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Contraction induced by (−)-tartaric acid on rat isolated gastric fundus and its inhibition with indomethacin

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Tartaric acid-evoked contractions of the rat isolated fundus could not be antagonized by atropine sulphate or methysergide hydrogen maleate, but were partially reduced by mepyramine hydrochloride. The contractions were prevented by indomethacin (25 μg ml^{-1}) although the tissue remained sensitive to PGE_2.

(−)-Tartaric acid, a dicarboxylic acid present in many plants, wine, etc., is known to be a moderately effective laxative that evokes contractions of rat isolated gastric fundus. We have examined its effect on rat fundus and the effect of indomethacin.

Materials and methods

(−)-Tartaric acid was obtained from Merck. All other drugs were donated by Sigma Chem. Co.

Male and female Wistar rats, 150–200 g, were killed by a blow to the head and exsanguinated. Gastric fundus strips (0·5 × 3 cm) were obtained and suspended in an organ bath containing Tyrode solution (in mmol, NaCl 140, KCl 2·7, $CaCl_2$ 1·36, $MgCl_2$ 0·53, $NaHCO_3$ 12, NaH_2PO_4 0·36 and glucose 5·6) gassed with 5% CO_2 in oxygen and maintained at 37 °C (Vane 1957). Experiments were made in three series (1–3) on each of 5 tissues from different rats: 1a. Reponse for acetylcholine in the presence of methysergide hydrogen maleate (0·5 μg ml^{-1}). 1b. Responses for acetylcholine, histamine, PGE_2 and (−)-tartaric acid on the same tissue as in (a), in the presence of methysergide hydrogen maleate (0·5 μg ml^{-1}) and atropine sulphate (0·5 μg ml^{-1}). 2. Responses for the same agonists as in 1b, on the same tissues in the presence of mepyramine hydrochloride (0·5 μg ml^{-1}) additional to the antagonists in 1b. 3. Responses for the same agonists as in 1b, on the same tissue, in the presence of indomethacin (25 μg ml^{-1}) additional to the antagonists in 2.

After addition of each antagonist, the tissue was left to stabilize for 40 min. The contractions evoked with the agonists were recorded using a 'Heart-Smooth Muscle Transducer', Harvard Apparatus 386 and a pen recorder without any additional amplification.

Results and discussion

The contraction heights obtained for all series of experiments are given in Table 1 as mean values of 4 to 7 applications on each tissue. The number of applications for each dose are shown in brackets in the Table.

The reduction of the contraction heights obtained with (−)-tartaric acid applications after the addition of mepyramine hydrochloride as a histamine antagonist suggests that this activity is to some extent related to the histamine liberation in the tissue.

However, it was not possible to inhibit completely the

Table 1. Contraction heights evoked with various agonists and their antagonism by atropine sulphate, 0·5 μg ml^{-1} (1a, b), mepyramine hydrochloride, 0·5 μg ml^{-1} (2) and indomethacin, 25 μg ml^{-1} (3).

		Height of contractions (mm), mean ± s.d.			
Drugs	Dose (n) (ng ml^{-1})	1a Meth	1b Meth + Atr	2 Meth + Atr + Mep	3 Meth + Atr + Mep + Ind
ACh	5 (4)	3·0 ± 0·07	0	0	0
	10 (4)	5·0 ± 0·91	0	0	0
	15 (4)	7·5 ± 0·28	0	0	0
PGE_2	2 (4)		7·0 ± 1·01	6·5 ± 0·79	5·0 ± 1·23
	3 (4)		9·5 ± 1·27	10·0 ± 1·06	10·0 ± 0·74
Hist.	1 (4)		6·5 ± 2·11	0	0
	3 (4)		14·0 ± 1·36	0	0
(−)-TA	1 (7)		4·0 ± 0·31	2·5 ± 0·04 ($P < 0·05$)	0
	3 (7)		14·0 ± 2·91	10·0 ± 0·69 ($P < 0·05$)	0
	6 (7)		25·0 ± 2·86	17·0 ± 3·11 ($P < 0·05$)	0

ACh: Acetylcholine, Hist: Histamine, (−)-TA; (−)-tartaric acid, Meth: Methysergide hydrogen maleate, Atr: Atropine sulphate, Mep: Mepyramine hydrochloride, Ind: Indomethacin, n: number of applications on each tissue, Statistical test was variance analysis.

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contractions produced by (−)-tartaric acid in the doses used with the histamine antagonist. In the presence of the prostaglandin synthesis inhibitor indomethacin (25 μg ml^{-1}), the activity of (−)-tartaric acid was abolished, although the tissue remained sensitive to applications of PGE_2.

Collier (1974) and Bennett (1978) have reviewed the role of PGs in diarrhoea. Recent investigations on the mechanism of the laxative activity of ricinoleic acid (Beubler & Juan 1979; Capasso et al 1984) have shown that this compound stimulates PG synthesis.

In conclusion, the laxative properties of (−)-tartaric acid may also be due to its PG synthesis stimulation as well as histamine liberation.

Since (−)-tartaric acid is present in many foods and plants, it will be useful to determine its possible relation to PG synthesis by in-vivo analytical studies.

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Three different ways in which 5-hydroxytryptamine can affect cholinergic activity in guinea-pig isolated ileum

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The effects of 5-hydroxytryptamine (5-HT) have been studied on electrically-evoked contractions mediated by cholinergic nerves in guinea-pig isolated ileum. Low concentrations of 5-HT (0·0001–0·01 μg ml^{-1}) caused a sustained increase in submaximal, electrically-evoked contractions. Higher concentrations of 5-HT (0·1–10 μg ml^{-1}) initially evoked a fast, rapidly-fading contraction of the muscle. Subsequently, 5-HT 0·1–10 μg ml^{-1} caused a sustained reduction in the height of the electrically-evoked contractions. The effects of 5-HT 0·01 and 0·1 μg ml^{-1} on the electrically-evoked contractions were not blocked by methysergide 0·1 μg ml^{-1} or by hexamethonium 10 μg ml^{-1}, and may be due to changes in neuronal acetylcholine (ACh) release, since contractions evoked by exogenous ACh were unaffected by 5-HT. The results therefore imply that 5-HT can affect gut cholinergic activity in at least three different ways, two of which may modulate evoked ACh release by mechanisms which may be insensitive to tachyphylaxis.

5-Hydroxytryptamine (5-HT) can affect gastrointestinal tissues by acting either on receptors located at the muscle membrane (5-HT D receptors) or on receptors which modulate neurotransmitter release (5-HT M receptors; Gaddum & Picarelli 1957). However, different types of responses can be evoked by 5-HT acting on D or M receptors, and these could indicate the existence of subtypes of receptor. For example in human and cat intestine, 5-HT acts on D receptors to cause muscle contraction or relaxation (Burleigh 1977; Ouyang & Cohen 1982), and in myenteric neurons of guinea-pig ileum, electrophysiological studies revealed three different responses to 5-HT (see North 1982). In the present study, three ways in which 5-HT can affect cholinergic activity are decribed for guinea-pig isolated ileum.

Methods

Albino guinea-pigs of either sex, 400–500 g, were used. Segments of distal ileum 3–4 cm long, were excised at least 10 cm proximal to the caecum. Each segment was prepared for transmural electrical stimulation, with the lumen of the intestine closed to the surrounding bathing solution (Paton 1955). Segments were suspended under an initial tension of 1 g in a 10 ml tissue bath containing Krebs solution (NaCl 7·1, $CaCl_2.6H_2O$ 0·55, KH_2PO_4 0·16, KCl 0·35, $MgSO_4.7H_2O$ 0·29, $NaHCO_3$ 2·1, dextrose 1·0 g litre^{-1}) maintained at 37 °C and bubbled with 5% CO_2 in O_2. Isometric responses were measured using transducers and pen recorders.

Contractions mediated by cholinergic nerves were evoked by transmural electrical stimulation, using rectangular bipolar pulses of 0·5 ms duration and 0·1 Hz frequency. Voltage was adjusted to give contractions which were maximal (15–42 V; measured using an oscilloscope) or approximately 50% of maximum (1·7–16·0 V). A single concentration of 5-HT was added to the bath 15 min after washout and replacement of the bathing solution. The effects of 5-HT on the muscle tension and on the electrically-evoked contractions were then recorded for a further 15 min. In experiments to test the actions of drugs on the 5-HT-induced responses, tissues were incubated with the drug before adding 5-HT to the bath, and the results were compared with similar experiments in which tissues obtained from the same animal were preincubated with the drug solvent.

The effects of 5-HT on contractions evoked by exogenous acetylcholine (ACh) were studied using