Receptors in intestinal muscles

The experiment was conducted in order to gain better understanding of the function of the receptors in the guinea pig ileum. For this reason, various agonists and antagonists were used and the muscle reaction was monitored. The results of our experiment are summarized in the following table.

As we can see acetylcholine and hexamethonium both have a triethylamine at one end and a straight chain of carbons. The basic difference is that hexamethonium has two tertiary amines, one on each end of the chain, whereas acetylcholine has the group -O-C(= O)-CH3 on one end. According to the SAR theory (Structure Activity Relationship) similar molecules in structure tend to have similar biological activity. As we know, both acetylcholine and hexamethonium bind to the nicotinic receptor, the first one to trigger a response and the second one to prevent acetylcholine from binding. Hexamethonium, having two active groups, can probably bind more easily to the receptor, effectively blocking the acetylcholine action.

b)

Histamine and mepyramine have less similarities in structure. Both of them have three nitrogen and an aromatic ring. Histamine has the two nitrogen inside the aromatic ring whereas mepyramine has only one nitrogen bound in the ring. Both compounds bind to the H1-Histamine receptor, to trigger different reactions. The difference in structure can be explained by the different action of the two compounds. Histamine causes contraction of the muscle and mepyramine causes its relaxation.

The drugs tested were classified as agonists and antagonists.

Acetylcholine: Acts as neurotransmitter. It binds on the muscarinic and nicotinic receptors and causes muscle contraction.

Histamine: Is also a neurotransmitter. It binds on the H1-Histamine receptor and causes smooth muscle contraction.

Nicotine: It acts on the nicotinic cholinergic receptors and mimics the neural transmission. It stimulates the muscle, then blocks stimulation.

Isoprenaline: Although isoprenaline was apparently an antagonist, it is actually a selective agonist for the Î²- adrenergic receptors that causes muscle relaxation. It is a sympathomimetic drug that mimics the effect of stimulating the postganglionic adrenergic sympathetic nerves.

Hexamethonium: It is a nicotinic antagonist and a ganglionic blocker. It binds to the nicotinic cholinergic receptors and blocks the actions of acetylcholine or cholinergic agonists. It has no effects on muscarinic (mAch) receptors.

Mepyramine: It is a histamine H1 antagonist and targets the H1- Receptor. Although it was believed to be an antagonist merely to block the actions of endogenous histamine without activating the receptors, it has recently been classified as an inverse agonist decreasing the spontaneous activity of gp-H1r. It also inhibits histamine induced inositol phosphate (InsP) production and intracellular calcium mobilization. It causes a marked decrease in the maximal response to histamine at high concentrations.

Atropine: It is a competitive antagonist for the muscarinic cholinergic receptor (mAch). It binds to the receptor without activating it, thus blocking the actions of endogenous acetylcholine or exogenous agonists.

a) The drug in this experiment were acting on three receptors. H1-Histamine receptors, muscarinic (mAch) receptors and nicotinic (nAch) receptors. Each agonist was acting on a different receptor and that is apparent from our results. When using an antagonist that blocked a specific receptor it only inhibited the action of the drug acting on that particular receptor, and had no effect on the rest of the drugs.

b) The receptors were obviously located on the surface of the muscle, so that the access of the drugs would be possible.

The first apparent antagonist which turned out to be an agonist was isoprenaline. It acts on the Î²- adrenergic receptors causing muscle relaxation and antagonized all the three agonists who acted on different receptors. This type of antagonism is called a physiological antagonist and describes the interaction of two drugs who cause opposing actions in the body and tend to cancel each other. In this case, the isoprenaline acts on the Î²- adrenergic receptors and causes relaxation of the muscle, whereas the agonist act on the histaminic, nicotinic and muscarinic receptors and cause contraction of the muscle.

The second apparent antagonist was mepyramine, which acts on the histamine receptor and blocks the action of histamine. It has recently been classified as an inverse agonist, causing muscle relaxation. This type of agonists show selectivity to the resting state of the receptor.

Atropine acts on the muscarinic receptors and blocks their action. Thus it prevents acetylcholine from binding to the receptor and stimulating it. Nicotine though activates the nicotinic receptor that apparently has nothing

to do with atropine. The reversal of nicotine action indicates the presence of inhibitory postganglionic (terminal) neurones, which respond to stimulation of their ganglion-cells by inducing relaxation of the gut. It is also suggested by other experiments [Phillis & York, 1968] that an intermediate type of receptor is involved. Assuming specificity of the antagonist these studies are explained by a non-classical cholinergic receptor with mixed pharmacological properties. Such receptors are the newest members of the nicotinic acetylcholine receptor (nAChR) family, encoded by the Î±9/Î±10 subunits, that possess a combined nicotinic-muscarinic sensitivity.

Barium Chloride is a water soluble salt. Once in contact with the muscle it induces release of intracellular stores of calcium, and causes the contraction of the muscle. If barium chloride comes in contact with sodium sulphate it loses its potency. That is explained by the chemical reaction between the two compounds.

Molecular equation:

BaCl2(aq) + Na2SO4(aq)–> BaSO4(s) + 2NaCl(aq)

ionic equation:

Ba+2(aq) + 2Cl-(aq) + 2Na+(aq) + SO4-2(aq) –> BaSO4(s) + 2Na+(aq)+2Cl-(aq)

These reactions show that once in contact with sodium sulphate, the barium chloride dissolves into BaSO4 which is an insoluble substance and NaCl. Thus, it can no longer act on the muscle. That type of antagonism is called Chemical Antagonism and it refers to the situation when two substances

combine in solution; as a result, the effect of the active drug (in this case the barium chloride) is lost.

The drugs were tested on guinea pig ileum which is a smooth muscle.