reduced the mortality caused by (+)-amphetamine (20 mg kg^{-1}) in aggregated mice (Maxwell et al 1981). Our observation that 30 min pretreatment with bupropion significantly antagonized induced methamphetamine-stereotyped behaviour is in agreement with those observations. Amphetamine is reported to release catecholamines from the brain tissue after being transported into the synaptosomes by the cocaine sensitive neuronal uptake mechanisms (Azzaro et al 1974). Bupropion is reported to be a selective dopamine uptake blocker. Thus prior treatment with it might be reponsible for preventing the access of amphetamine to dopamine-containing synaptosomes. The blockade of neuronal uptake of dopamine released by methanphetamine might explain the potentiation of methamphetamine's effects when bupropion is administered 5 min after it.

Monoamine oxidase inhibitor pretreatment is reported to increase all the monoamine concentrations in the central nervous system (Baldessarini 1980). In the pargyline-pretreated animals, clomipramine elicited head-twitches and abduction and extension of hind limbs, behaviour reported to be mediated by central actions of 5-hydroxytryptamine (Corne et al 1963), while bupropion produced intense locomotor stimulation and stereotypic movements but no head-twitches. The weak inhibitory action of bupropion on the 5-HT uptake as opposed to the more selective 5-HT uptake inhibition by clomipramine (Baldessarini 1980) may explain these differing behavioural observations in the two groups.

As expected, clomipramine also potentiated 5-HTP induced behaviour. Bupropion failed to potentiate the 5-HT-mediated behaviour, except at 50 mg kg^{-1}. These behavioural observations confirm the biochemical in-vitro reports that bupropion is a more potent uptake blocker of dopamine than that of 5-HT.

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Contractile effect of 1-*O*-hexadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine on strips of isolated rat intestine

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The contractile effects of AGEPC were examined on various regions of rat isolated intestine. The duodenum, jejunum and ileum showed only the tonic component of contraction to AGEPC at the low dose ($<10^{-9}$ M) but at the high dose (10^{-7} M) biphasic contractions were induced, consisting of a phasic followed by a tonic component. In the colon, however, the AGEPC-induced maximum contraction was comparable in magnitude to that produced by acetylcholine; also the contraction profile was different from that elicited from the other regions of the intestine. Low doses of AGEPC caused a slow, sustained contraction and at high doses phasic and tonic components were not dissociated.

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The unique phospholipid, 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine (AGEPC) was first identified as a potent platelet-activating factor (Demopoulos et al 1979; Benveniste et al 1979). Subsequent studies showed that it had stimulatory effects on a variety of other cells besides blood platelets. Two research groups (Findlay et al 1981; Stimler et al 1981) have reported independently that AGEPC contracts strips of isolated guinea-pig ileum; the contraction which is slow and resistant to washing is followed by a desensitization of the muscle to further doses of AGEPC. To clarify whether AGEPC has similar effects on intestinal

smooth muscles in another species, its actions have been examined on various regions of rat isolated intestine.

Method

Male Wistar rats (200–250 g) were stunned and killed. The duodenum, jejunum, ileum and colon were removed and 2–3 cm strips of muscle from these regions were mounted in a 10 ml organ bath of aerated Tyrode solution at 37 °C of the following composition (mM) NaCl 136·9, KCl 2·7, $CaCl_2$ 2·5, $MgCl_2$ 1·0, NaH_2PO_4 0·4, $NaHCO_3$ 11·9, glucose 5·5, pH 7.8. Changes in tension were measured isotonically. AGEPC, 1-*O*-hexadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine (Bachem, Bubendorf, Switzerland) was dissolved in Tyrode solution containing 0·1% bovine serum albumin and 0·1 ml of the solution was added to the 10 ml bath.

Results

AGEPC evoked a contraction of the duodenum, jejunum, ileum and colon. An effective threshold concentration for each tissue was 10^{-10}–10^{-9} M. The patterns of the contractions of the duodenum are shown in Fig. 1a. The muscles slowly contracted after addition of low doses of AGEPC (<10^{-9} M) and showed only one component. On increasing the dose, the strips contracted more rapidly, but the magnitude of the contraction increased only slightly. At 10^{-7} M, AGEPC caused a composite response (Fig. 1) consisting of a phasic followed by tonic component. The pattern of AGEPC-induced contractions of jejunum, ileum and duodenum were similar. These results indicate that AGEPC stimulates intestinal muscles by at least two different mechanisms. Possibly different sources of Ca^{2+} are involved in the contractions induced by high and low doses of AGEPC.

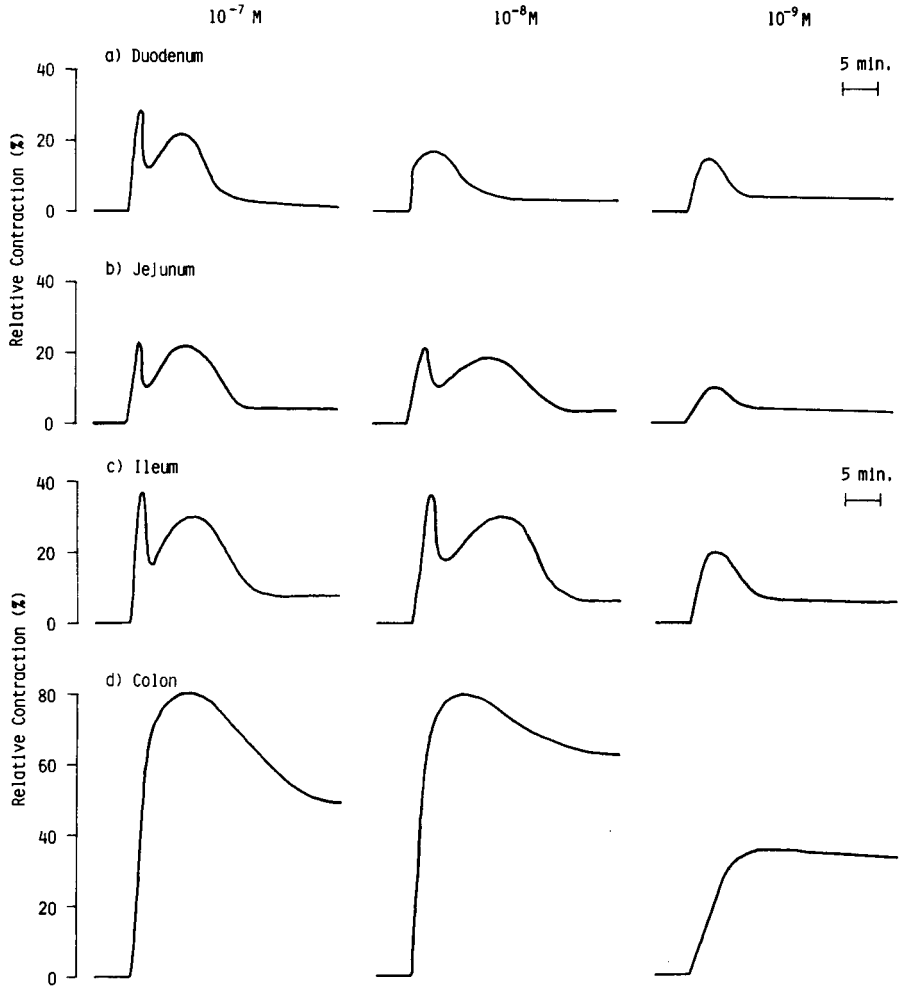

FIG. 1. Typical responses of duodenum (a), jejunum (b), ileum (c) and colon (d) to AGEPC (10^{-7}, 10^{-8} and 10^{-9} M). The ordinate represents the contraction produced by AGEPC expressed as a % of the maximum contraction produced by acetylcholine (100%).

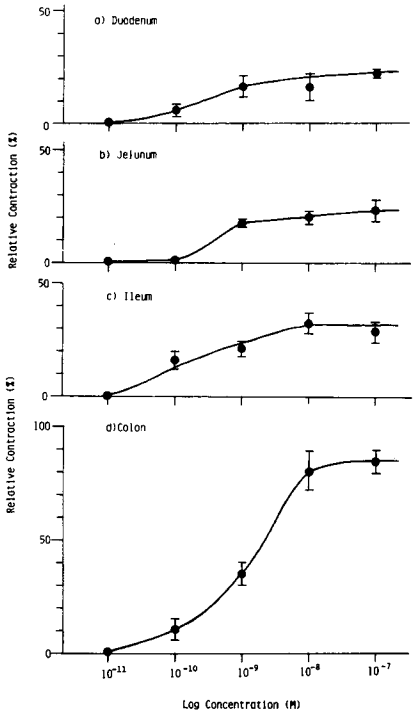

FIG. 2. Dose-response relationships for AGEPC-induced contractions of the duodenum (a), jejunum (b), ileum (c) and colon (d). The ordinate is the same as for Fig. 1. Points and bars are means ± standard errors from six preparations.

Fig. 2a, b, c show dose-response curves for the tonic components of the AGEPC-induced contractions of duodenum, jejunum and ileum, respectively. The contractions are expressed as % of maximum acetylcholine response (100%). The maximum responses of these muscles were observed at 10^{-8} M AGEPC, and the magnitudes far less than that produced by acetylcholine in each tissue.

The profile of dose-related AGEPC-induced contractions of rat colon was different from those of other regions of the intestine (Fig. 1d). At a low dose of AGEPC, the colon showed a slow sustained contraction, and only after repeated washing did the tone return to the basal level. This is consistent with the resistance to washing down by Findlay et al (1981) and Stimler et al (1981) for the AGEPC-induced sustained contractions of guinea-pig. With an increase in dose, both the magnitude and rate of the contraction of colon increased, and there was no clear differentiation of phasic and tonic components. As shown in Fig. 2d, unlike the duodenum, jejunum and ileum, the AGEPC-induced maximum contraction of the colon was almost comparable in magnitude to that produced by acetylcholine.

Over a wide range of doses, AGEPC desensitized the duodenum, jejunum, ileum and colon to a further challenge with the same or a ten-times higher dose of AGEPC. This tachyphylactic effect seems to be mediated postsynaptically and restricted to AGEPC, because both nerve stimulation and addition of acetylcholine and histamine induced a normal contraction of AGEPC-desensitized muscles.

Although some common features of the AGEPC-induced contraction of different regions of the intestine were observed, the present results suggest that AGEPC stimulates smooth muscles of different regions by a different mechanism, depending on its dose and region of the intestine. Further studies are needed to clarify the mechanism by which the stimulant signal from AGEPC is transduced to the units of contractile protein within the cells.

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