COMPARATIVE STUDIES WITH 5-HYDROXYTRYPTAMINE AND ITS DERIVATIVES IN ISOLATED, BLOOD-PERFUSED SMALL INTESTINE AND ILEUM STRIP OF THE RAT

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Abstract—The mode of action of 5-hydroxytryptamine (5-HT) and its derivatives, tryptophan (TP), 5-hydroxytryptophan (5-HTP) and 5-hydroxyindole acetic acid (5-HIAA) was studied on the isolated, blood-perfused small intestine and isolated ileum strip of rats. In the isolated, blood-perfused intestinal preparations, 5-HT and 5-HTP injected into the superior mesenteric artery caused a monophasic fast contraction, while TP and 5-HIAA had no effects on the intestine. The contractile responses to 5-HT and 5-HTP were abolished by tetrodotoxin (TTX), hexamethothium (C₆) and morphine, but were resistant to blockade of either atropine, methysergide or phentolamine. On the other hand, in the ileum strip preparations, 5-HT contracted the ileum, but its derivatives had no effects on the ileum. TTX, C₆, morphine and atropine failed to prevent the contractile response to 5-HT, whereas methysergide effectively antagonized the response. The present results indicate that 5-HT acts by exciting intramural neuronal elements or by directly contracting the smooth muscle of the intestine. 5-HTP seems to act in the same manner as 5-HT.

5-Hydroxytryptamine (5-HT) has been shown to contract smooth muscle of the isolated intestine by a direct action on the muscle fibres or by an indirect effect through excitation of the intrinsic network of nerves (1-5). These findings, however, were obtained in isolated intestinal preparations bathed in physiological salt solutions. In view of this, it was considered that recordings of response of the intestinal smooth muscle with an intact blood supply may reveal features of the intestinal musculature. In the present experiments, we perfused the isolated small intestine of the rat through the superior mesenteric artery with blood from a donor, using a cross-circulation technique. This method enabled injection of drugs into the superior mesenteric artery and we could observe simultaneously vascular and muscular responses of the intestine.

Our objective herein was to determine whether comparable information about the actions of 5-HT and its derivatives could be obtained from isolated, blood-perfused small intestine and from isolated ileum strips of the rat.

MATERIALS AND METHODS

Male Sprague-Dawley rats were used.

Isolated, blood-perfused small intestine: Donor rats (550–750 g) were anesthetized with pentobarbital sodium (65 mg/kg i.p.). The animal was placed on a table maintained by a
heating device at about 37°C throughout the experiment. The right jugular vein and carotid artery were exposed and cannulated with a polyethylene cannulae. Heparin sodium (1000 U/kg) was injected into the femoral vein, and the systemic blood pressure was measured from the left femoral artery by means of a pressure transducer (Nihon Kohden, MPU-0.5). The carotid and jugular cannulae of the donor were connected to the perfusion circuit after the circuit had been filled with about 15 ml of blood freshly obtained from heparinized rats.

Recipient rats (130-150 g) were deprived of food overnight before the experiment but water was allowed ad libitum. Under anesthesia with pentobarbital sodium (65 mg/kg i.p.), the abdomen was opened in the midline, and the intestine was gently exteriorized. Both ends of the small intestine were ligated and cut off, proximally at the junction between the pylorus and duodenum and distally at the ileum about 10 cm above the cecum. A polyethylene cannula was inserted into the ileum at the distal end to allow for a free flow of the intestinal juice. The celiac artery was tied and cut near its origin from the aorta. The superior mesenteric artery and the portal vein were separated from the surrounding tissue, respectively. The gastro-duodenal and the splenic veins were tied off. After the injection of heparin sodium (1000 U/kg) into the femoral vein, a polyethylene cannula (ID 1.6 mm, OD 2.0 mm) was inserted into the portal vein. A metal cannula (ID 0.4 mm, OD 0.6 mm) was then inserted into the superior mesenteric artery. Arterial blood led from the donor was conducted to the mesenteric artery at a fixed flow rate by means of a non-pulsatile peristaltic pump (Mitsumi Science, SJ-1210). Flow rate was precalibrated and re-checked at the end of the experiment. A square-wave electromagnetic flowmeter (Nihon Kohden, MF-25) was used for the measurement of the mesenteric arterial inflow. Mean perfusion pressure was measured with a pressure transducer (Nihon Kohden, MPU-0.5). The perfused intestine was then removed from the recipient rat and transferred to a plastic box. Venous blood from the portal vein was returned to the donor through a reservoir by the gravity. The experimental set-up is illustrated schematically in Fig. 1. The time required to make the preparation and to set up the perfusion circuit was about 40 min.

The acrylic plastic box (20×5×15 cm) to which the isolated intestine was transferred contained 0.9% saline and was placed on the heating table (see Fig. 1B). In the box a small plastic plate (5×1×6 cm) with metal arms was placed so that the isolated intestine mounted on the plate was allowed to float in saline maintained at 37°C throughout the experiment. The intestine was covered with cellophane to prevent drying.

A small opening was made in the wall of the ileum about 20 cm apart from its end, and through the opening a water-filled balloon made of thin rubber, 3-5 mm long, was inserted into the lumen of the intestine in the direction of the duodenum. The amount of water filled in the balloon was adjusted initially to give a resting intraluminal pressure ranging between 1 and 5 cm H₂O. The pressure of the ileal region was measured with a pressure transducer (Nihon Kohden, MPU-0.1). All recordings were made on an ink-writing rectigraph (TOA Electronics, EPR-3T).

Tissue oxygen consumption was calculated from PO₂ (arterial and venous) by converting the oxygen tensions into percent oxygen saturation of hemoglobin at 37°C, and expressed
in ml of oxygen consumed per gram of the intestine dry weight (DW) per min. Oxygen consumption (ml-min$^{-1}$·g$^{-1}$·DW) = blood flow (ml-min$^{-1}$)·hemoglobin concentration (g·ml$^{-1}$·blood)·1.34 O$_2$·g$^{-1}$·hemoglobin ·$^{\circ}$O$_2$ saturation of arterial blood·$^{\circ}$O$_2$ saturation of venous blood·g$^{-1}$·DW·100$^{-1}$. Measurements of PO$_2$, PCO$_2$, and pH in blood samples were made using the blood gas analyzing system (Radiometer, BMS3-MK2, Copenhagen, Denmark). Hemoglobin concentration was determined with a HB-Meter (Model-303-A, Erma Optical Works, Ltd., Tokyo).

Drug solutions in a volume of 0.01 ml were injected into the superior mesenteric artery over a period of 4 sec by individual microsyringes (Jintan Terumo Co.).
Isolated ileum strips: Rats (300-400 g) were sacrificed and the ileum was excised. The oral end of a segment (approx. 2 cm) of the ileum was tied to a supporting hook and the other end to the recording lever, and the movement was recorded on an ink-writing rectigraph (Custom Demand Recorder, Model CDR-12A, TOA Electronics Ltd.) through a transducer connected to an isotonic amplifier (Medical Electronics Commercial, ME-4012). The lever was weighted with 0.5 g. An organ bath containing 10 ml Krebs solution at 37 °C aerated with a mixture of 95°% oxygen and 5°% carbon dioxide was used. The composition of the Krebs solution was (mM): NaCl 119, KCl 4.8, CaCl₂ 2.5, NaHCO₃ 25, KH₂PO₄ 1.2, MgSO₄ 1.2, glucose 11.0.

5-HT was added to the bath in a single or cumulative manner. At least 10 min were allowed between successive administrations. The drugs to be tested as antagonists were added to the bath in appropriate doses and after 5 min 5-HT was re-applied to the ileum. In order to avoid errors due to the persistence of effects, a different piece of ileum was used for each experiment. The final concentrations of the compounds in the bath are expressed as M.

Drugs used: 5-hydroxytryptamine creatinine sulfate (5-HT), 5-hydroxy-L-tryptophan (5-HTP), 5-hydroxyindole-3-acetic acid (5-HIAA) and dopamine hydrochloride (Sigma), L-tryptophan (TP) (Wako Junyaku), carbachol chloride (Tokyo Kasei), acetylcholine chloride (Daiichi Seiyaku), atropine sulfate (Takeda), morphine hydrochloride, tetrodotoxin, (±)-adrenaline chloride and (±)-noradrenaline hydrochloride (Sankyo), methysergide tartrate (Sandoz), phenolamine mesylate (CIBA-Geigy) and hexamethonium bromide (Yamanouchi). All drugs were dissolved in or diluted with 0.9°% saline. The doses of 5-HT, 5-HTP, 5-HIAA, TP and tetrodotoxin refer to their bases and those of other drugs to their salts.

Statistical analysis: Values in the text are means±S.E. Student’s t-test was used for statistical analysis. A P value of 0.05 or less was considered statistically significant.

RESULTS

Isolated blood-perfused intestine

Control observations: Six preparations were used for control experiments. A stable situation of the preparation was established within 20 min after start of perfusion and was maintained for 3 hr or more. At this stage, the perfusion pressure, intraluminal pressure and mesenteric arterial flow were 95.5±5.0 mm Hg, 2.9±0.2 cm H₂O and 5.4±0.5 ml/min,g⁻¹ DW, respectively. Thirty minutes after the onset of the perfusion, the tissue oxygen consumption was calculated as 0.078±0.004 ml/min⁻¹·g⁻¹ DW, and this value was in good agreement with that determined 2 hr after start of the perfusion.

Intestinal and vascular responses to 5-hydroxytryptamine (5-HT), 5-hydroxytryptophan (5-HTP), tryptophan (TP) and 5-hydroxyindole acetic acid (5-HIAA): Single doses of 5-HT (0.01-1 μg) were given at intervals of at least 5 min into the mesenteric artery. With this dose-range of 5-HT, increases in the perfusion pressure (vasoconstriction) appeared in a dose-dependent manner (0.01 μg, 5.0±1.2 mm Hg; 0.1 μg, 12.5±1.6 mm Hg; 1 μg, 27.6±1.9
With 0.03-1 μg of 5-HT, a monophasic fast contraction of the intestine occurred immediately after the administration (Fig. 2). However, unlike the vasoconstrictor responses, the dose-response relation for the fast contractile responses to 5-HT of the intestine was so flat that 0.01 μg of 5-HT produced no response in all 8 preparations and a 3-fold increase in the dose of 5-HT elicited the responses of about 27 cm H_2O in all 8 preparations, but with further increasing doses of 5-HT, the amplitude of the response remained virtually unchanged (see Fig. 4). Both the vasoconstrictor responses and the contractile responses of the intestine showed no tachyphylaxis to repeated injections of 1 μg of 5-HT.

An intra-arterial injection of 0.1 μg of 5-HTP caused no intestinal response in the tested 4 preparations. With the dose-range of 0.3-3 μg of 5-HTP, a fast contraction of the intestine appeared in similar magnitude (0.3 μg, 21.0 ±1.9 cm H_2O; 3 μg, 19.2 ± 3.2 cm H_2O, N = 4) abruptly after a latent period of 30-60 sec. Thus, 5-HTP at concentrations ranging from 0.3 to 3 μg did not produce a dose-dependent fast contractile response. The fast contractile response by 5-HT (0.03-1 μg) also was not dose-dependent (Fig. 4). The potency of 5-HTP

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**Table 1. Effects of tetrodotoxin (TTX), hexamethonium (C_6), morphine, atropine, methysergide and phentolamine on the intestinal response to 5-HT (1 μg)**

| Treated         | Amplitude of Contraction (cmH_2O) |
|-----------------|----------------------------------|
|                 | Before             | After        |
| TTX (6)         | 1 μg               | 27.0 ± 1.8   | 0            |
| C_6 (7)         | 100-250 μg         | 24.4 ± 1.7   | 0            |
| Morphine (6)    | 10-50 μg           | 24.9 ± 2.3   | 0            |
| Atropine (8)    | 3-10 μg            | 27.6 ± 3.0   | 22.1 ± 2.1   | N.S. |
| Methysergide (8)| 1 μg               | 27.7 ± 1.8   | 26.8 ± 2.1   | N.S. |
| Phentolamine (5)| 5-10 μg            | 23.3 ± 2.0   | 24.2 ± 2.5   | N.S. |

Values are expressed as mean ± S.E. and the number of experiments is given in parentheses. N.S., not significant.
in producing the fast contraction was roughly 1/10 of that of 5-HT. 5-HTP had no or only a slight vasoconstrictor effect in large doses. On the other hand, TP (0.3–3 μg) and 5-HIAA (0.3–3 μg) were ineffective on either the intestine or the vasculature (Fig. 2).

**Effects of various blocking agents on the intestinal contraction caused by 5-HT and 5-HTP:** Summarized data are shown in Table 1.

*Tetrodotoxin (TTX), hexamethonium (C₆) and morphine:* As shown in Fig. 3, the fast intestinal contraction in response to 5-HT (1 μg) and 5-HTP (1 μg) was abolished by treatment with TTX (1 μg). C₆ (100–250 μg) and morphine (10–50 μg) also blocked the contraction in response to 5-HT and 5-HTP. Blockade of the responses to 5-HT and 5-HTP wore off within 30 min.

**Atropine and methysergide:** A single injection of atropine (3–10 μg) abolished an intestinal contraction (27.4 ± 3.3 cm H₂O, N = 6) in response to carbachol (1 μg), but did not significantly reduce that to 5-HT (0.03–1 μg) (Fig. 4). The intestinal response to 5-HT

![Fig. 3. Effects of tetrodotoxin, hexamethonium and morphine on the contractile responses of the intestine to 5-HT and 5-HTP.](image)

![Fig. 4. Absence of the effect of atropine (3–10 μg) on the intestinal contraction caused by increasing doses (0.03–1 μg) of 5-HT. Untreated, ●; treated, ○. There were no significant differences between the corresponding values obtained from both groups. Vertical bars represent mean ± S.E. from 8 experiments.](image)
(1 \mu g) also was unaffected by methysergide (1 \mu g), although the vasoconstrictor one to 5-HT was significantly reduced (untreated, 13.5 ± 0.8 mm Hg; treated, 5.4 ± 3.3 mm Hg; P < 0.05, N = 8). The intestinal response to 5-HTP (1 \mu g) also was resistant to these blockades (not shown).

**Phentolamine:** Unlike 5-HT and 5-HTP, single injections of catecholamines, noradrenaline (1 \mu g), adrenaline (1 \mu g) and dopamine (1-10 \mu g) caused a decrease in the intestinal tone. The contractile responses of the intestine to 5-HT (1 \mu g) and 5-HTP (1 \mu g) were resistant to the blocking action of phentolamine (5 \mu g), in a dose sufficient to inhibit the vasoconstrictor response to noradrenaline (1 \mu g) (untreated, 28.4 ± 2.9 mm Hg; treated, 4.8 ± 0.7 mm Hg; P < 0.01, N = 5). Fig. 5 shows a typical experiment.

**Isolated ileum strip**

**Responses to 5-HT and its derivatives:** A single dose of 5-HT (10^{-5} M) contracted the ileum, while 5-HTP (10^{-5} M), TP (10^{-5} M) and 5-HIAA (10^{-5} M) were ineffective or caused a slight relaxation of the ileum (Fig. 6A). When at least 10 min were allowed between determinations of successive cumulative dose-response curves for 5-HT, there was no difference in the magnitude of the contraction between the first and second cumulative dose-response curves of 5-HT (Fig. 6B). Namely, the dose-response curves of 5-HT could be constructed with no tachyphylaxis by at least a second time under the present conditions. In the presence of 5-HTP (10^{-5} M), the contractile response to the administered 5-HT (10^{-5} M) was not modified (Fig. 6C).

![Graph](image-url)

**Fig. 5.** Absence of the effect of phentolamine (5 \mu g) on the contractile responses of the intestine to 5-HT and 5-HTP. Note that noradrenaline (NA), adrenaline (AD) and dopamine (DA) did not induce such a fast contraction as that seen with 5-HT.
A) Response to a single dose of TP, 5-HTP, 5-HT or 5-HIAA. B) Response to the repeated administrations of cumulative doses of 5-HT. Upon determination of dose-response relations for the response to 5-HT, the dose was cumulatively increased by a factor of about 3. Compare with the response to a single dose of 5-HT.

C) Response to 5-HT in the presence of 5-HTP.

Influence of tetrodotoxin (TTX), hexamethonium (C₆), morphine or atropine on the contractile response to 5-HT: The administration of cumulative doses of 5-HT (10⁻⁷–10⁻³ M) contracted the ileum. As shown in Fig. 7, TTX (2 × 10⁻⁷ M), C₆ (10⁻⁴ M) and morphine (3 × 10⁻⁷ M) failed to block the contractile response to 5-HT. Also, atropine (3 × 10⁻⁸ M), in a dose sufficient to antagonize the effect of acetylcholine (10⁻⁷–10⁻⁵ M), had no effect on the contractile response to 5-HT.

Effect of methysergide on the contractile response to 5-HT: As in the methysergide-treated preparations, the contractile response to 5-HT reached a maximum and fell rapidly. The cumulative administrations of 5-HT were not adequate to test the effect of methysergide, therefore, the effect of this drug (3 × 10⁻⁸ M) was tested with single doses of 5-HT. Fig. 7
shows that methysergide effectively antagonized contractions of muscle to 5-HT.

**DISCUSSION**

In this study, the rat isolated small intestine was perfused with blood from the donor through the cannulated superior mesenteric artery. The preparation remained stable for about 3 hr and gave responses that could be subjected to pharmacological analysis. Thus, the arterially blood-perfused intestinal preparation of the rat seems to be suitable for the analysis of drug actions on the intestinal musculature and vasculature, as it is free from the influence of the central nervous system.

In the isolated, blood-perfused intestinal preparations, 5-HT and 5-HTP injected into the mesenteric artery caused a monophasic fast contraction of the intestine, while TP and 5-HIAA had no effects on the intestine. The mode of action of 5-HTP, except for the latency, mimicked that of 5-HT. The dose-response relation for the contractile responses to 5-HT and 5-HTP was extremely flat. The contractile responses to these two substances were abolished by tetrodotoxin, which is known to block only the neurally mediated fraction of the response without interference with excitation of smooth muscle (6–7). This indicates that the fast contraction of the intestine caused by 5-HT and 5-HTP was produced by excitation of neural elements in the intestine. Morphine, a potent 5-HT antagonist at neural tryptaminergic receptors (2, 8, 9), also prevented the intestinal contraction in response to 5-HT and 5-HTP. However, methysergide failed to inhibit the contractile responses to these substances. Thus, it appears that the neuronal receptors involved were specific tryptaminergic receptors in neural elements in the intestine. However, the contractile
responses to 5-HT and 5-HTP were abolished by C₆, the nicotinic receptor antagonist. Thus, the question arises as to how the susceptibility to C₆ of the contractile responses to 5-HT and 5-HTP can be reconciled with the conclusion drawn that 5-HT and 5-HTP stimulated specific neural tryptaminergic receptors. Since C₆ is not an antagonist of neural tryptaminergic receptors (9-11), the abolition of the contractile responses to 5-HT and 5-HTP by C₆ cannot be ascribed to the pharmacological antagonism at the same receptors. However, the question can be resolved if it can be shown that the 5-HT and 5-HTP sensitive neurons in the neural plexus in the intestine are cholinergic and neurons serving as the common pathway are cholinoceptive i.e. having nicotinic receptors.

In the present experiments, atropine did not block the fast contraction produced by 5-HT and 5-HTP. The persistence of contractile responses to these substances in the presence of atropine suggests that neurons serving as the final common pathway to the intestinal smooth muscle cell may not be cholinergic. Furthermore, intra-arterial injections of catecholamines produced only a decrease in the intestinal tone and phentolamine did not prevent the contractile responses to 5-HT and 5-HTP. Thus, these data taken together suggest that the fast contraction produced by 5-HT and 5-HTP was elicited by a stimulating action of these substances on cholinergic neurons presynaptic to final non-cholinergic and non-adrenergic neurons in the intestinal neural plexus.

On the other hand, in the isolated ileum strip preparations, 5-HT contracted the ileum, while 5-HTP, TP and 5-HIAA had no effects. The contractile response to 5-HT was not blocked by tetrodotoxin, hexamethonium, morphine or atropine, while methysergide effectively blocked the response to 5-HT. These results differ with those obtained in guinea-pig ileum (1-4) and such may be due to species differences. According to the present investigation, with the rat ileum strip, 5-HT seems to induce the contraction by directly stimulating tryptaminergic receptors in the smooth muscle of the intestine.

Finally, it should be considered why 5-HTP did not cause a contraction in the ileum strip. From the results in the strip of ileum, 5-HTP itself would be an essentially inactive substance. It is well known that 5-HTP, when administered to various animals, localizes in many tissues and is decarboxylated to 5-HT (12-14). It is likely, therefore, that the fast contractile response of the intestine to 5-HTP was induced through 5-HT formed locally from the exogenously administered 5-HTP. On the other hand, Bülbring and Crema (15) reported that the administration of 5-HTP into the mesenteric artery of the guinea-pig increased the release of 5-HT into the lumen of the intestine. Taking into consideration the facts that the fast contraction caused by 5-HTP appeared after a latent period of 30-60 sec., and that the doses required were about 10 times larger than those of 5-HT producing a similar effect, it may be assumed that the contractile response of the intestine to 5-HTP was mediated through the 5-HT released from the stores.

Thus, there was a certain difference in the mode of action of 5-HT examined in the present two different preparations. However, the present findings are in agreement with those obtained by other workers (1-5), in that 5-HT acts through two types of receptors of neuronal components and smooth muscle in the intestine.
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