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Pentazocine increases rhythmic action and potential activity in the circular muscle of rabbit isolated intestine

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Smooth muscle cells exhibit changes in electrical properties after denervation (Westfall 1981). When neuronal activity is experimentally inhibited, the excitability of intestinal circular layer is greatly increased. In fact each cycle of the myogenic pacesetting system (electrical slow waves) triggers a regular discharge of action potentials (Wood 1981). Extracellular and intracellular studies demonstrate that circular muscle becomes rhythmically active when exposed to morphine (Konturek et al 1980; Wood 1980). Excitatory effects of morphine have been interpreted in terms of blockade of spontaneously active inhibitory neurons of intramural plexuses. Since low doses of naloxone counteracted the action potential activity induced by morphine, specific μ opiate receptors seem to be involved (Wood 1980; Konturek et al 1980; Karras & North 1981). The benzomorphan derivative pentazocine exerts agonistic analgesic activity and it was suggested that benzomorphans act at κ receptors (Snyder & Goodman 1980). The myenteric plexus contains neurons which are sensitive to narcotic analgesics (for reference see Karras & North 1981) and the existence of multiple opiate receptors in intestinal preparations has been proposed (Wüster et al 1981). The aim of this communication was to investigate the effect of pentazocine on mechanical and electrical activity of isolated small intestine.

Method

Rabbits of either sex (900–1800 g) were used. Segments (5–6 cm long) of terminal ileum were removed and mounted horizontally in a 100 ml organ bath containing Tyrode solution bubbled with 5% CO_2 in O_2, at 36 °C. The oral end of the segment was tied over a glass tube connected to a Mariotte bottle containing Tyrode solution and the lumen was perfused continuously at a flow rat of 2 ml min^{-1}. The aboral end was connected to an isotonic transducer under a load of 1–2 g to measure muscle contractions. The intraluminal pressure was measured by means of a pressure transducer. Extracellular electrical activity was measured with glass electrodes, tip diameter 0·1–0·2 mm, filled with Tyrode solution and placed on the serosal surface of the preparations. The electrode arrangement was of the floating type to permit flexibility of movement with that of the bowel. Signals were led via chlorided silver wires to an AC-pre-amplifier (time constant 0·2 s). The electromyograms were recorded on an inkwriting polygraph. Electrical activity of the rabbit small isolated intestine consists of rhythmic fluctuations of resting membrane (slow waves), and of rapid action potentials (spikes) which appear during slow wave depolarization. According to Ruckebusch (1978), action potentials are accompanied by contraction of the circular muscle.

Drugs used were: atropine sulphate, methysergide maleate, piperoxan hydrochloride, propranolol hydrochloride, tetrodotoxin, prostaglandin E_1, isoprenaline hydrochloride, pentazocine lactate and (−)-naloxone hydrochloride.

Results and discussion

In all preparations (20 experiments) the slow waves were accompanied by small spikes similar to those obtained from isolated longitudinal muscle by Small & Weston (1971) and associated with longitudinal contractions. The frequency of the waves was 10–14 cycles min^{-1}. As shown in Fig. 1a, faster action potentials related to the circular activity, occurred in bursts during segmentation or peristalsis. The mean (±) s.e.) frequency of burst was 6·6 ± 0·4 min^{-1} and lasted 2·0 ± 0·1 s. When propagated during peristalsis, each burst travelled aborally at a velocity of 2·0 ± 0·06 cm s^{-1}.

Pentazocine (at a final concentration of $2{\cdot}3 \times 10^{-5}$ M) completely blocked intestinal peristalsis. However, as shown in Fig. 1b, after pentazocine, circular muscle activity increased with regular spike discharge at the beginning of each slow wave associated with rhythmic oscillations of intraluminal pressure. In 10 experiments pretreatment with atropine ($1{\cdot}4 \times 10^{-6}$ M), with α- and β-blocking drugs (propranolol and piperoxan, both at 1×10^{-4} M), with tetrodotoxin (3×10^{-7} M), or with a 5-HT antagonist (methysergide, 1×10^{-5} M), did not modify spike discharge

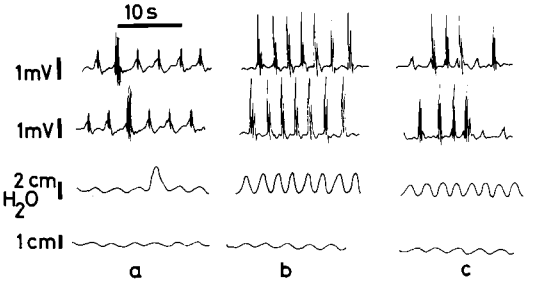

FIG. 1. Effect of pentazocine on the electrical and mechanical activity of the rabbit isolated small intestine. From top to bottom are two records of extracellular electrical activity, intraluminal pressure representing circular muscle activity and longitudinal movements. a: control; b: in the presence of pentazocine $2{\cdot}3 \times 10^{-5}$ M; c: in the presence of pentazocine $2{\cdot}3 \times 10^{-5}$ M and naloxone $1{\cdot}4 \times 10^{-5}$ M.

* Correspondence.

or rhythmic activity induced by pentazocine. In contrast, the excitatory effect of pentazocine was antagonized by isoprenaline (3×10^{-6} M) or prostaglandin E_1 (1×10^{-5} M). Pharmacological actions of opiates can be blocked by (−)-naloxone (Snyder & Goodman 1980), although higher doses are required to block κ than μ effects. As shown in Fig. 1c, (−)-naloxone ($1{\cdot}4 \times 10^{-5}$ M) slightly reduced the excitatory effect of pentazocine.

The action of pentazocine does not seem to be mediated through acetylcholine or 5-HT, or through an adrenergic pathway. Moreover, a nervous pathway does not seem to be involved, as indicated by the lack of effect of tetrodotoxin. The partial antagonism of pentazocine by high concentrations of naloxone suggests that pentazocine does not act entirely on κ receptors.

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Effect of cyclo-alkyl lactamimides upon amylase, lipase, trypsin and chymotrypsin

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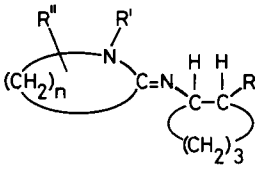
Recent studies of certain cyclo-alkyl lactamimides have indicated a potential therapeutic usefulness arising from their ability to reduce gastric hydrogen ion secretion (Cheng et al 1976), inhibit the activation of pepsinogen to pepsin (Roberts & Taylor 1978) and inhibit adenylate cyclase activity (Siegel & Wiech 1976).

We now report further in vitro observations of the effect of various lactamimides upon the activity of the pancreatic enzymes amylase, lipase, chymotrypsin and trypsin. Of particular interest was whether there were any inhibition characteristics relating the pancreatic enzymes to pepsinogens and pepsins, as was noted with various triterpenoid derivatives (Waft et al 1974).

The general formula for the lactamimides studied can be written (Grisar et al 1973) as



where, for the compounds studied so far, R = C_6H_5 and usually R′ = H, R″ = H, and n, which determines the size of the lactam ring, was varied as shown in Table 1.

Materials and methods

Human pancreatic juice, from a patient with a pancreatic cyst and fistula, was used as the source of α-amylase (E.C. 3.2.1.1.). Purified bovine pancreatic chymotrypsin (E.C. 3.4.21.1.) and trypsin (E.C. 3.4.21.4) and semipurified porcine pancreatic lipase (E.C. 3.1.1.3.) were obtained from the Sigma Chemical Co Ltd, St Louis, U.S.A. The cyclo-alkyl lactamimides, as the hydrochloride, were kindly donated by Dr N. L. Wiech of Merrell-National Laboratories, Cincinnati, Ohio, U.S.A. Measurements of pH were carried out with the Vibron pH meter (model 39A, Electronic Instruments Ltd, Richmond, Surrey, U.K.). Bovine haemoglobin substrate powder was obtained from Armour Laboratories, Eastbourne, Sussex, U.K.

The reagents for amylase and lipase measurement were obtained from American Hospital Supply (U.K.) Ltd, Didcot, Oxfordshire, U.K. Amylase substrate was a stable suspension of 0·8% (w/v) amylopectin in 0·1 M Tris HCl buffer of pH 7·2 prepared as described by the manufacturers (Amylase test reagent kit D-674, Perkin-Elmer, Coleman Instruments Division, Oakbrook, Illinois, U.S.A.). Lipase substrate (kit D-675 of the same manufacturers) was a stable emulsion of 0·076% (w/v) glycerol trioleate, purified from olive oil, in 0·01 M sodium deoxycholate, 0·001 M ascorbic acid and 0·04 M Tris HCl buffer at pH 9·0. When prepared according to the manufacturer's instructions, the triolein emulsion was stable at 4 °C for a period of at least seven days. Pancreatic lipase has a pH-optimum of 9·0 (Vogel & Zieve 1963); other lipases in plasma show relatively little activity at pH 9·0.

Amylase and lipase activity were measured with the Hyland laser nephelometer (Hyland, Costa Mesa, California 92626, U.S.A.) using the procedures set out by the manufacturers. Basically the method consisted in taking 1 ml of the appropriate substrate suspension and incubating

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