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Effect of adrenergic drugs on the isolated colon of *Rhesus cynomolgus*

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The effects of adrenaline, noradrenaline, isoprenaline and dopamine were studied on the longitudinal muscle of the ascending and descending colon of the rhesus monkey. All these drugs induced a relaxation of the preparation, dopamine being the less active agonist. The responses seem to be the result of β_2-adrenoceptor stimulation since their inhibition by practolol (β_1) is weaker than their inhibition by propranolol (β_1 and β_2 dopaminergic). There is no evidence for the presence of dopaminergic receptors in this preparation.

The effects of catecholamines on the gastrointestinal tract of many mammalian species are mediated by either α- or β-adrenoceptors (Ahlqvist & Levy 1959; Furchgott 1960; Bowman & Hall 1970). The relative importance of these two types of receptors varies according to the level of the GI tract studied and the animal species. Their stimulation produced essentially inhibitory responses (Ahlqvist & Levy 1959; Ek & Lundgren 1982). However, in some preparations, a contraction can be induced by α-adrenoceptor stimulation (Fontaine et al 1984).

We have previously shown that α- and β-adrenoceptors are present in the longitudinal muscle of the mouse and the dog colon (Fontaine et al 1984; Grivegnée et al 1984). With the availability of tissue from animals used by industry for anatomy and pathology tests, we studied the effect of various sympathomimetic drugs on the ascending and descending colon of the monkey, *Rhesus cynomolgus*.

Materials and methods

Segments of ascending and descending colon which had been removed under pentobarbitone sodium anaesthesia (30 mg kg^{-1}) were excised and immersed in Krebs solution (mM): NaCl 118·1; KCl 4·7; $CaCl_2$ 2·5; KH_2PO_4 1·2; $MgSO_4$ 1·2; glucose 5; $NaHCO_3$ 25, aerated with 95% O_2 and 5% CO_2. The mucosa was then removed and longitudinal strips (0·5 × 5 cm) were each set up in 50 ml organ baths containing Krebs solution at 37 °C gassed with 95% O_2, 5% CO_2 and allowed to equilibrate for at least 60 min.

The load on the tissues was 2 g. Responses were recorded on a kymograph, using an isotonic lever (× 5 magnification). Concentration-response curves were established for adrenaline, noradrenaline, dopamine and isoprenaline and the IC 50 values (concentration needed to develop 50% of the maximal response) determined. As these curves were not very reproducible on the same preparation, the effects of α- and β-adrenoceptor blocking drugs (15 min preincubation period) were studied on responses to the same agonists obtained by repetition of a concentration producing about 75% of the maximal response in the absence of blocking drug.

Drugs used were adrenaline bitartrate (Fluka), dopamine hydrochloride (Winthrop), phentolamine methane sulphonate (Ciba), practolol hydrochloride and propranolol hydrochloride (ICI).

Results

Adrenaline (10 nM to 1 μM), noradrenaline (10 nM to 1 μM), dopamine (1 μM to 100 μM) and isoprenaline (10 nM to 1 μM) all induced relaxations of the longitudinal muscle of the ascending or descending colon. The responses developed slowly and reached their maximum in about 4 min and persisted for more than 10 min. After the agonist had been washed out (after 4 min), a rapid return of the tone of the preparation towards the basal level was observed. The IC50 values for these four agonists are given in Table 1. The results are similar for the descending and the ascending part of the colon, except for dopamine which is more active (IC 50 about ten times higher) for the ascending than the descending part.

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Table 1. IC50 values (nM) of various agonists on the monkey isolated colon.

	Descending colon	Ascending colon
Adrenaline	40 ± 13	50 ± 4
Noradrenaline	15 ± 6	10 ± 2
Dopamine	4670 ± 265	500 ± 60
Isoprenaline	15 ± 4	20 ± 4

Values (m ± s.e.m.) have been determined from concentration-effect curves. n= 4 to 12 for each agonist.

Table 2. Inhibitory effects of phentolamine, propranolol and practolol on the relaxations induced by various agonists in the isolated descending colon of the monkey.

	Adrenaline 0·1 μM	Noradrenaline 0·1 μM	Dopamine 0·1 μM	Isoprenaline 0·1 μM
Phentolamine 3 μM	8 ± 13 (4) $P < 0.20$	12 ± 5 (4) $P = 0.20$	10 ± 4 (12) $P = 0.35$	8 ± 3 (4) $P < 0.10$
Propranolol 1 μM	90 ± 5 (4) $P < 0.001$	68 ± 9 (6) $P < 0.001$	87 ± 4 (10) $P < 0.001$	86 ± 9 (4) $P < 0.001$
Phentolamine 3 μM + Propranolol 3 μM	85 ± 6 (7) $P < 0.001$	87 ± 7 (10) $P < 0.001$	83 ± 6 (14) $P < 0.001$	82 ± 9 (4) $P < 0.01$
Phentolamine 3 μM + Practolol 3 μM	10 ± 3 (4) $P < 0.005$	46 ± 3 (4) $P < 0.01$	10 ± 8 (6) $P < 0.05$	33 ± 3 (4) $P < 0.001$

Results (mean ± s.e. mean) are expressed as a % of inhibition of the response observed in the presence of the agonist alone (control responses). Numbers in parentheses indicate the number of experiments. Statistical analysis has been made using the Student's *t*-test for paired data.

The effects of phentolamine 3 μM, propranolol 1 μM, and a mixture of phentolamine and propranolol (each 3 μM) were studied on a submaximal response to each agonist (see Table 2). The inhibitory effect of phentolamine was weak (inhibition of 6 to 10% of the responses) and non-significant ($P > 0.05$) whereas propranolol was a powerful antagonist of the responses to adrenaline, noradrenaline, dopamine and isoprenaline ($P < 0.01$). The noradrenaline-induced relaxations were, however, less inhibited by propranolol than those induced by adrenaline, dopamine and isoprenaline. The inhibition observed in the presence of a mixture of phentolamine and propranolol was not significantly higher than that in the presence of propranolol alone. In a few experiments, the inhibitory effect of a mixture of phentolamine and practolol (each 3 μM) was tested on the response induced by adrenaline, noradrenaline, dopamine or isoprenaline. It appeared that that combination had much less inhibitory activity on the preparation than the combination of phentolamine and propranolol (each 3 μM) (Table 2).

Discussion

Adrenaline, noradrenaline and isoprenaline (each from 10 nM) and dopamine (from 1 μM) relaxed the longitudinal muscle of the descending and ascending colon of the monkey. Since these responses are clearly antagonized by propranolol (3 μM) they result, at least partly, from β-adrenoceptor stimulation.

The presence of postsynaptic inhibitory α- and β-adrenoceptors has been demonstrated in the longitudinal muscle of the colon in various mammalian species including the rabbit, cat, mouse and dog (Bowman & Hall 1970; Ek & Lundgren 1982; Fontaine et al 1984; Grivegnée et al 1984). In most of these preparations the coexistence of β_1- and β_2-adrenoceptor subtypes has been demonstrated. However, in the monkey colon, as the combination of phentolamine and practolol (a selective β_1-adrenoceptor antagonist) is much weaker in antagonizing the amine-induced relaxations than the combination of phentolamine and propranolol, the predominant population of adrenoceptors stimulated by these drugs may be deduced as being β_2. On the other hand, there are few α-adrenoceptors in the preparation. These results point to the great variability of adrenoceptor population in the same part of the gastrointestinal tract, i.e. the colon, from one species to another.

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