals. Binding of the nt noradrenaline to the alpha 2 receptor leads to inhibition of further release of nt from the same axon terminal. This is a feed – back mechanism. This is also the mode of action of the antihypertensive drug clonidine which is a alpha 2 agonist.

Cholinergic Pharmacology is the drugs that act either as cholinergic agonists or antagonists and either mimic or inhibit the nt acetylcholine.

Drugs to know:

Acetylcholine

Nicotine

Atropine

Cogentin ( Benztropine)

Different places in the body where the cholinergic receptors are found:

1. psns
2. the sympathetic fibers to the sweat gland and blood vessels of skeletal muscles are cholinergic.
3. all preganglionic synapses of the ans are cholinergic
4. these are also found in the pns and controls the voluntary skeletal muscle action.
5. they are also found in the cns.

Hence cholinergic drugs can have an effect on the ans, cns and the voluntary neuromuscular movements.

Drugs that mimic acetylcholine are said to be cholinergic and antagonists are said to be anticholinergic.

Cholinergic effect:

Acetylcholine is released in a cholinergic synapse and it diffuses across and binds to postsynaptic cholinergic receptors and this will trigger an appropriate effector response.

Autonomic ganglion: continuation of impulse to post ganglionic fibers in both sympathetic and parasympathetic fibers.

Psns: rest and repose response

Sns: only the cholinergic fibers – vasodilation in the skeletal muscle and sweating.

Neuromuscular junction – somatic nervous system – skeletal muscle contraction and inc muscle tone

CNS – varies – alertness, stimulation, relaxation and well being.

Acetylcholine is broken down by the enzyme acetylcholine esterase.

The drugs involve:

Cholinergic agonist

Cholinergic antagonists

Acetylcholine esterase inhibitors – these are the drugs that block the action of the Acetylcholine esterase and as a result of which there is more concentration of acetylcholine and there is more of the cholinergic effect seen.

Cholinergic receptors:

Two types:

Nicotinic receptors : respond to stimulation by nicotine

Muscarinic receptors: these respond to muscarine. These are further divided into M1, M2 and M3.

Muscarinic receptors are found in the psns effectors and the cholinergic sympathetic effectors.

Nicotinic receptors are found in the neuromuscular junction of the somatic ns controlling the voluntary muscle contraction. Also found in the preganglionic neuron of the ans.

Nicotinic receptors: in the ans – preganglionic effect inc both the sns response such as bp and psns such as GI tract activity. It also leads to an inc in the amount of adrenaline and noradrenaline hence inc heart rate.  
In the cns there is a feeling of wellbeing and relaxation.

Muscarinic receptors:

Ans – psns

M3 effect: inc Gi activity, inc insulin secretion, bronchioconstriction and inc mucus secretion, pupils contract and promotion of defecation

M2 effect: dec heart rate and force of contractions

M1 effect: inc GI tract activity and secretion.

Sns

M3 effect – vasodilation in skeletal muscle sweating

Cns – m1 effect – improves memory enhanced cognition.

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Anticholinergic side effects:

Disipal and cogentin are anticholinergic drugs used to control the tremors in parkinsons. It is due to the action on the cns.

Adverse effects are dose related and include dry mouth, blurred vision, problems passing urine and constipation, these are all anticholinergic side effects and are muscarinic in origin.