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Stimulation of colonic mucus output in the rat

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Mucus secreted by the colon provides a vital protective and lubricative lining. However the pharmacology of colonic secretion is a neglected field of investigation.

The colonic mucosa is rich in goblet cells and also in 5-hydroxytryptamine (5-HT). A technique has been developed to explore the possible relation of this amine (and also other pharmacological agents) to colonic mucus output.

The lumen of the colon of the anaesthetized rat was perfused at 20 ml/min by recirculating 20 ml of 6 mM N-acetyl cysteine in 155 mM NaCl. Mucus was estimated as the amount (in mg) of total hexose recovered per hour (Winzler, 1955).

The table shows that 5-HT, L-5-hydroxytryptophan (L5HTP) and L-tryptophan, all significantly increased hexose output from the rat colon, as compared with the response in saline-treated control animals. Carbachol also produced increased hexose output, but isoprenaline and histamine did not.

As the dosage of the effective agonists was increased, mean mucus output rose, and then fell again with high doses of the agonists. The dose of each agonist which produced the greatest mucus output was used in studies of the effects of antagonists. As expected, atropine (i.v. load 5 μmole/kg, infusion 100 nmole kg^{-1} min^{-1}) abolished the effect of carbachol but it had no effect on the response to 5-HT or 5HTP. On the other hand chlorpromazine (i.v. load 3 μmole/kg, infusion 100 nmole kg^{-1} min^{-1}) abolished the response to the indoles but did not affect that to carbachol.

Phentolamine (i.v. 110 nmole kg^{-1} min^{-1}) and morphine (i.v. load 0.1 μmole/kg, infusion 10 nmole kg^{-1} min^{-1}) were ineffective in suppressing the actions of 5-HT and L5HTP on colonic mucus output. However, methysergide (i.v. load 4 μmole/kg, infusion 100 nmole kg^{-1} min^{-1}) did reduce the effect of L5HTP and 5-HT, but it also produced a significant increase in hexose output when given alone.

Table 1

Exp.		*No of Rats*	*Mucus Output mg Hex/h (Mean ± 2 s.e. mean)*	*t*
1	Saline	8	0.28 (0.21–0.37)	
	5HT (10 n mol kg^{-1} min^{-1})	8	1.03 (0.85–1.24)	6.52**
	L5HTP (5 μmol kg^{-1} min^{-1})	8	0.98 (0.69–1.41)	6.30**
	L-Tryptophan (122 μmol kg^{-1} + 12.2 μmol kg^{-1} min^{-1})	8	0.69 (0.52–1.92)	4.51**
2	Saline	8	0.25 (0.19–0.32)	
	Carbachol (30 nmol kg^{-1} min^{-1})	8	1.41 (1.11–1.78)	9.76***
3	Saline	4	0.315 (0.253–0.394)	
	Isoprenaline (30 nmol kg^{-1} min^{-1})	4	0.318 (0.29–0.349)	0.129 N.S.
4	Saline	4	0.449 (0.395–0.511)	
	Histamine (100 nmol kg^{-1} min^{-1})	4	0.400 (0.332–0.481)	1.8 N.S.

** $P < 0.01$.
*** $P < 0.001$.
Asymmetric limits are derived from calculation with logarithmically transformed data.

Histological inspection of colons after experiments showed no differences attributable to drug treatments.

These results show that two distinct pharmacological stimuli can evoke mucus output.

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A hyoscine sensitive component of vagal gastric relaxation

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Stimulation of the vagus nerve to the guinea-pig stomach during muscarinic blockade results in gastric relaxation, an effect mediated by non-cholinergic, non-adrenergic nerves and sensitive to ganglion blocking drugs (Beani, Bianchi & Crema, 1971).

We have found that vagal stimulation during ganglionic blockade alone also caused a gastric relaxation which is sensitive to hyoscine.

Whole stomachs with vagi attached were removed from albino guinea-pigs of either sex (wt. range 300–500 g) and set up in a 100 ml organ bath containing McEwans' (1956) ringer. Intraluminal pressure changes were recorded by a method similar to that described by Paton & Vane (1963) but using a Devices low pressure transducer (UPI) and pen recorder.

Supramaximal stimulation of the vagi at frequencies of between 1.0 and 40 Hz resulted in a contraction of the musculature and a rise in intraluminal pressure. Hexamethonium (55.2 μM) and pempidine (15 μM) caused a reversal of this vagal response to a relaxation and a consequent fall in intraluminal pressure. This is similar to the effect seen with hyoscine (0.23 μM) but the following differences were apparent: (a) The latency of the relaxations with ganglion blockers alone was longer (1.65 ± 0.08 s (mean ± s.e. mean; $n = 9$) than that seen with hyoscine (1.23 ± 0.11 s (mean ± s.e. mean; $n = 7$) ($P < 0.01$). For these experiments the vagi were stimulated 20 mm from the point of entry into the stomach. (b) With hyoscine alone, following cessation of stimulation, the tone returns to the baseline slowly (up to 90 s). In contrast, with ganglion blockers alone, the relaxations were followed by an immediate return to the baseline; or a rebound contraction. The amplitude of the rebound contractions increased with frequency of stimulation, with duration of bursts of stimuli and with physostigmine (0.015 μM).

Low concentrations of hyoscine (0.023 μM), which had little or no effect on basal tone, caused a 53.6 ± 5.2% (mean ± s.e. mean; $n = 12$) reduction of vagal relaxations produced in the presence of ganglion blockers. Hyoscine also reduced or abolished the rebound contractions.

These observations could be explained by the presence of muscarinic receptors on the non-cholinergic, non-adrenergic ganglion cells. In this context it is germane to note that Crema, Frigo & Lecchini (1970) have shown that descending inhibition in guinea-pig and cat colon is selectively inhibited by hyoscine.

The rebound contractions following nerve stimulation could be due to acetylcholine released preganglionically diffusing to muscarinic receptors on the smooth muscle.

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