Lecture 3:-Cholinergic drugs

Direct-Acting Cholinergic Agonists

Cholinergic agonists (also known as parasympathomimetics) mimic the effects of acetylcholine by binding directly to cholinoceptors. These agents may be broadly classified into two groups: choline esters, which include acetylcholine and synthetic esters of choline, such as *carbachol* and *bethanechol*. Naturally occurring alkaloids, such as *pilocarpine* constitue the second group . All of the direct-acting cholinergic drugs have longer durations of action than acetylcholine. Some of the more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents.

Acetylcholine

Acetylcholine is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it is therapeutically of no importance because of its multiplicity of actions and its rapid inactivation by the cholinesterases. Acetylcholine has both muscarinic and nicotinic activity.

The effects of muscarinic agonists:-

Cardiovascular effects. These include cardiac slowing and a decrease in cardiac output due both to the reduced heart rate and to a decreased force of contraction of the atria (the ventricles have only a sparse parasympathetic innervation and a low sensitivity to muscarinic agonists). Generalised vasodilatation also occurs (mediated by nitric oxide, NO) and, combined with the reduced cardiac output, produces a sharp fall in arterial pressure.

Smooth muscle. Smooth muscle generally *contracts* in direct response to muscarinic agonists, in contrast to the indirect effect via NO on vascular smooth

muscle. Peristaltic activity of the gastrointestinal tract is increased, which can cause colicky pain, and the bladder and bronchial smooth muscle also contract.

Sweating, lacrimation, salivation and bronchial secretion.

These result from stimulation of exocrine glands. The combined effect of bronchial secretion and constriction can interfere with breathing.

Effects on the eye. These effects are clinically important. The parasympathetic nerves to the eye supply the constrictor pupillae muscle, which runs circumferentially in the iris, and the ciliary muscle, which adjusts the curvature of the lens. Contraction of the ciliary muscle in response to activation of mAChRs pulls the ciliary body forward and inward, thus relaxing the tension on the suspensory ligament of the lens, allowing the lens to bulge more and reducing its focal length. This parasympathetic reflex is thus necessary to accommodate the eye for near vision. The constrictor pupillae is important not only for adjusting the pupil in response to changes in light intensity, but also in regulating the intraocular pressure. Aqueous humour is secreted slowly and continuously by the cells of the epithelium covering the ciliary body, and it drains into the *canal of Schlemm* which runs around the eye close to the outer margin of the iris. The intraocular pressure is normally 10–15 mmHg above atmospheric, which keeps the eye slightly distended. Abnormally raised intraocular pressure (which leads to the pathological condition of *glaucoma*) damages the eye and is one of the commonest preventable causes of blindness.In acute glaucoma, drainage of aqueous humour becomes impeded when the pupil is dilated, because folding of the iris tissue occludes the drainage angle, causing the intraocular pressure to rise. Activation of the constrictor pupillae muscle by muscarinic agonists in these circumstances lowers the intraocular pressure, although in a normal individual it has little effect. The increased tension in the ciliary muscle produced by these drugs may

also play a part in improving drainage by realigning the connective tissue trabeculae through which the canal of

Schlemm passes