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Involvement of Different Receptors in the Central and Peripheral Effects of Histamine on Intestinal Motility in the Rat

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Abstract—The effects of histamine on intestinal motility have been investigated in conscious rats, fed or fasted, using an electromyographic method. Histamine peripherally administered (10 mg kg^{-1}) in 15 h fasted rats induced an inhibition followed by a period of irregular spiking activity disrupting the duodeno-jejunal migrating myoelectric complexes (MMC) and suppressed the postprandial motor spiking activity when administered 50 min after a meal. The selective agonist of the H_1-receptors, 2-pyridylethylamine (2-PEA) induced an irregular spiking activity while dimaprit acting on H_2-receptors, inhibited the MMC pattern. Effects of peripherally administered histamine were antagonized by previous administration of chlorpheniramine (0·5 mg kg^{-1} i.p.) and in a lesser extent by cimetidine (10 mg kg^{-1} i.p.). Histamine (1–10 μg) administered intracerebroventricularly (i.c.v.) in fasted rats increased the motor cycle frequency and immediately restored the MMC pattern when given to fed rats. Among the three agonists of the H_1- H_2- and H_3-receptors (2-PEA, dimaprit and *R*-α-methylhistamine, respectively) only *R*-α-methylhistamine (1–10 μg i.c.v.) was able to reproduce this effect. It is concluded that the effects of histamine on intestinal motility were centrally and peripherally mediated involving mainly H_1-receptors at the peripheral level and H_3-receptors at the CNS level.

In the past it was considered that the effects of histamine on the digestive tract were mediated by two different types of receptors named H_1- and H_2- receptors. H_1- receptors were responsible for smooth muscle contraction while H_2-receptors were involved in the stimulation of gastric acid secretion (Ash & Schild 1966; Black et al 1972). The existence of inhibitory histamine receptors in guinea-pig ileum resembling the H_2-receptors was later postulated by Ambache et al (1973) and Fjalland (1979), but was disproved by another study performed with several agonists and antagonists which failed to support the existence of H_2-receptors that mediate relaxation (Bertaccini et al 1979). Later studies have shown that stimulation of H_2- sites on myenteric plexus resulted in an increased amplitude of electrically induced contractions (Zavecz & Yellin 1982) and a release of contractile substances (Barker & Ebersole 1982). Thus, the inhibitory action of histamine shown on in-vitro preparations of guinea-pig ileum cannot be attributed to its action on the classical H_1- or H_2-receptors.

Recently a third type of histamine receptor termed H_3 was found in slices of rat brain and was identified as an autoreceptor controlling the synthesis and the release of histamine at the level of nerve endings and presumably the perikarya (Arrang et al 1983, 1987 a,b). In addition to this, the existence of H_3 type receptors outside the brain was suggested, especially at the level of perivascular nerve terminals (Ishikawa & Sperelakis 1987), and also in segments of guinea-pig ileum, the stimulation of these H_3-receptors inducing an inhibition of the stimulated contractile activity (Trzeciakowski 1987).

Neurochemical, neurophysiological and pharmacological evidences (Green et al 1978; Schwartz et al 1980) has given great support to the theory that histamine is a neurotransmitter in the mammalian central nervous system. This has been enhanced by the availability of new reliable immunohistochemical methods which have given a wider knowledge of the distribution of histaminergic systems. Several studies (Taylor & Snyder 1971; Brownstein et al 1974; Palacios et al 1980; Watanabé et al 1983) have shown that the highest concentrations of histamine in the brain were found in the ventral posterior hypothalamus where there are histaminergic neurons from which arise widespread projections distributed to various regions of the brain (Watanabé et al 1984). These findings suggested that histamine may be involved in many vegetative and endocrine regulatory systems. Moreover recent studies have highlighted the importance of neuropeptides and neuromediators in the CNS control of gastrointestinal motility (Buéno & Ferré 1982; Fargeas et al 1984, 1986).

Consequently, keeping in mind that histamine does not easily cross the blood-brain barrier, this work was carried out (i) to study the effects of peripheral and central administration of histamine on intestinal motility of conscious rats during fasting and after feeding, (ii) to determine the type of receptors involved using selective agonists and antagonists of the three classes of histamine receptors.

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Materials and Methods

Animals

30 male Wistar rats, 300–350 g, were individually housed and fed with laboratory pellets (U.A.R., France). Under halothane anaesthesia animals were prepared for long term electromyographic recordings using a previously described procedure (Ruckebusch & Fioramonti 1975). Nichrome wire electrodes (Microfil Industrie, Renens, Switzerland) 80 μm in diameter and 60 cm in length were implanted in the duodenal and jejunal wall at 5, 15 and 30 cm intervals from the pylorus. The electrode wires were drawn under the skin, exteriorized

on the back of the neck and protected by a glass tube attached to the skin. In addition a small polyethylene tube (catheter PE 10) was inserted in one lateral ventricle of the brain (Stewart et al 1978) in order to perform intracerebroventricular (i.c.v.) injections.

Motility recordings

Electromyographic recordings started 3 days after surgery. Electrical activity of the gut was registered on an electroencephalograph machine (Reega VIII, Alvar, Paris) 24 h day^{-1}. Spiking activity was summated every 20 s by an integrator circuit connected to a potentiometric recorder having a paper speed of 6 cm h^{-1} (Latour 1973). This integrated record permitted a clear determination of the fasted and post-prandial patterns of intestinal motility.

Experimental procedure

Experiments were performed at two day intervals. Rats were fasted for 15 h with free access to water. Drugs were given after the phase III of a migrating myoelectric complex had passed the duodenum. Fed rats were given a 5 g food pellet 50 minutes before the administration of the injections. The amount ingested was checked before injections were given.

Histamine (Merck, Darmstadt, FRG) has been administered intraperitonally (i.p.) in previous experiments in a dose range of 0·1 to 20 mg kg^{-1}. The dose of 10 mg kg^{-1} was chosen in this instance for the good reproductibility of the effects and according to recent data (Takeuchi 1988). By i.c.v. route, histamine was administered in a dose range of 1 to 10 μg; 2-pyridylethylamine (2-PEA) and dimaprit (a gift from SK F, Welwyn Garden City, UK) were administered at 10 mg kg^{-1} i.p. and up to 100 μg i.c.v. *R*-α-methylhistamine (*R*-α-Mehist) was injected in the same dose-range as histamine (1 to 10 μg i.c.v.) and thioperamide at a dose of 10 mg kg^{-1} i.p. and 20 μg i.c.v. *R*-α-Mehist and thioperamide were a gift from Dr Schwartz, Unité 109 INSERM, Paris. Cimetidine (Aldrich Strasbourg, France), ranitidine (Lab. FOURNIER, Dijon, France) and chlorpheniramine (Sigma, St Louis, MO) were injected at the usual blocking doses.

Intraperitoneal injections were given in 0·5 mL while i.c.v. injections did not exceed 10 μL. All drugs were dissolved in sterilized water except for thioperamide and cimetidine which were dissolved in dimethylsulfoxide (DMSO) and 0·2 M HCl, respectively, before dilution with water to the final concentrations. Blocking agents were given 10 min before drugs. Control studies consisted of injections of sterilized water or vehicle performed in the same conditions as in experimental studies.

Changes in motility pattern were evaluated by measuring the time between injection and the occurrence of the effects, as well as their duration. Mean values $\pm$ s.e.m. were determined from at least six measures and compared using Student's *t*-test.

Results

Control studies

In 15 h fasted rats, the electrical activity of the small intestine was organized into migrating myoelectric complexes (MMCs) which recurred at regular intervals (12–15 min) as previously described (Fargeas et al 1984). MMCs were propagated from the duodenum to the jejunum at an average velocity of $3{\cdot}4 \pm 0{\cdot}7$ cm min^{-1}. Each MMC consisted of an irregular spiking activity (phase II) followed by a short period (4–5 min) of intense and regular spiking activity named phase III. These phases of activity lasted 10–12 min and were separated by a quiescent period (phase I).

After a 5 g pellet meal the MMC pattern was immediately disrupted and replaced by a continuous and irregular spiking activity for 251 ± 48 min.

Experiments in fasted animals

(a) Effects of peripherally administered histamine. Histamine (10 mg kg^{-1} i.p.) induced a biphasic response consisting of a primary phase of inhibition lasting about 10 min (Table 1, Fig. 1) followed by a period of disruption of the MMC pattern, lasting longer in the duodenum than in the jejunum ($65{\cdot}2 \pm 22{\cdot}3$ vs $47{\cdot}2 \pm 16$). The H_1 antagonist chlorpheniramine (0·5 mg kg^{-1} i.p.) significantly reduced the inhitory phase by 52% and the following irregular spiking activity by 71%. Cimetidine (10 mg kg^{-1} i.p.) an H_2 antagonist failed to block the phase of irregular activity but reduced, by nearly 50% the duration of MMC inhibition. Thioperamide described as an H_3 antagonist was inefficient to modify the effects of histamine injected i.p. (Table 1).

2-PEA (10 mg kg^{-1} i.p.) elicited a phase of irregular spiking activity lasting $41{\cdot}6 \pm 21{\cdot}2$ min in the duodenum and $20{\cdot}2 \pm 8{\cdot}9$ in the jejunum. Dimaprit administered at a similar dose (10 mg kg^{-1} i.p.) induced a phase of inhibition of spiking activity with disruption of duodenal but not jejunal MMC for about 60 min (Fig. 1).

(b) Effects of histamine i.c.v. administered. Histamine (5 or 10 μg) i.c.v. administered to fasted rats induced for 4–5 h a duodenal motor change characterized by a succession of phases III-like activities that occurred at a two fold higher frequency than in normal MMCs ($8{\cdot}2 \pm 1{\cdot}6$ vs $4{\cdot}5 \pm 0{\cdot}4$ h^{-1} before injection). They were longer lasting than the phase III of the normal MMCs ($6{\cdot}5 \pm 1{\cdot}3$ vs $4{\cdot}06 \pm 0{\cdot}8$ min) and were not propagated to the jejunum, the motor activity of which remained unchanged (Fig. 2).

Experiments in fed animals

(a) Effects of peripherally administered histamine. Histamine administered 50 min after the beginning of the meal in a dose range of 0·5 to 10 mg kg^{-1} i.p., induced a transient dose-related inhibition of motility. This inhibition was blocked by previous administration of chlorpheniramine (0·5 mg kg^{-1} i.p.) (Fig. 3).

(b) Effects of i.c.v. administered histamine. Histamine administered i.c.v. in a dose range from 1 to 10 μg, 50 min after the meal, immediately restored the MMC pattern at the duodenal level (Fig. 4). The first phase III appeared in the jejunum with a delay of about 10 min, except for the higher dose where there was no delay. The duration of this effect was dose-related (Table 2). At the lowest dose (1 μg i.c.v.) histamine induced initially a MMC pattern for $32 \pm 3{\cdot}4$ min followed by a typical post-prandial pattern ($55 \pm 5{\cdot}1$ min in the duodenum and $32 \pm 4{\cdot}2$ min in the jejunum). After which the MMC pattern reappeared for about 2 h.

Among the histamine receptor agonists, *R*-α-Mehist, an

Table 1. Effects of peripheral administration of histamine and their antagonism by selective H_1, H_2 and H_3 receptor antagonists on intestinal motor pattern in fasted rats.

	Dose mg kg^{-1} i.p.	Duodenum		Jejunum	
		Inhibition	Disruption	Inhibition	Disruption
Histamine	10	12·1±3·5	65·2±22	9·8±3·1	47·2±16
Chlorpheniramine+histamine	0·5	6·2±2·6*	18·3±4·5*	3·5±1·1*	15·2±28*
Cimetidine+histamine	10	6·5±1·8*	52·6±18	4·9±2·5*	35·1±11
Thioperamide+histamine	10	8·6±2·1	76·8±11	7·4±2·7	58·2±15

Values represent the duration of the effects (mean±s.e.m.) determined in 10 animals (n=10).
* Significantly different ($P \leq 0{\cdot}05$) from values obtained after administration of histamine alone.

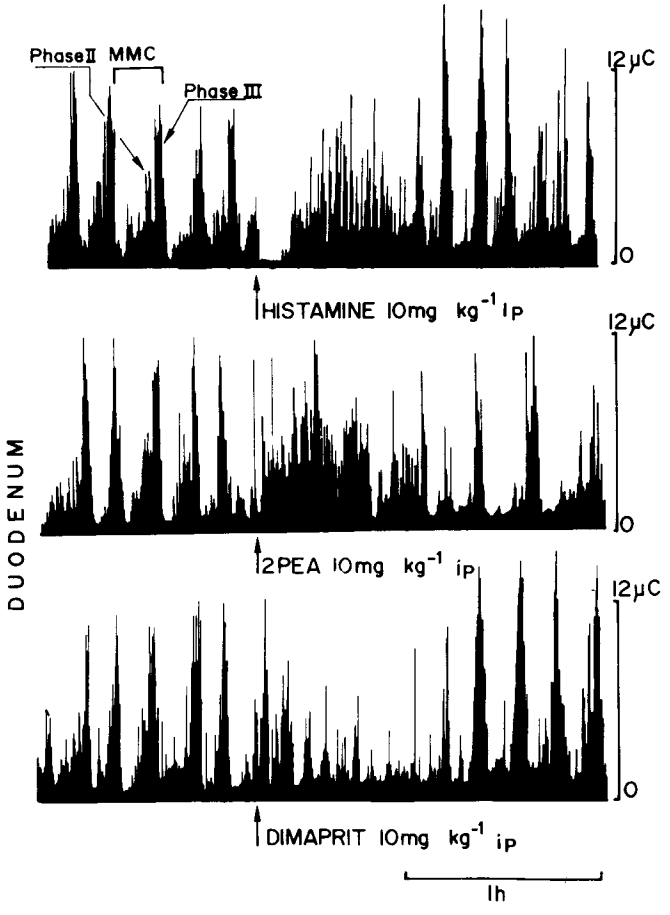

FIG. 1. Effects of histamine (10 mg kg^{-1} i.p.) and selective H_1 (2-PEA) and H_2 (dimaprit) agonists on myoelectrical (integrated record) activity of the duodenum in fasted rats. Histamine induced an inhibition followed by a disruption of the migrating myoelectric complexes. 2-PEA elicited only a phase of irregular spiking activity whereas dimaprit induced an inhibition.

H_3 agonist, was only able to reproduce the effects of histamine in the same dose-range after a delay inversely proportional to the dose administered (Table 2). The duration of the effect was dose-related, but at a similar dosage the duration was shorter than those induced by histamine.

2-PEA up to 100 μg i.c.v. did not modify the post-prandial pattern while dimaprit at high dosage (50, 100 μg i.c.v.) was able to transiently restore the MMC pattern.

Attempts to block the change from the post-prandial to the fasted pattern induced by i.c.v. histamine was not successful. Chlorpheniramine (20, 50 μg i.c.v.), cimetidine or ranitidine (20, 50 μg) failed to block the effects of histamine and had no action on the intestinal pattern when injected alone. In contrast thioperamide alone induced an MMC pattern when injected either i.p. (10 mg kg^{-1}) or i.c.v. (10, 20 μg) during a post-prandial period.

Discussion

Several studies have suggested the existence of a neuronal pool of histamine in the gut wall (Hakanson et al 1983).

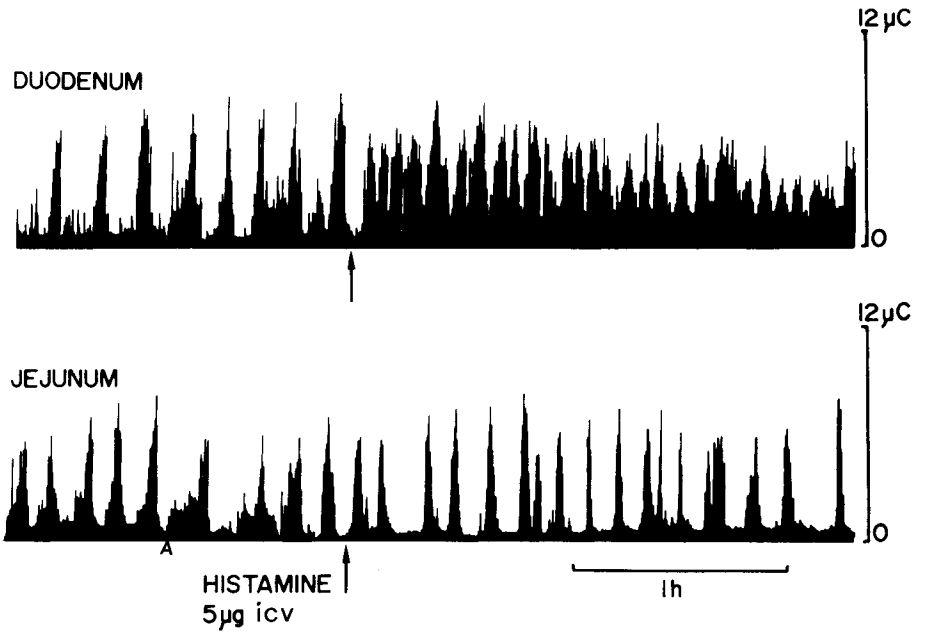

FIG. 2. Effects of histamine administered i.c.v. in fasted state on intestinal motility (integrated record): histamine increased by two fold the frequency of the motor cycle at the duodenal level.

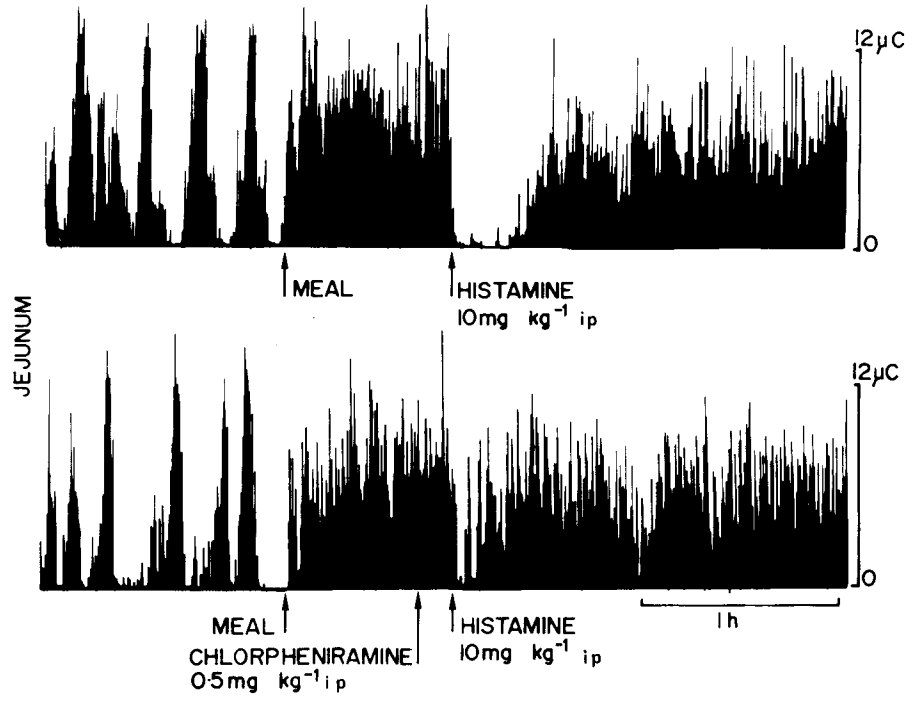

FIG. 3. Effects of histamine (10 mg kg^{-1} i.p.) after feeding and antagonistic action of chlorpheniramine (integrated record). Feeding induced a disruption of the MMC pattern which was replaced by an irregular spiking activity. Histamine had an inhibiting action on the postprandial motility which was antagonized by chlorpheniramine.

Recent research using immunohistochemical methods, has provided evidence for the presence of histamine containing nerve fibres originating from the submucous ganglion cell layer mainly in the proximal duodenum (Panula et al 1985; Ekblad et al 1985). These findings lead to the supposition that histamine may function as a neurotransmitter in the gut.

Indeed, our results show that histamine (10 mg kg^{-1}) peripherally administered induces a disruption of the migrating myoelectric complexes during the fasted state and only a transient inhibition during the fed state. These effects are mainly mediated by H_1-receptors since chlorpheniramine can antagonize both the primary inhibitory phase as well as the late occurrence of irregular spiking activity. Moreover, cimetidine reduces the duration of the inhibitory phase

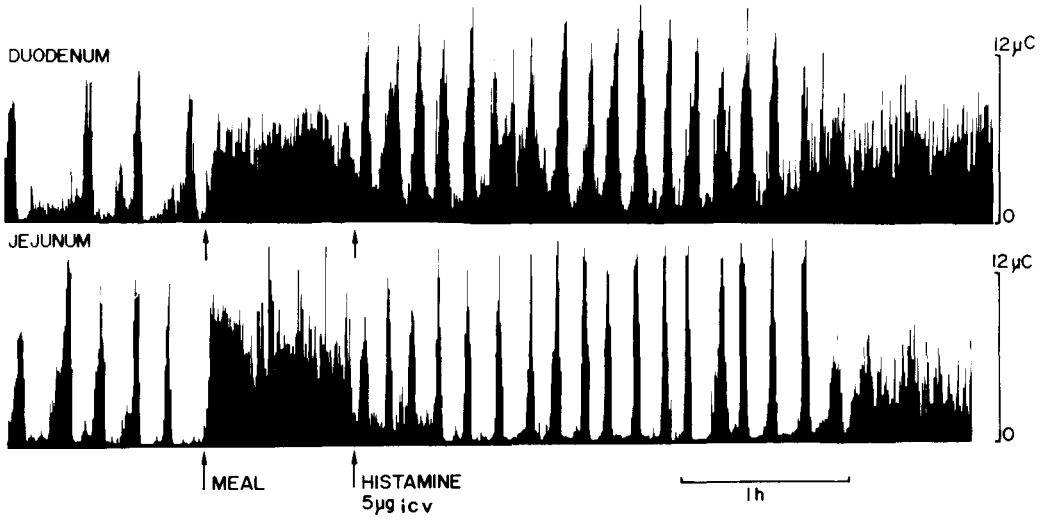

FIG. 4. Effects of histamine (5 μg) administered i.c.v. after the meal (integrated record). Feeding disrupted the MMC pattern; the postprandial irregular activity lasted about 4 h after a 5 g pellet meal. Histamine administered i.c.v. 50 min after the meal immediately restored the MMC pattern typical of the fast state.

Table 2. Effects of histamine and *R*-α-methylhistamine i.c.v. administered on the postprandial motility of the small intestine in fed rats.[a]

	Dose ($\mu g\,kg^{-1}$)	Delay* (min)		Duration** (min)	
		Duodenum	Jejunum	Duodenum	Jejunum
Histamine	1	0	12±3·5	162±28	192±32
	5	0	11±2·5	190±42	220±58
	10	0	0	240±68	263±55
R-α-Mehist	1	40±18	18±3·2	90±35	116±27
	5	25±9	17·5±2·8	115±51	165±47
	10	15±7	16·5±3·5	130±42	185±49

* Delay of apparition of the effects (mean±s.e.m.)
** Duration of histamine or *R*-α-Mehist induced MMC pattern (mean±s.e.m.)
(a) drugs were administered 50 min after food disposal. Experiments were performed in 12 rats.

leading to the view that H_2-receptors are also involved but that the stimulation of H_1-receptors is predominant. The effects obtained with 2-PEA (H_1 agonist) and dimaprit (H_2 agonist) agree with such an hypothesis; 2-PEA induces a stimulated irregular spiking activity while dimaprit mainly inhibits spiking activity. These results partly agree with the classical idea that H_1-receptors induce contraction and H_2-receptors relaxation of smooth muscle; however, with inhibition also being antagonized by chlorpheniramine, it is likely that histamine causes contraction by acting on H_1-receptors and relaxation by acting at both H_1- and H_2-receptors. These results are in agreement with studies performed in in-vivo models refering to gastric motility of anaesthetized rats (Tani & Muto 1982); but they disagree with other results with in-vitro preparations of guinea-pig ileum showing that stimulation of histamine H_2-receptors mediates the release of contractile agents (Barker & Ebersole 1982) and may potentiate the contractile response to acetylcholine (Zavecz & Yellin 1982). However, the motor effects induced by histamine do not seem to be secondary to a stimulated gastric acid secretion since cimetidine fails to antagonize these effects. Besides, 2-PEA (a specific H_1-receptor agonist) which does not affect gastric secretion (Takeuchi 1988), elicits a motor response.

Histamine administered i.c.v. induces surprising effects on intestinal motility which differ from those observed after it is peripherally administered. During fasting, histamine injected i.c.v. produces an increase of the motor cycle frequency and after feeding an almost immediate restoration of the MMC pattern typical of the fasted state. The discrepancies between these effects and those obtained by the i.p. route as well as the ratio of active doses strongly support a central site of action. Furthermore histamine does not easily cross the blood brain barrier so, the observed effects cannot result from a leakage of histamine in the systemic circulation. Histamine peripherally administered 50 min after a meal is unable to restore the MMC pattern even if a dose three thousand fold greater than the i.c.v. one is used.

The MMC-inducing effects of i.c.v. histamine after a meal is antagonized neither by an H_1-antagonist nor an H_2-antagonist. Moreover, among the different agonists, the H_3-agonist *R*-α-Mehist is only able to reproduce the effects of histamine in a similar dose-range. 2-PEA is ineffective up to 100 μg i.c.v. and dimaprit can induce a MMC pattern but

with doses 50 to 100 fold greater than *R*-α-Mehist. It is known that H_3-receptors are highly sensitive to histamine; they are activated by histamine at concentrations much lower than those required to activate post-synaptic H_1- and H_2- receptors (Arrang et al 1987a). Consequently, the effects occurring after histamine and *R*-α-Mehist administered i.c.v. may correspond to a stimulation of H_3-receptors at the central nervous system level. In this hypothesis the difference in the latencies between histamine and *R*-α-Mehist effects may be related to different vascular effects (Leng & Oudart 1988) or to the possibility that the methylation of histamine modifying physicochemical properties of the compound could increase the time for reaching target neurons. From recent data, *R*-α-Mehist is presented as a highly potent and selective H_3-receptor agonist inhibiting the release and synthesis of histamine at H_3 autoreceptors, as did exogenous histamine itself by a negative feedback (Arrang et al 1987a). Consequently, the effects that we observed on intestinal motility may result from a decrease in histamine level in brain structures particularly in the hypothalamus which is known to contain most of the histaminergic neurons (Watanabé et al 1983).

At variance with such an hypothesis, thioperamide a selective H_3 antagonist, when injected alone i.p. or i.c.v., changed the post-prandial pattern of motility into a cyclic one, as did histamine or *R*-α-Mehist. Two possible explanations for this paradoxical action may be proposed: either the effects of thioperamide on motility are non-specific and unrelated to H_3-receptor blockade, or thioperamide acts as a partial agonist on H_3 receptors. The first hypothesis is in agreement with some effects of the H_2-antagonists on gastrointestinal motility which are also unrelated to the blockade of H_2-receptors (Bertaccini & Scarpignato 1982). Also, thioperamide is really considered to have partial agonistic properties (Arrang et al 1987a).

In conclusion our results show that histamine acts on intestinal motility mainly through H_1-receptors at the peripheral level. Moreover, they suggest that the central effect of histamine on intestinal motility involves the stimulation of H_3-receptors. These H_3-receptors are at present considered as autoreceptors allowing an inhibitory feedback control of histamine release and synthesis (Arrang et al 1987b).

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