ELSEVIER

European Journal of Pharmacology 392 (2000) 71–77

ejp

www.elsevier.nl/locate/ejphar

Acceleration of gastrointestinal transit by momordin Ic in mice: possible involvement of 5-hydroxytryptamine, 5-HT_2 receptors and prostaglandins

Yuhao Li, Hisashi Matsuda, Johji Yamahara, Masayuki Yoshikawa *

Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan

Received 29 July 1999; received in revised form 28 January 2000; accepted 4 February 2000

Abstract

Possible involvement of 5-hydroxytryptamine (5-HT), 5-HT receptors and prostaglandins in the acceleration of gastrointestinal transit by momordin Ic was investigated in mice. Accelerative effect of momordin Ic (25 mg/kg, p.o.) on gastrointestinal transit was attenuated by pretreatment with a bolus of DL-*p*-chlorophenylalanine methyl ester (an inhibitor of 5-HT synthesizing enzyme), but not repeated pretreatment with DL-*p*-chlorophenylalanine methyl ester. Furthermore, cyproheptadine (a nonselective 5-HT_2 receptor antagonist), ritanserin (a 5-$HT_{2A/2B/2C}$ receptor antagonist) and clozapine (a 5-$HT_{2A/2C}$ receptor antagonist) also attenuated the effect of momordin Ic, but methiothepin (a 5-HT_1 receptor antagonist), MDL 72222 (3-tropanyl-3,5-dichlorobenzoate) and metoclopramide (5-HT_3 receptor antagonists), tropisetron (a 5-$HT_{3/4}$ receptor antagonist), ketanserin and haloperidol (5-HT_{2A} receptor antagonists) did not. These results suggested a possible involvement of endogenous 5-HT and 5-$HT_{2B/2C}$ over 5-HT_{2A} receptors. Attenuation by pretreatment with indomethacin (an inhibitor of prostaglandins synthesis) suggested involvement of prostaglandins. It is postulated that momordin Ic accelerates gastrointestinal transit partially by stimulating synthesis of 5-HT to act through 5-HT_2, possibly 5-HT_{2C} and/or 5-HT_{2B} receptors, which, in turn, increases synthesis of prostaglandins.

Keywords: Momordin Ic; Gastrointestinal transit; 5-HT (5-hydroxytryptamine, serotonin); 5-HT_2 receptor; Prostaglandin

1. Introduction

The largest amount of 5-hydroxytryptamine (5-HT; serotonin) in the body is contained in the gut. 5-HT is an important neurotransmitter and paracrine effector (local hormone) that mediates enteric functions. The role of 5-HT in the gut is very complicated due to the presence of multiple 5-HT receptor subtypes. 5-HT receptors in the gut are now classified into four main subclasses with various locations on the mucosa, smooth muscle, and neurons. All of the four subclasses of 5-HT receptors in the gut are involved in the gastrointestinal motility. The activation of 5-HT_1-like and 5-HT_{1A} receptors relaxes the longitudinal smooth muscle (Dhasmana et al., 1993). 5-HT_3 receptors are found exclusively associated with neurons of both central and peripheral origin. At the level of the gastrointestinal tract, 5-HT_3 receptors mediate diverse effects in the control of intestinal tone and secretion (Hoyer et al., 1994). The activation of 5-HT_3 receptors induces the contraction of guinea pig ileum (Dhasmana et al., 1993). In the alimentary tract, the 5-HT_4 receptor is located on neurons, smooth muscle cells and secretory cells. 5-HT_4 receptors enhance nicotinic (fast) neurotransmission at enteric ganglia via the release of acetylcholine from presynaptic nerve endings (Hoyer et al., 1994), and contract the ascending colon (Dhasmana et al., 1993). The selective 5-HT_4 receptor agonist RS67506 [1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-(2-methyl sulfonylamino)ethyl-4-piperidinyl]-1-propane hydrochloride] enhances lower intestinal propulsion in mice (Nagakura et al., 1997), but are not involved in the control of small intestinal transit in the fasted conscious rats (Clayton and Gale, 1996).

5-HT_2 receptors are widely distributed in peripheral tissues and enriched in many areas of the cortex, and the receptors partially mediate the contractile effect of 5-HT in guinea pig ileum (Hoyer et al., 1994). The activation of

* Corresponding author. Tel.: +81-75-595-4633; fax: +81-75-595-4768.
E-mail address: shoyaku@mb.kyoto-phu.ac.jp (M. Yoshikawa).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00121-7

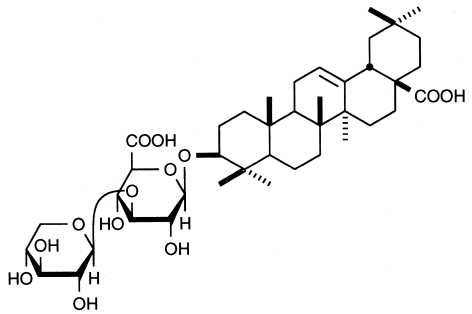

Fig. 1. Chemical structure of momordin Ic.

5-HT_2 receptors induced the contraction of longitudinal smooth muscles of the small intestine (Dhasmana et al., 1993). 5-HT-induced contraction of isolated distal ileum in rats is evoked via 5-HT_1 and 5-HT_2 receptors on the muscle (Yamano et al., 1997). Recently, the 5-HT_2 receptor family was expanded to accommodate three subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} (5-HT_{1C}) receptors (Baxter et al., 1995).

Effects of prostaglandins on gut motility both in vivo and in vitro are documented and extensively reviewed in the last decade (Bennett et al., 1975; Thor et al., 1985; Frantzides et al., 1992). Prostaglandin E series contract the longitudinal smooth muscle layer and relax the circular layer. In contrast, prostaglandin F series contract both small muscle layers (Sanders and Ross, 1978).

Momordin Ic (Fig. 1), a principal saponin constituent in various Chinese and Japanese natural medicines such as the fruit of *Kochia scoparia* (L.) Schrad., has been shown to prevent the increase of serum glucose or ethanol levels in the oral glucose- or ethanol-loaded rats (Yoshikawa et al., 1997), inhibit the ethanol- or indomethacin-induced gastric mucosal lesions, but increase the gastric secretion in pylorus-ligated rats (Matsuda et al., 1998b). Recently, we have reported that momordin Ic inhibited gastric emptying in non-nutrient, glucose, milk, or ethanol test meal-loaded mice or rats (Matsuda et al., 1998a, 1999a,b), and interestingly accelerated gastrointestinal transit and prevent the ileus induced by peritoneal irritation or laparotomy with manipulation in mice (Li et al., 1999), in which the small intestinal transit was suggested to be accelerated.

In the present study, the possible involvements of 5-HT, 5-HT receptors and endogenous prostaglandins in the acceleration of gastrointestinal transit by momordin Ic were investigated in fasted mice.

2. Materials and methods

2.1. Chemicals

Momordin Ic was isolated from the dried fruit of *K. scoparia* L. (Schrad.), and purified by high performance liquid chromatography using the reported method previously (Yoshikawa et al., 1997). DL-*p*-Chlorophenylalanine methyl ester hydrochloride, haloperidol and cyproheptadine hydrochloride were purchased from Sigma-Aldrich, USA. Ritanserin, clozapine, ketanserin tartrate, methiothepin mesylate, MDL 72222 (3-tropanyl-3,5-dichlorobenzoate), tropisetron (3-tropanyl-indole-3-carboxylate hydrochloride) were purchased from Research Biochemical, USA. Metoclopramide, indomethacin and other reagents were purchased from Wako, Japan.

2.2. Animals

Male ddY mice weighing 27–30 g were purchased from Kiwa Laboratory Animal, Japan. The animals were maintained at a constant temperature of 23 ± 2°C and fed a standard laboratory chow (MF, Oriental Yeast, Japan) and water ad libitum for a week. The animals were fasted for 18–20 h prior to experiments, but were given water ad libitum. The experiments were performed in conscious animals unless otherwise noted.

2.3. Measurement of gastrointestinal transit in mice

A charcoal meal containing a solution of 1.5% carboxymethyl cellulose sodium salt (CMC–Na) and 5% charcoal as a marker was given intragastrically (0.2 ml/mouse) to conscious mice. Thirty minutes later, mice were sacrificed by cervical dislocation. The abdominal cavity was opened, and the gastrointestinal tract was removed. The traveled distance of the marker was measured and expressed as a percentage of the total length of the small intestine from the pylorus to caecum. The test sample was given orally by means of a metal orogastric tube 60 min before the administration of the test meal. In order to investigate the involvement of the synthesis of endogenous 5-HT in the effect of momordin Ic on gastrointestinal transit, DL-*p*-chlorophenylalanine methyl ester (an inhibitor of 5-HT synthesizing enzyme, dissolved in distilled water) was administered orally once at 1, 6 or 24 h (1000 mg/kg), or twice at 72 and 48 h (300 mg/kg × 2) before administration of the sample. In order to investigate the involvement of 5-HT receptors and endogenous prostaglandins, methiothepin (a 5-HT_1 receptor antagonist), cyproheptadine (a nonselective 5-HT_2 receptor antagonist), ritanserin (a 5-$HT_{2A/2B/2C}$ receptor antagonist), clozapine (a 5-$HT_{2A/2C}$ receptor antagonist), ketanserin and haloperidol (5-HT_{2A} receptor antagonists), metoclopramide and MDL 72222 (5-HT_3 receptor antagonists), tropisetron (a 5-$HT_{3/4}$ receptor antagonist) and indomethacin (an inhibitor of prostaglandins synthesis) were dissolved in saline or suspended in 0.5% CMC-Na saline solution, and the solution was injected subcutanously 30 min before administration of the sample. All of the above drugs were administered at 10 ml/kg.

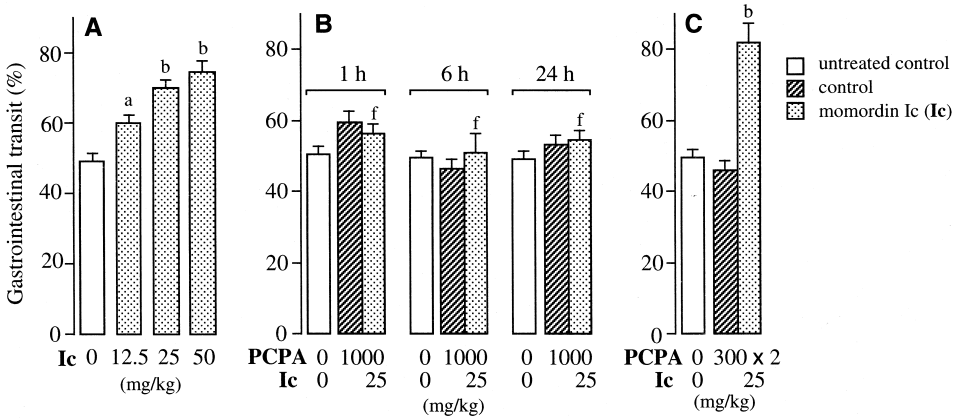

Fig. 2. Effects of momordin Ic on gastrointestinal transit in mice (A) or DL-*p*-chlorophenylalanine methyl ester (B, C)-pretreated mice. (A) A charcoal meal (0.2 ml/mouse, p.o.) was administered 60 min after oral administration of momordin Ic. Gastrointestinal transit (%) was determined 30 min after the charcoal meal. (B) DL-*p*-Chlorophenylalanine methyl ester (PCPA, 1000 mg/kg, p.o.) was given 1, 6 or 24 h before administration of momordin Ic. (C) DL-*p*-Chlorophenylalanine methyl ester (PCPA, 300 mg/kg × 2, p.o.) was given 72 and 48 h before administration of momordin Ic. Bars represent the means with S.E.M. ($n = 8$ or 10). Significantly different from each control group, $^{a}P < 0.05$, $^{b}P < 0.01$, and from the group treated with momordin Ic (25 mg/kg) in (A), $^{f}P < 0.01$.

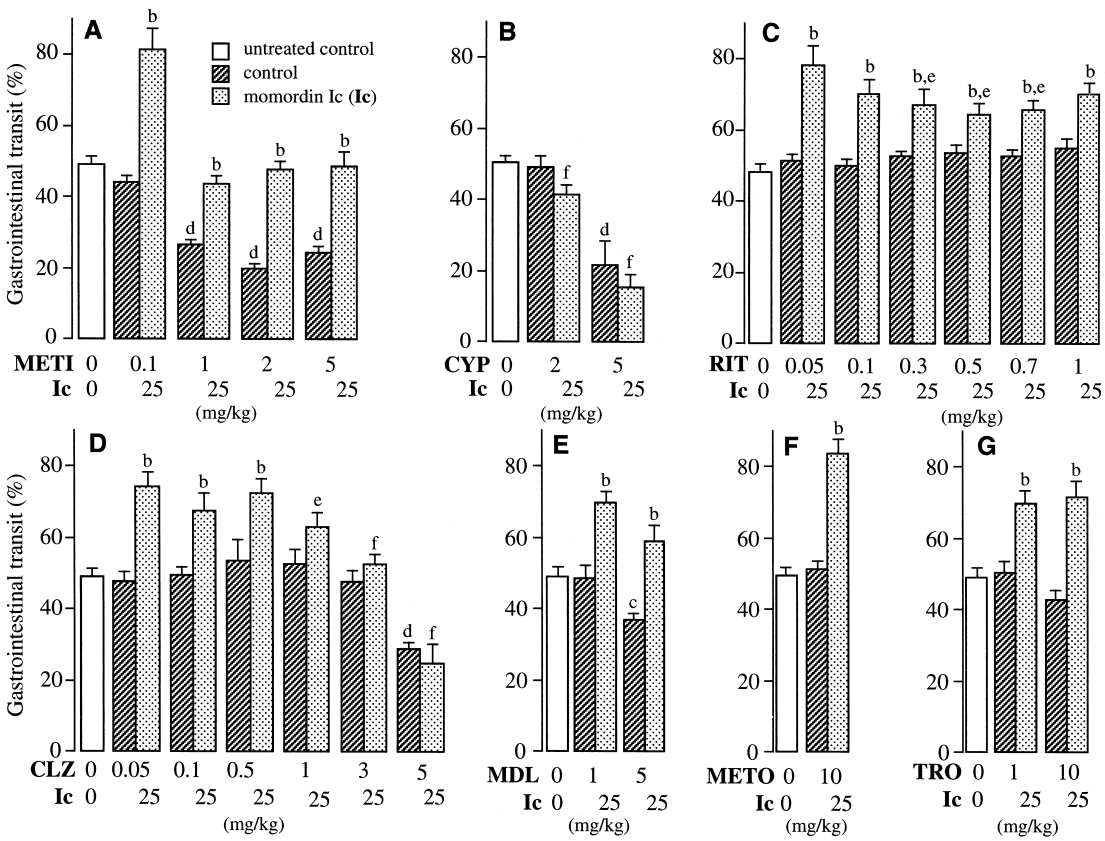

Fig. 3. Effects of momordin Ic on gastrointestinal transit in methiothepin- (A) , cyproheptadine- (B) , ritanserin- (C) , clozapine- (D) , MDL 72222- (E) , metoclopramide- (F) or tropisetron- (G) pretreated mice. Methiothepin (METI, 0.1–5 mg/kg), cyproheptadine (CYP, 2 and 5 mg/kg), ritanserin (RIT, 0.05–1 mg/kg), clozapine (CLZ, 0.05–5 mg/kg), MDL 72222 (MDL, 1 and 5 mg/kg), metoclopramide (METO, 10 mg/kg) and tropisetron (TRO, 1 and 10 mg/kg) were injected subcutaneously 30 min before administration of momordin Ic. The charcoal meal was administered 60 min after administration of momordin Ic. Gastrointestinal transit (%) was determined 30 min after the charcoal meal. Bars represent the means with S.E.M. ($n = 8$ or 10). Significantly different from each control group, $^{b}P < 0.01$, from the untreated control group, $^{c}P < 0.05$, $^{d}P < 0.01$, and from the group treated with momordin Ic (25 mg/kg) in Fig. 2A, $^{e}P < 0.01$, $^{f}P < 0.01$.

2.4. Statistics

Values are expressed as means ± S.E.M. For statistical analysis, Student's *t*-test or one-way analysis of variance following Dunnett's test was used. Probability (P) values less than 0.05 were considered significant.

3. Results

3.1. Effects of momordin Ic on gastrointestinal transit in normal or DL-p-chlorophenylalanine methyl ester-pretreated mice

As shown in Fig. 2A, the traveled distance of the charcoal within 30 min was about 50% of the small intestine. Administration of momordin Ic (12.5, 25 and 50 mg/kg, p.o.) 1 h before the charcoal accelerated the 30-min gastrointestinal transit in a dose-related manner in normal mice (acceleration: 22.4, 42.4 and 51.9%, respectively). As shown in Fig. 2B and C, a single bolus of DL-*p*-chlorophenylalanine methyl ester (1000 mg/kg, p.o., an inhibitor of 5-HT synthesizing enzyme) and repeated DL-*p*-chlorophenylalanine methyl ester (300 mg/kg × 2, p.o.) before administration of the charcoal meal did not significantly alter gastrointestinal transit. Pretreatment with a single bolus of DL-*p*-chlorophenylalanine methyl ester markedly attenuated the effect of momordin Ic (25 mg/kg) on gastrointestinal transit (acceleration: −4.9–9.7%), whereas repeated pretreatment with DL-*p*-chlorophenylalanine methyl ester tended to augment the effect of momordin Ic (acceleration: 78.0%).

3.2. Effects of momordin Ic on gastrointestinal transit in methiothepin-, cyproheptadine-, ritanserin-, clozapine-, MDL 72222-, metoclopramide- or tropisetron-pretreated mice

As shown in Fig. 3, methiothepin (s.c., a 5-HT_1 receptor antagonist) at 1, 2 and 5 mg/kg, cyproheptadine (s.c., a nonselective 5-HT_2 receptor antagonist), clozapine (s.c., a 5-$HT_{2A/2C}$ receptor antagonist) and MDL 72222 (s.c., a 5-HT_3 receptor antagonist) at 5 mg/kg significantly inhibited the gastrointestinal transit. Pretreatment with cyproheptadine (2 and 5 mg/kg) completely abolished the effect of momordin Ic (25 mg/kg) on gastrointestinal transit (acceleration: −15.7 and −29.8%, respectively). Ritanserin (a 5-$HT_{2A/2B/2C}$ receptor antagonist) at 0.3–0.7 mg/kg attenuated the effect of momordin Ic (25 mg/kg) on gastrointestinal transit (acceleration: 19.9–24.3%). Pretreatment with clozapine (1–5 mg/kg) dose-dependently attenuated the effect of momordin Ic (acceleration: 13.9–19.6%). Whereas methiothepin (0.1–5 mg/kg), MDL 72222 (1 and 5 mg/kg), metoclopramide (10 mg/kg, a 5-HT_3 receptor antagonist) and tropisetron (1 and 10 mg/kg, a 5-$HT_{3/4}$ receptor antagonist) showed no attenuation (acceleration: 38.2–41.4%).

3.3. Effects of momordin Ic on gastrointestinal transit in ketanserin- or haloperidol-pretreated mice

As shown in Fig. 4, ketanserin (s.c., a 5-HT_{2A} receptor antagonist) at 4 mg/kg inhibited the gastrointestinal transit. Pretreatment with ketanserin (0.05–4 mg/kg) or haloperidol (0.1–5 mg/kg, s.c., a 5-HT_{2A} receptor antagonist) did not attenuate the acceleration of gastrointestinal transit by momordin Ic (25 mg/kg) (acceleration: 41.6–78.8%).

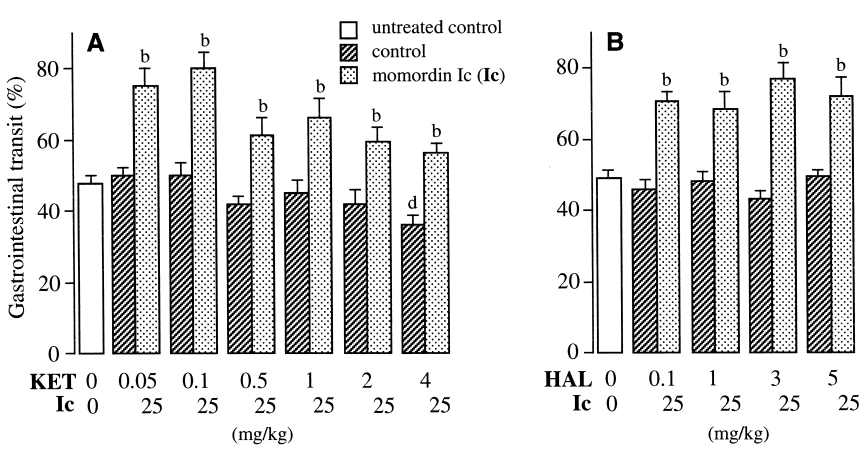

Fig. 4. Effects of momordin Ic on gastrointestinal transit in ketanserin- (A) or haloperidol- (B) pretreated mice. Ketanserin (KET, 0.05–5 mg/kg) and haloperidol (HAL, 0.1–5 mg/kg) were injected subcutaneously 30 min before administration of momordin Ic. The charcoal meal was administered 60 min after administration of momordin Ic. Gastrointestinal transit (%) was determined 30 min after the charcoal meal. Bars represent the means with S.E.M. ($n = 8$ or 10). Significantly different from each control group, $^{b}P < 0.01$, and from the untreated control group, $^{d}P < 0.01$.

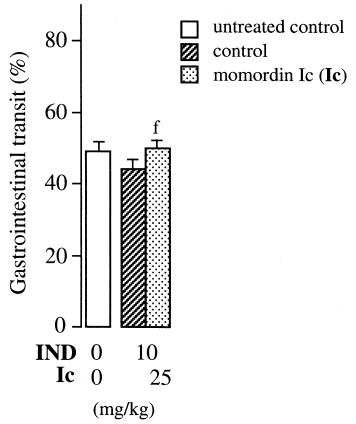

Fig. 5. Effects of momordin Ic on gastrointestinal transit in indomethacin-pretreated mice. Indomethacin (IND, 10 mg/kg) was injected subcutaneously 30 min before administration of momordin Ic. The charcoal meal was administered 60 min after administration of momordin Ic. Gastrointestinal transit (%) was determined 30 min after the charcoal meal. Bars represent the means with S.E.M. ($n = 8–11$). Significantly different from the group treated with momordin Ic (25 mg/kg) in Fig. 2A, $^{f}P < 0.01$.

3.4. Effects of momordin Ic on gastrointestinal transit in indomethacin-pretreated mice

As shown in Fig. 5, indomethacin (10 mg/kg, s.c., an inhibitor of prostaglandins synthesis) did not significantly alter gastrointestinal transit. Pretreatment with indomethacin markedly attenuated the effect of momordin Ic (25 mg/kg) on gastrointestinal transit (acceleration: 12.9%).

4. Discussion

Consistent with our previous reports (Li et al., 1999), the present study demonstrated that momordin Ic (12.5–50 mg/kg, p.o.) accelerated gastrointestinal transit in a dose-related manner in fasted mice. Momordin Ic has been reported to inhibit gastric emptying in mice (Matsuda et al., 1999a,b). In the present study, 30-min gastrointestinal transit of the control group in normal mice was about 50% of the small intestine. Therefore, momordin Ic actually enhanced upper small intestinal transit.

DL-*p*-Chlorophenylalanine methyl ester, an inhibitor of the 5-HT synthesizing enzyme tryptophan hydroxylase, induces a decrease in level of 5-HT (Gilman et al., 1985). It caused an increase of 5-HT levels in the mouse brain 2 h after the administration, but decreased the levels 48 h after administration (Leadbetter and Parmar, 1989). Repeated treatment with DL-*p*-chlorophenylalanine methyl ester induces hypersensitivity of 5-HT receptors secondary to 5-HT depletion (Meltzer et al., 1983). In the present study, pretreatment with a single bolus of DL-*p*-chlorophenylalanine methyl ester markedly attenuated the effect of momordin Ic on gastrointestinal transit. The results suggested the involvement of 5-HT in the acceleration of gastrointestinal transit by momordin Ic. Attenuation of the effect of momordin Ic 1 h after administration of DL-*p*-chlorophenylalanine methyl ester implied that the synthesis, but not release, of 5-HT is involved, because the 5-HT levels in the storage were not markedly decreased at that time. The failure of repeated pretreatment with DL-*p*-chlorophenylalanine methyl ester to attenuate the effect of momordin Ic was possibly due to the hypersensitivity of 5-HT receptors secondary to 5-HT depletion.

It has been reported that the activation of 5-HT_1-like receptors relaxes the longitudinal smooth muscle (Dhasmana et al., 1993). 5-HT_{1A} receptors are inhibitory, resulting in depression of cholinergic (as well as non-cholinergic) synaptic transmission and release of acetylcholine from cholinergic motor neuron (Talley, 1992). Cyproheptadine and ritanserin have low or very low affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} and 5-HT_3 receptors (Zifa and Fillion, 1992). In the present study, momordin Ic-induced acceleration of gastrointestinal transit was antagonized by pretreatment with cyproheptadine and ritanserin, but not with methiothepin [a 5-HT_1 receptor antagonist (Dhasmana et al., 1993; Hoyer et al., 1994)]. Therefore, 5-HT_1-like receptors appeared not to be involved.

Both 5-HT_3 and 5-HT_4 receptors have been shown to exit in the mammalian gastrointestinal tract where they seem to be involved in the control of gastrointestinal propulsion (Tonini et al., 1991; Talley, 1992). The functional role of the 5-HT_3 receptors remains incompletely understood, but it is probably involved in the modulation of colonic motility and visceral pain in the gut (Talley, 1992). 5-HT_4 receptors are not involved in the control of the small intestinal transit in rats (Clayton and Gale, 1996). In mice, a selective 5-HT_4 receptors agonist RS67506 enhanced lower intestinal propulsion, but did not affect upper gastrointestinal transit (Nagakura et al., 1997). MDL 72222 and metoclopramide are 5-HT_3 receptor antagonists (Dhasmana et al., 1993; Hoyer et al., 1994), whereas tropisetron is a 5-$HT_{3/4}$ receptor antagonist at a large dose (Dhasmana et al., 1993; Hoyer et al., 1994). In the present study, pretreatment with MDL 72222, metocloporamide and tropisetron did not antagonize the effect of momordin Ic on gastrointestinal transit. These results ruled out the involvement of 5-HT_3 and 5- HT_4 receptors.

When 5-HT_2 receptors are stimulated directly, they cause contraction of some gastrointestinal smooth muscle and gut vascular smooth muscle (Talley, 1992). Both cyproheptadine and ritanserin have high or very high affinity for 5-HT_2 receptors (Zifa and Fillion, 1992). The former is a nonselective 5-HT_2 receptor antagonist (Dhasmana et al., 1993; Hoyer et al., 1994; Baxter et al., 1995), whereas the latter is a selective antagonist of 5-$HT_{2A/2B/2C}$ receptor (Hoyer et al., 1994; Baxter et al., 1995; Costall and Naylor, 1995; Redrobe and Bourin, 1997). Clozapine, an atypical antipsychotic drug which affects numerous neurotransmitter receptors, has been

shown to be a 5-HT_2 receptor antagonist (Conn and Sanders-Bush, 1985). The results of the radioligand binding studies showed that clozapine had a high affinity for the 5-HT_{2C} and 5-HT_{2A} receptors, which suggested that clozapine was a potent 5-HT_{2C} receptor antagonist (Kuoppamäki et al., 1993). *N*-Desmethylclozapine, one of the major metabolites of clozapine, is a more potent 5-HT_{2C} receptor antagonist than itself (Kuoppamäki et al., 1993). In the present study, ritanserin, clozapine and cyproheptadine markedly attenuated the acceleration of gastrointestinal transit by momordin Ic. These results suggested that 5-$HT_{2A/2B/2C}$ receptors are possibly involved in the effect of momordin Ic on gastrointestinal transit in mice.

5-HT_{2A} receptors are widely distributed in the central nervous system (Baxter et al., 1995) and peripheral tissues (Bradley et al., 1986). The effects mediated by these receptors include part of the contractile effect of 5-HT in guinea pig ileum (Hoyer et al., 1994). 5-HT_{2B} receptors are present in the central nervous system of mouse and human (Baxter et al., 1995). Foguet et al. (1992) were able to detect 5-HT_{2B} mRNA by a quantitative polymerase chain reaction procedure in a variety of tissues, including the fundus, gut, heart, kidney, and lung, and to some extent in brain. Loric et al. (1992) also cloned the mouse homologue of the rat receptor which appears to be expressed in mouse intestine and heart and to a lesser extent in brain and kidney. Functionally, little is known about 5-HT_{2B} receptors, except in the rat stomach fundic strip where the main effect appears to be contraction (Hoyer et al., 1994). In general, the 5-HT_{2B} receptors has low affinity for compounds like spiperone, cinanserin and ketanserin (Hoyer et al., 1994). There is, as yet, little evidence for expression of any 5-HT_{2C} gene products outside the central nervous system and although it has been proposed that the 5-HT_{2C} receptors mediates vasodilatation in peripheral blood vessels (Bodelsson et al., 1992; Glusa 1992), recent evidence (Ellis et al., 1995) suggests that these actions are more likely to be 5-HT_{2B} receptors mediated.

Ketanserin, a ligand with an affinity one hundred times less for the 5-HT_{2C} than 5-HT_{2A} receptors (Costall and Naylor, 1995), is one of the most selective antagonist of 5-HT_{2A} receptors (Hoyer et al., 1994; Baxter et al., 1995; Redrobe and Bourin, 1997). Haloperidol is a potent dopamine receptor antagonist, with an affinity for the dopamine receptor considerably (100 fold) greater than for the 5-HT_{2A} site, but with a very low affinity for 5-HT_{2C} site (Leysen, 1992; Zifa and Fillion, 1992). In the present study, the effect of momordin Ic was not attenuated by pretreatment with ketanserin or haloperidol. The combination of these and above results suggested a greater involvement of the 5-HT_{2C} and/or 5-HT_{2B} than 5-HT_{2A} receptors.

The enterotoxin may use 5-HT to stimulate prostaglandins in formation via 5-HT_2 receptors and to activate neuronal structures via 5-HT_3 receptors (Beubler et al., 1992). Cholera toxin stimulates the release of 5-HT, which in turn causes the release of prostaglandin E_2 (Rask-Madsen et al., 1990). 5-HT, acting through 5-HT_2 receptors, is largely responsible for the transport abnormalities seen in intestinal anaphylaxis induced by egg albumin while prostaglandins appear to play a partial roles (Catto-Smith et al., 1989). In the present study, the acceleration of gastrointestinal transit by momordin Ic was attenuated by pretreatment with indomethacin (an inhibitor of prostaglandins synthesis). These results suggested that the synthesis of prostaglandins was also involved. Taken together, it is postulated that momordin Ic accelerates gastrointestinal transit partially by stimulating the synthesis of 5-HT to act through 5-HT_2, possibly 5-HT_{2C} and/or 5-HT_{2B} receptors, which, in turn, causes the synthesis of prostaglandins.

References

Baxter, G., Kennett, G., Blaney, F., Blackburn, T., 1995. 5-HT_2 receptor subtypes: a family re-united?. Trends Pharmacol. Sci. 16, 105–110.

Bennett, A., Eley, K.G., Stockley, H.L., 1975. The effects of prostaglandins on guinea-pig isolated intestine and their possible contribution to muscle activity and tone. Br. J. Pharmacol. 54, 197–204.

Beubler, E., Badhri, P., Schirgi-Degen, A., 1992. 5-HT receptor antagonists and heat-stable *Escherichia coli* enterotoxin-induced effects in the rat. Eur. J. Pharmacol. 219, 445–450.

Bodelsson, M., Törnebrandt, K., Arneklo-Nobin, B., 1992. Endothelial relaxing 5-hydroxytryptamine receptors in the rat jugular vein: similarity with the 5-hydroxytryptamine$_{1C}$ receptors. J. Pharmacol. Exp. Ther. 264, 709–716.

Bradley, P.B., Engel, G., Feniuk, W., Fozaed, J.R., Humphrey, P.P.A., Middlemiss, D.N., Mylecharan, eE.J., Richardson, B.P., Saxena, P.R., 1986. Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. Neuropharmacology 25, 563–576.

Catto-Smith, A.G., Partrick, M.K., Hardin, J.A., Gall, D.G., 1989. Intestinal anaphylaxis in the rats: mediators responsible for the ion transport abnormalities. Agents Actions 28, 185–191.

Clayton, N.M., Gale, J.D., 1996. 5-HT_4 receptors are not involved in the control of small intestinal transit in the fasted conscious rat. Neurogastroenterol. Motil. 8, 1–8.

Conn, P.J., Sanders-Bush, E., 1985. Serotonin-stimulated phosphoinositide turnover: mediation by the S_2 binding site in rat cerebral cortex but not in subcortical regions. J. Pharmacol. Exp. Ther. 234, 195–203.

Costall, B., Naylor, R.J., 1995. Behavioural interactions between 5-hydroxytryptophan, neuroleptic agents and 5-HT receptor antagonists in modifying rodent responding to aversive situations. Br. J. Pharmacol. 116, 2989–2999.

Dhasmana, K.M., Zhu, Y.N., Cruz, S.L., Villalón, C.M., 1993. Gastrointestinal effects of 5-hydroxytryptamine and related drugs. Life Sci. 53, 1651–1661.

Ellis, E.S., Byrne, C., Murphy, O.E., Tilford, N.S., Baxter, G.S., 1995. Mediation by 5-hydroxytryptamine$_{2B}$ receptors of endothelium-dependent relaxation in rat jugular vein. Br. J. Pharmacol. 114, 400–404.

Foguet, M., Hoyer, D., Pardo, L.A., Parekh, A., Kluxen, F.W., Kalkman, H.O., Stuhmer, W., Lubbert, H., 1992. Cloning and functional characterisation of the rat stomach fundus serotonin receptor. EMBO J. 11, 3481–3487.

Frantzides, C.T., Lianos, E.A., Wittmann, D., Greewood, B., Edmiston, C.E., 1992. Prostaglandins and modulation of small bowel myoelectric activity. Am. J. Psychol. 262, G488–G497.

Gilman, A.G., Goodman, L.S., Rall, T.W., Murad, F., 1985. Drugs acting

on the central nervous system. In: Pharmacological Basis of Therapeutics. Macmillan, New York, pp. 236–259.

Glusa, E., 1992. In: Olesen, J., Saxena, P.R. (Eds.), Mechanisms in Primary Headaches. Raven Press, pp. 168–172.

Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R., Humphrey, P.P.A., 1994. International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol. Rev. 46, 157–203.

Kuoppamäki, M., Syvälahti, E., Hietala, J., 1993. Clozapine and *N*-desmethylclozapine are potent 5-HT_{1C} receptor antagonists. Eur. J. Pharmacol. 245, 179–182.

Leadbetter, M.I., Parmar, S.S., 1989. Serotonin as a facilitatory neurotransmitter in the anticonvulsant activity of methaqualone. Physiol. Behav. 46, 105–106.

Leysen, J.E., 1992. 5-HT_2 receptors: location, pharmacological and physiological role. In: Langer, S.Z., Brunello, N., Racagni, G., Mendlewicz, J. (Eds.), Serotonin Receptor Subtypes: Pharmacological Significance and Clinical Implications. Karger, Basel, pp. 31–43.

Li, Y., Matsuda, H., Yoshikawa, M., 1999. Effects of oleanolic acid glycosides on gastrointestinal transit and ileus in mice. Bioorg. Med. Chem. 7, 1201–1205.

Loric, S., Launay, J.M., Colas, J.F., Maroteaux, L., 1992. New mouse 5-HT_2-like receptor. Expression in brain, heart and intestine. FEBS Lett. 312, 203–207.

Matsuda, H., Li, Y., Murakami, T., Matsumura, N., Yamahara, J., Yoshikawa, M., 1998a. Antidiabetic principles of natural medicine: III. Structure-related inhibitory activity and action mode of oleanolic acid glycosides on hypoglycemic activity. Chem. Pharm. Bull. 46, 1399–1403.

Matsuda, H., Li, Y., Murakami, T., Yamahara, J., Yoshikawa, M., 1998b. Protective effects of oleanolic acid oligoglycosides on ethanol- or indomethacin-induced gastric mucosal lesions in rats. Life Sci. 63, PL245–PL250.

Matsuda, H., Li, Y., Murakami, T., Yamahara, J., Yoshikawa, M., 1999a. Strcture-related inhibitory activity of oleanolic acid glycosides on gastric emptying in mice. Bioorg. Med. Chem. 7, 323–327.

Matsuda, H., Li, Y., Yamahara, J., Yoshikawa, M., 1999b. Inhibition of gastric emptying by triterpene saponin, momordin Ic, in mice: Roles of blood glucose, capsaicin-sensitive sensory nerves, and central nervous system. J. Pharmacol. Exp. Ther. 289, 729–734.

Meltzer, H.Y., Simonovic, M., Gudelsky, G.A., 1983. Effect of yohimbine on rat prolactin secretion. J. Pharmacol. Exp. Ther. 224, 21–27.

Nagakura, Y., Ito, H., Kiso, T., Naitoh, Y., Miyata, K., 1997. The selective 5-hydroxytryptamine (5-HT)$_4$-receptor agonist RS67506 enhances lower intestinal propulsion in mice. Jpn. J. Pharmacol. 74, 209–212.

Rask-Madsen, J., Bukhave, K., Beubler, E., 1990. Influence on intestinal secretion of eicosanoids. J. Intern. Med. Suppl. 732, 137–144.

Redrobe, J.P., Bourin, M., 1997. Partial role of 5-HT_2 and 5-HT_3 receptors in the activity of antidepressants in the mouse forced swimming test. Eur. J. Pharmacol. 325, 129–135.

Sanders, K.M., Ross, G., 1978. Effects of endogenous prostaglandin E on intestinal motility. Am. J. Physiol. 234, E204–E208.

Talley, N.J., 1992. Review article: 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications. Aliment. Pharmacol. Ther. 6, 273–289.

Thor, P., Konturek, J.W., Konturek, S.J., Anderson, J., 1985. Role of prostaglandins in control of intestinal motility. Am. J. Physiol. 248, G353–G359.

Tonini, M., Rizzi, C.A., Manzo, L., Onori, L., 1991. Novel enteric 5-HT_4 receptors and gastrointestinal prokinetic action. Pharmacol. Res. 24, 5–14.

Yamano, M., Ito, H., Miyata, K., 1997. Species differences in the 5-hydroxytryptamine-induced contraction in the isolated distal ileum. Jpn. J. Pharmacol. 74, 267–274.

Yoshikawa, M., Shimada, H., Morikawa, T., Yoshizumi, S., Matsumura, N., Murakami, T., Matsuda, H., Hori, K., Yamahara, J., 1997. Medicinal foodstuffs. VII. On the saponin constituents with glucose and alcohol absorption-inhibitory activity from a food garnish ‘‘Tonburi’’, the fruit of Japanese *Kochia scoparia* (L.) SCHRAD.: structures of scoparianosides A, B, and C. Chem. Pharm. Bull. 45, 1300–1305.

Zifa, E., Fillion, G., 1992. 5-Hydroxytryptamine receptors. Pharmacol. Rev. 44, 401–458.