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COMMUNICATIONS

Effects of some drugs on the circular muscle of the isolated lower oesophagus

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It is known that between the oesophagus and the stomach a differentiated region exists in the lower oesophagus and that the control systems to this junction differ in some respects from those for the muscle of the oesophageal body and proximal stomach (Christensen, 1975; Lipshutz & Cohen, 1971). The pharmacology of the circular muscle of the lower oesophagus is, however, obscure. We have tested the effects of some drugs on a preparation of this tissue.

After male Wister rats (400 to 450 g body wt) or male guinea-pigs (350 to 500 g body wt) had been killed by a blow on the neck, segments 0·2 cm in length were taken from the lowest and middle parts of the oesophagus. The segments were opened by a longitudinal incision and used as a circular muscle preparation of the lower oesophagus or oesophageal body. Silk threads were tied to both ends of the strips which were suspended in a 10 ml organ bath filled with Locke Ringer solution gassed with 5% CO_2 in oxygen at 37°. One end of each strip was fixed and the other end was attached to an isometric forced-displacement transducer connected to a recorder. The initial tension was 1·0 g. The Locke Ringer solution used had the following composition (g litre^{-1}): 9·0 NaCl, 0·4 KCl, 0·2 $CaCl_2$, 0·2 $MgCl_2$, 0·5 $NaHCO_3$ and 0·5 glucose. All results are presented as the means of at least 8 experiments.

Rat lower oesophagus. The circular muscle of the lower oesophagus showed spontaneous activity. Acetylcholine chloride, caerulein, tetragastrin and 5-hydroxytryptamine creatinine sulphate (5-HT) contracted the circular muscle dose-dependently (Fig. 1). The dose response curves for caerulein, tetragastrin and 5-HT were less steep than that for acetylcholine and the maximum responses (mean ± standard deviation) relative to that to acetylcholine were 25 ± 9% for caerulein, 13 ± 6% for tetragastrin and 38 ± 14% for 5-HT. The response to acetylcholine was abolished by atropine sulphate (10^{-7} g ml^{-1}), indicating that the site of action of acetylcholine is a muscarinic receptor. The responses to caerulein (10^{-7} g ml^{-1}), tetragastrin (5×10^{-6} g ml^{-1}) and 5-HT (10^{-5} to 10^{-4} g ml^{-1}) were little affected by atropine (3×10^{-7} g ml^{-1}) or tetrodotoxin (10^{-5} g ml^{-1}). Histamine hydrochloride (up to 3×10^{-5} g ml^{-1}) did not contract the preparation. An α-adrenoceptor stimulant, phenylephrine hydrochloride (10^{-7} to 10^{-6} g ml^{-1}) relaxed the lower oesophageal preparation and the relaxation by phenylephrine was greatly reduced by an α-adrenoceptor blocker, tolazoline hydrochloride (10^{-5} g ml^{-1}) or phenoxybenzamine hydrochloride (10^{-7} g ml^{-1}) but not by a β-adrenoceptor blocker, propranolol hydrochloride (10^{-7} g ml^{-1}). The relaxation by a β-adrenoceptor stimulant, (—)-isoprenaline hydrochloride (3×10^{-8} to 10^{-6} g ml^{-1}) was abolished by propranolol (10^{-6} g ml^{-1}). Phenylephrine, however, did not contract the lower oesophageal preparation even in the presence of propranolol (10^{-6} g ml^{-1}).

Rat oesophageal body. The circular muscle of the rat oesophageal body was also spontaneously active. To test whether or not the circular muscle of the lower oesophagus had characteristics different from the circular muscle of the oesophageal body, the actions of some drugs were also tested on the oesophageal body. Acetylcholine caused a dose-related rise in the basal tension of the preparation with a threshold dose of 3×10^{-5} g ml^{-1}. Tetragastrin (up to 10^{-5} g ml) and caerulein (up to 10^{-6} g ml^{-1}) were without any effect on basal tension.

Guinea-pig lower oesophagus. This preparation was used to study a response on histamine receptors, because the

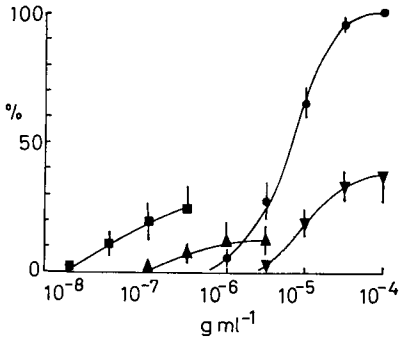

FIG. 1. Dose response curves for ● acetylcholine, ■ caerulein, ▲ tetragastrin and ▼ 5-HT on the circular muscle of the lower oesophagus isolated from the rat. The results are presented as means ± standard deviation of at least 8 experiments. Ordinate—Increase tension (%).

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preparations from rats were much less sensitive to histamine. Histamine (10^{-6} to 3×10^{-5} g ml^{-1}) and acetylcholine (10^{-6} to 3×10^{-4} g ml^{-1}) contracted the preparation. The maximum response (mean ± standard deviation) to histamine was 38 ± 7% of that to acetylcholine. The contractile response to histamine was converted to relaxation in the presence of the histamine H_1-receptor antagonist, chlorpheniramine maleate (3×10^{-7} g ml^{-1}). The relaxation by histamine in the presence of chlorpheniramine was blocked by the histamine H_2-receptor antagonist drug, cimetidine (10^{-4} g ml^{-1}). The maximum contractile response to histamine was potentiated by cimetidine alone (10^{-4} g ml^{-1}). The response to histamine was abolished by application of both chlorpheniramine and cimetidine. These are demonstrated in Fig. 2. Since metiamide, a H_2-receptor antagonist, potentiated the excitatory response to gastrin I in the opossum (Cohen & Snape, 1975), we tested the effect of cimetidine on the response to tetragastrin on the circular muscle of guinea-pig lower oesophagus. Tetragastrin (5×10^{-7} to 5×10^{-6} g ml^{-1}) slowly contracted the preparation. The maximum response (mean ± standard deviation) to it was 11 ± 4% of that to acetylcholine. The effect of cimetidine on the contractile response to tetragastrin was not clear because of the slow and small response.

The effective concentrations of the drugs used on the lower oesophageal preparations of the rat were lower than those on the oesophageal body preparations. This fact suggests the view that the circular smooth muscle of the lower oesophagus has physiological and pharmacological characteristics different from the muscle from the oesophageal body (Christensen, 1975: Lipshutz & Cohen, 1971). Administration of gastrin is well known to contract the circular muscle of the lower oesophagus in man and animals (Castell & Harris, 1970; Lipshutz & Cohen, 1971; Cohen, Fisher & Lipshutz, 1972). Though tetragastrin contracted the circular muscle of the rat lower oesophagus, the maximum response to it was much smaller than that to acetylcholine in the present study. Gastrin is also reported to contract the circular muscle of the isolated opossum lower oesophagus by stimulating cholinergic neurons (Lipshutz & Cohen, 1971; Cohen & others, 1972). In contrast to these results are the findings of Ratten, Colin & Gayal (1976) who reported that the contraction of the circular muscle of the lower oesophagus of the anaesthetized opossum induced by gastrin I or pentagastrin was not influenced by tetrodotoxin or atropine. We have demonstrated on the rat that the action of tetragastrin and caerulein may be direct action on the smooth muscle and that the excitatory effect of 5-HT on the rat lower oesophagus like its effect on the rat fundus may be exerted directly on the smooth muscle.

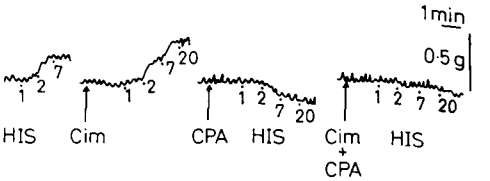

FIG. 2. Effects of chlorpheniramine and cimetidine on the response of the isolated circular muscle of the guinea-pig lower oesophagus to histamine (HIS) ($\times 10^{-6}$ g ml^{-1}). Chlorpheniramine (CPA, 3×10^{-7} g ml^{-1}). Cimetidine (Cim, 10^{-4} g ml^{-1}).

The existence of the excitatory H_1-receptors and inhibitory H_2-receptors of histamine has been clearly demonstrated in the present study. This supports the finding of Cohen & Snape (1975) that metiamide augmented the maximum response of the circular muscle of the lower oesophagus of the opossum to histamine. Cohen & Snape (1975) also reported that metiamide potentiated the excitatory response to gastrin in the opossum, but this observation could not be reproduced by Ratten & others (1976). We would withhold our conclusion concerning with the effect of the H_2-receptor antagonist on the excitatory response to tetragastrin, as we could not obtain clear-cut results on the isolated guinea-pig lower oesophagus in the present study.

The present results also suggest that there are α- and β-inhibitory adrenoceptors in the circular muscle of the rat lower oesophagus as observed in the stomach and intestine. These agree with results in the rabbit (Böhmig & Brücke, 1962).

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