Concentration-dependent stimulation of intestinal phase III of migrating motor complex by circulating serotonin in humans

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INTRODUCTION

The biogenic amine 5-hydroxytryptamine (5-HT, serotonin) is present in the enterochromaffin cells of the mucosa [1] and in nerve cells of the myenteric plexus [2,3] in the gastrointestinal tract. Occasionally, 5-HT can also be found together with various neuropeptides such as somatostatin, substance P and vaso-active intestinal peptide in gut neurons [4]. In blood, 5-HT is predominantly stored in platelets, and may be released by activation of these cells. The fate of intravenously infused 5-HT has not been studied in humans, but animal experiments have shown that 5-HT is rapidly removed from the circulation [5,6], presumably due to uptake by platelets and endothelial cells, as well as by metabolism.

5-HT has been shown to stimulate gastrointestinal motility in man, both in vitro and in vivo [7,8]. However, these studies were carried out before the recognition of the migrating motor complex (MMC) in man [9]. Insights into the control of gastrointestinal motility may be studied through analysis of the MMC, since this is the only motor pattern that can be predicted to recur within a certain, though variable, time interval. The effects of 5-HT on MMC have been most extensively studied in animals [10-12], while human studies are few. Serotoninergic mechanisms may be involved in the regulation of MMC in man, as suggested by the finding that treatment with a selective 5-HT reuptake inhibitor, paroxetine, shortens the MMC interval and increases the propagation velocity of phase III of MMC in the proximal jejunum [13]. Furthermore, we have previously found that bolus injections of 5-HT given intravenously induce phase III-like activity in the small intestine of healthy volunteers [14].

5-HT exerts its effects through interactions with different receptor subtypes on nerves and muscle cells in the small intestine. A number of 5-HT receptor subtypes exist. Seven main subgroups are defined (5-HT1-7) of which three (5-HT1A, 5-HT1B and 5-HT1D) are further divided into two or more subtypes (5-HT1A,B,5-HT1C, 5-HT1D,E and 5-HT1F,G) [15]. 5-HT may inhibit (5-HT1A) or facilitate (5-HT1D) the release of acetylcholine from nerves. Similarly, 5-HT may contract or relax smooth muscle directly. For example, 5-HT1B receptors, present on human intestinal muscle cells, mediate contraction of longitudinal muscle [16]. 5-HT1A and 5-HT1D receptors, also present on human

Key words: 5-hydroxytryptamine, motility, serotonin, small intestine.
Abbreviations: 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine; MMC, migrating motor complex.
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intestinal muscle cells, have opposite effects, the former mediating contraction and the latter mediating relaxation of smooth muscle cells [17]. The aim of the present study was to investigate the effect of systematically administered 5-HT on the MMC in healthy humans. Furthermore, we intended to study the concentration–effect relationship for 5-HT by measurements of its plasma levels and to analyse the relationship between plasma 5-HT and the urinary excretion of both 5-HT and its main metabolite, 5-hydroxyindole acetic acid (5-HIAA).

MATERIALS AND METHODS

Twenty-two healthy volunteers, 12 males and 10 females [mean age 28 (range 21–39) years], participated in the study. Two subjects participated in two different experiments, with at least 1 month between the experiments. The study protocol was approved by the Ethics Committee of the Karolinska Hospital, and informed consent was obtained from all volunteers.

Experimental protocol

Experiments were undertaken after an overnight fast during a period of 8 h, with subjects in the recumbent position. Each experiment consisted of two consecutive motility registration periods of 4 h each. The controls (n = 8) received saline (0.9% NaCl) during both 4-h periods for recordings of basal gastrointestinal motor activity. In the experimental groups, saline was given during the first 4-h period and 5-HT at doses of either 15 nmol·min⁻¹·kg⁻¹ (n = 8) or 60 nmol·min⁻¹·kg⁻¹ (n = 8) during the second 4-h period.

Intestinal motility recordings

The motility pattern of the proximal small intestine was monitored by means of a multichannel polyvinylchloride tube (William Cook, Bjaeverskov, Denmark). The tube was 250 cm in length and 4.7 mm in outer diameter, and had six channels 0.7 mm in width ending as side-holes at different levels. The tube had a set of four side-holes 3 cm apart for recordings of duodenal motility, and 10 cm further aborally another two side-holes 10 cm apart for recordings of duodenoejejunal motility. The tube was passed through a nostril. Fluoroscopy was used to position the tube in the small intestine, with the most distal side-hole 10 cm aboral to the angle of Treitz. Each channel was continuously perfused with degassed water from a low-compliance pneumohydraulic system (Armdorfer Medical Specialties, Greendale, WI, U.S.A.). The channels were connected to external pressure transducers (Synectics, Stockholm, Sweden). Digital recordings were attained by connecting the pressure transducers via a PC POLYGRAPH HR (Synectics) to a personal computer (486D/66 MHz, Dell Corporation, Austin, TX, U.S.A.). The software program used was POLYGRAM LOWER GI 6.31C3 (Synectics) with a sampling frequency of 4–16 Hz. The pressure rise velocity upon sudden occlusion of the recording system exceeded 200 mmHg/s in each channel.

Analysis of motility recordings

Recordings were inspected by two independent observers who worked separately and agreed upon the presence or absence of motor patterns. Contractions exceeding a cut-off amplitude of 10 mmHg at the angle of Treitz were included in the analysis. MMCs were identified according to the criteria of Vantrappen et al. [9], i.e.: (a) appearance of uninterrupted bursts of pressure waves with a frequency of 11–12 contractions per min (phase III), (b) aboral migration of phase III activity passing at least the distal two registration points, and (c) a period of complete quiescence after phase III activity. Phase III of MMC (activity front) was defined as the presence of uninterrupted phasic pressure changes for at least 2 min at the maximum frequency for that locus. The duration of phase III at the angle of Treitz was measured from onset of regular contractions to quiescence. The propagation velocity of phase III was calculated by dividing the traversed distance from onset of phase III by the time interval from one registration point to the next. Phase II was defined as having > 2 phasic contractions per min, whereas phase I was defined as < 2 phasic contractions per min.

The fraction of time occupied by either phase I, II or III of the MMC cycle was calculated during the control period and during infusion of either saline or 5-HT. The number of contractions and their amplitude, as well as the overall motility index, during the control and infusion periods were calculated.

Urine samples

Urine was collected during the two infusion periods. One portion was acidified with hydrochloric acid (6 mol/l, 0.1–10 ml of urine). A second portion was frozen without additives. The urine was kept frozen (−20 °C) until analysis.

Blood sampling and cell counts

Blood samples were collected after 2 h in the first 4-h period and after 1 and 3 h in the second 4-h period. Clean venipunctures without stasis were performed using 21 G needles connected to 10 ml vacutainer tubes containing 1.0 ml of a platelet stabilizing solution [final concentrations: 9 mmol/l EDTA, 1 mmol/l theophylline and 0.2 µg/ml Iloprost (Schering AG, Berlin, Germany), a stable prostaclin analogue], as previously described and validated [18]. All samples were immediately centrifuged at 15000 g (4 °C, 30 min). Plasma was carefully removed from the mid-layer and stored at −80 °C for measurements of 5-HT.

Platelet counts in whole blood anticoagulated with EDTA (final concentration 10 mmol/l) were determined by a semi-automated cell counter (Cellanalyzer 460, Medonic AB, Solna, Sweden).
Determinations of 5-HT and 5-HIAA

5-HT in plasma and urine, and 5-HIAA in urine, were analysed by GC-MS as previously described and validated [18,19]. Urine creatinine was measured by the Jaffé reaction using a Hitachi 717 instrument (Boehringer Mannheim GmbH, Mannheim, Germany).

Chemicals

5-HT (serotonin hydrochloride) was purchased from Fluka Chemie AG (Neu-Ulm, Germany). The compound was dissolved and diluted in sterile 0.9% NaCl and the solution was filtered (Millipore-Micropore, pore size 0.22 μm) to sterility by the Karolinska Hospital Pharmacy. Ten-millilitre vials were prepared containing sterile stock solution (100 μmol/ml) and ascorbic acid (17.6 μg) was added as antioxidant.

Vital signs

Measurements of haemodynamic and respiratory parameters started 2 h before commencing 5-HT infusions and continued throughout the experiments. Heart rate, as well as systolic and diastolic blood pressures, was monitored every 15 min, while respiratory frequency and peak expiratory flow were monitored every 30 min.

Statistics

Results are presented as medians and interquartile range, except for haemodynamic data which are presented as mean and 95% confidence interval. Kruskal–Wallis one-way analysis of variance, Mann–Whitney’s U-test or Wilcoxon’s signed-rank test were used where appropriate. P < 0.05 was considered significant.

RESULTS

Baseline motility of small intestine

In control studies with saline, the MMC pattern did not differ between the two recording periods. No changes were observed with regard to either the frequency of phase III of the MMC or the duration, propagation velocity, contraction frequency or motility index of phase III during the two periods (Tables 1 and 2, Figures 1 and 2).

The time fraction of MMC occupied by phase I, II and III did not differ during the two periods (Figure 3).

Effects of 5-HT on motility of small intestine

Infusion of 5-HT increased the number of phase III of MMC in a dose-dependent manner. However, at the dose of 60 nmol·min⁻¹·kg⁻¹ some MMC started in the proximal jejunum instead of in the proximal duodenum (Figure 1 and Table 1).

The interval between phase III decreased dose-dependently during infusion of 5-HT as the number of MMC increased (Figure 2).

The time fraction of MMC occupied by phase I did not change during infusion of 5-HT, whereas phase III increased dose-dependently, and phase II decreased to a corresponding extent during infusion of 5-HT (Figure 3). 5-HT dose-dependently increased the propagation velocity of phase III as well as the amplitude of contractions belonging to phase III. However, the contraction frequency, motility index and duration of phase III did not change during infusion of 5-HT (Table 2).

Effect on vital functions and side effects of 5-HT

Although 5-HT infusion did not influence systolic or diastolic blood pressures at either dose level, an increase in heart rate was observed at the high-dose level from 60.5 (57.5–66.0) beats/min at baseline to a maximum of 72 (72–72) beats/min after 30 min of infusion. Respiratory rate and peak expiratory flow were not altered during infusion of 5-HT at either dose. Platelet counts in peripheral venous blood decreased slightly over time during infusion of both 5-HT and saline.

All subjects receiving 5-HT experienced smarting pain in the arm where the infusion was given. In the group receiving 5-HT at a dose of 60 nmol·min⁻¹·kg⁻¹ abdominal cramps were noted in four subjects, nausea in three, mental discomfort in three and vomiting in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of phase III of the MMC during control period and infusion of 5-HT at different doses respectively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Values are medians and interquartile ranges. *P &lt; 0.05 compared with control period.</td>
</tr>
<tr>
<td></td>
<td>Total no. of phase III</td>
</tr>
<tr>
<td>Control period</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>NaCl</td>
<td>2.0 (2.0–3.5)</td>
</tr>
<tr>
<td>Control period</td>
<td>2.0 (1.0–2.0)</td>
</tr>
<tr>
<td>S-HT, 15 nmol·min⁻¹·kg⁻¹</td>
<td>6.0 (4.0–6.5)*</td>
</tr>
<tr>
<td>Control period</td>
<td>1.5 (0.5–2.0)</td>
</tr>
<tr>
<td>S-HT, 60 nmol·min⁻¹·kg⁻¹</td>
<td>13.5 (9.5–21.5)*</td>
</tr>
</tbody>
</table>
Table 2  Characteristics of phase III of the MMC during control period and infusion of 5-HT at different doses respectively

<table>
<thead>
<tr>
<th></th>
<th>Duration (min)</th>
<th>Velocity (cm/min)</th>
<th>Contraction frequency/min</th>
<th>Amplitude (mmHg)</th>
<th>Motility index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control period</td>
<td>5.5 (4.7–6.6)</td>
<td>10.1 (6.7–14.1)</td>
<td>11.7 (11.5–12.0)</td>
<td>22.3 (19.6–26.6)</td>
<td>6.8 (6.4–6.9)</td>
</tr>
<tr>
<td>NaCl</td>
<td>5.2 (3.9–7.2)</td>
<td>9.1 (5.8–19.9)</td>
<td>11.6 (11.0–11.9)</td>
<td>24.4 (21.8–32.8)</td>
<td>6.8 (6.6–7.0)</td>
</tr>
<tr>
<td>Control period</td>
<td>6.6 (5.4–7.1)</td>
<td>12.0 (8.0–19.8)</td>
<td>11.8 (11.6–12.1)</td>
<td>23.8 (19.6–29.8)</td>
<td>6.7 (6.3–7.2)</td>
</tr>
<tr>
<td>5-HT, 15 nmol·min⁻¹·kg⁻¹</td>
<td>4.6 (3.2–7.1)</td>
<td>18.5 (12.3–33.3)</td>
<td>11.5 (11.2–11.8)</td>
<td>27.3 (24.1–33.8)</td>
<td>7.1 (6.8–7.2)</td>
</tr>
<tr>
<td>Control period</td>
<td>6.2 (4.4–7.1)</td>
<td>15.8 (13.9–21.3)</td>
<td>12.0 (11.7–18.7)</td>
<td>22.5 (19.9–35.4)</td>
<td>6.7 (6.6–7.2)</td>
</tr>
<tr>
<td>5-HT, 60 nmol·min⁻¹·kg⁻¹</td>
<td>3.6 (2.5–5.2)</td>
<td>28.8 (12.0–50.0)</td>
<td>11.4 (11.1–11.8)</td>
<td>26.6 (21.7–36.2)</td>
<td>7.1 (6.7–7.5)</td>
</tr>
</tbody>
</table>

One. In the group receiving 5-HT at a dose of 15 nmol·min⁻¹·kg⁻¹ nausea and vomiting were noted in one test subject only.

Plasma concentration of 5-HT

Data from several experiments were omitted due to technically inadequate sampling, as this causes artifactual elevation of 5-HT in plasma [19]. In five subjects receiving saline plasma 5-HT levels were stable around 1.5–2 nmol/l. During infusion of 5-HT, the plasma concentrations of 5-HT appeared to increase dose-dependently, but the number of observations were few. When pooled, the plasma concentrations of 5-HT increased significantly during infusion of 5-HT (Table 3). A strong correlation between the plasma
Serotonin and the migrating motor complex

Figure 2 Interval between activity fronts (phase III of the MMC) during infusion of saline or 5-HT

Infusion of 5-HT dose-dependently decreased the interval between the activity fronts. *P < 0.05 compared with the control group (NaCl). **P < 0.05 compared with the control period (NaCl).

The urinary excretions of 5-HT and 5-HIAA did not change during infusion of saline, but both parameters increased dose-dependently during infusion of 5-HT (Table 4).

DISCUSSION

The present study shows that the interdigestive rhythm of the small intestine in man is dose-dependently stimulated by circulating 5-HT, as verified by an increased number of phase III of MMC, and an increased propagation velocity and amplitude of contractions during phase III. The effect was shown to positively correlate to the plasma concentration of 5-HT. The present results confirm and extend our previous findings with bolus injections of 5-HT [14] and studies in which 5-HT has been shown to stimulate the contractile activity of the small intestine in man [8].

The phase III activity induced by 5-HT in this study meets all the criteria of phase III postulated by Vantrappen et al. [9], namely contraction frequency, aboral migration of phase III activity passing at least the distal two registration points, and a period of complete quiescence after phase III activity.

The 5-HT-induced phase III activity originated in the small intestine. This is in accordance with the effects of sumatriptan, a 5-HT1 receptor agonist, which induces premature intestinal phase III activity and increases the proportion of phase III originating in the jejunum instead of in the stomach [20]. Both 5-HT (present data) and sumatriptan [20] increase the fraction of time occupied by phase III at the expense of phase II. Furthermore, treatment with the selective 5-HT uptake inhibitor, paroxetine, enhances intestinal motility in humans [13]. Thus, the present data are supported by pharmacological data indicating that 5-HT is involved in the initiation and control of MMC in humans.

A role for 5-HT in the regulation of MMC has also been proposed in other species such as pigs, opossums, rats and guinea pigs. 5-HT has been shown to increase both the cycling frequency and propagation velocity of MMC in pigs [21] and opossums [22]. Animal studies have also shown that the MMC cycling frequency is...
Table 3 Plasma concentration (nmol/l) of S-HT during infusion of S-HT at different doses and during control conditions

<table>
<thead>
<tr>
<th>Group</th>
<th>Control period</th>
<th>Infusion of S-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 h</td>
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<tr>
<td>Control group</td>
<td>1.9 (0.6-8.7)</td>
<td>2.0 (1.8-3.1)</td>
</tr>
<tr>
<td>S-HT, 15 nmol·min⁻¹·kg⁻¹</td>
<td>1.7 (1.2-3.8)</td>
<td>8.7 (7.2-13.0)*</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-HT, 60 nmol·min⁻¹·kg⁻¹</td>
<td>2.2 (2.0-5.1)</td>
<td>24.4 (21.8-26.9)*</td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-HT, all subjects</td>
<td>2.1 (1.6-3.8)</td>
<td>18.4 (8.4-23.4)*</td>
</tr>
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<td>(n = 9)</td>
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</table>

Table 4 Urinary excretion of S-HT (nmol/mmol creatinine) and S-HIAA (μmol/mmol creatinine) during infusion of S-HT at different doses and during control conditions

<table>
<thead>
<tr>
<th>Group</th>
<th>S-HT</th>
<th>S-HIAA</th>
<th>S-HT</th>
<th>S-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control period</td>
<td>Infusion of S-HT</td>
<td>Control period</td>
<td>Infusion of S-HT</td>
</tr>
<tr>
<td>Control group</td>
<td>52 (39-60)</td>
<td>1.3 (0.6-2.6)</td>
<td>45 (43-66)</td>
<td>1.0 (1.0-1.7)</td>
</tr>
<tr>
<td>(n = 7)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>S-HT, 15 nmol·min⁻¹·kg⁻¹</td>
<td>59 (43-62)</td>
<td>1.2 (1.0-1.6)</td>
<td>108 (85-121)*</td>
<td>36.6 (34.7-43.6)*</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-HT, 60 nmol·min⁻¹·kg⁻¹</td>
<td>57 (36-62)</td>
<td>1.4 (1.1-1.6)</td>
<td>331 (228-953)**</td>
<td>106.9 (14.4-134.7)**</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
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</tbody>
</table>

Figure 4 Relationship between the plasma concentration of S-HT and the number of MMC induced by infusion of S-HT

The number of MMC increases with increasing plasma concentration of S-HT. N = 13, r² = 0.79, P = 0.0003 (Spearman correlation test).

increased by the S-HT precursor 5-hydroxytryptophan [23], and decreased by neuronal depletion of S-HT [24], or by selective destruction of S-HT neurons in the myenteric plexus using 5,6- and 5,7-dihydroxytryptamine [25].

The net effect of S-HT on small intestinal motility is a stimulatory one, but we can only speculate on the S-HT receptor subtypes involved. As noted above, S-HT₁-receptor stimulation by sumatriptan induces premature intestinal phase III in humans [20]. Stimulation of S-HT₄ receptors contracts human small intestinal muscle cell strips [16], but possible influences on the basal interdigestive rhythm are not known. Blockade of S-HT₅ receptors by ondansetron does not influence duodeno-jejunal phase III activity [26], and the role of S-HT₄ receptors in the modulation of small bowel motility in humans has not been studied, as potent and selective S-HT₄ antagonists are not available for clinical use. Animal studies with different S-HT₄ receptor agonists have given conflicting results regarding the role of S-HT₄ receptors in the generation of propagated motor activity. In dogs, renzapride, a S-HT₄-receptor agonist, induces phase III-like activity in the small bowel [27], while cisapride, also a S-HT₄-receptor agonist, given orally or parenterally to healthy volunteers, did not induce phase III activity or increase its propagation velocity [28,29]. Possible explanations for the disparate results obtained in dogs and man are species differences as well as differences between the two compounds renzapride and cisapride.

Thus, the available evidence suggests that stimulation of S-HT₁ receptors on myenteric cells changes the basal rhythm, i.e. increases the number of phase III and their propagation velocity, and that stimulation of
5-HT<sub>3</sub> receptors on smooth muscle cells may increase their contractile force.

The plasma concentration of 5-HT, as well as the urinary excretion of 5-HT and 5-HIAA, increased dose-dependently during infusion of 5-HT. The plasma concentration of 5-HT, however, increased by less than expected with the doses given, indicating a very rapid clearance from plasma. Pharmacokinetic parameters for 5-HT were not calculated in the present study, but a comparison with the turnover of other biogenic amines, such as catecholamines, is relevant. Thus infusion of noradrenaline, which has a half-life of approximately 1 min in plasma, elevated arterial plasma noradrenaline levels almost 20-fold, from basal levels of approximately 1 nmol/l, at an infusion rate of 0.5 nmol·min<sup>-1</sup>·kg<sup>-1</sup> [5]. In the present study, 5-HT infusion at the rate of 60 nmol·min<sup>-1</sup>·kg<sup>-1</sup>, i.e. 120 times higher than the dose of noradrenaline used by Hjemdahl and Linde [5], elevated venous plasma 5-HT only 10-fold, demonstrating a still more rapid turnover of 5-HT in plasma. Early animal studies indicated an extremely short half-life for 5-HT in plasma [6,30], and our present data are compatible with these observations.

It can be speculated that 5-HT is rapidly cleared from plasma via uptake by platelets and endothelial cells together with extensive metabolism in the liver and lungs. The rapid clearance of 5-HT from plasma suggests that 5-HT exerts its stimulatory action locally, after release from enteric neurons, enterochromaffin cells or platelets.

In the present study 5-HT, at doses resulting in a 5- to 12-fold increase of the plasma concentration of 5-HT, stimulated the motility of the small intestine and caused abdominal symptoms. In this connection, a comparison can be made to the carcinoid syndrome which is characterized by attacks of, among other things, cutaneous flushing and diarrhoea. The diarrhoea can be explained by either intestinal hypersecretion or intestinal hypermotility, or both. In a study by Ahlman et al. [31], attacks of carcinoid syndrome were provoked by intravenous pentagastrin. They found an increase in the whole-blood concentration of 5-HT accompanied by cutaneous flushing and abdominal symptoms such as borborygmi, urgency and colicky cramps. The abdominal symptoms were prevented or relieved by pretreatment with the 5-HT<sub>3</sub>-receptor antagonist ketanserin. Against this background, our findings indicate that 5-HT is involved in the pathophysiology of diarrhoea in the carcinoid syndrome in part by stimulating motility of the small intestine.

5-HIAA is normally the predominant metabolite of 5-HT [32]. It has been shown that over 90% of total body 5-HT turnover is reflected by the urinary excretion of 5-HIAA [33]. In the present study, the urinary excretion of 5-HT increased approximately 6-fold while the urinary excretion of 5-HIAA increased 75-fold during infusion of 5-HT at the highest dose level.

The side effects of 5-HT in our study differ somewhat from earlier human studies. In the study by Hendrix et al. [8], intravenous bolus injections of 5-HT, at doses approximately three times higher than in our study, caused a transitory burning sensation in the throat, tongue, lips and cheeks together with transient tachypnoea and occasionally difficulties in breathing. A possible explanation for the difference in side effects is the doses used and the mode of administration of 5-HT. A higher dose and a rapid injection should result in higher peak concentrations in plasma and a greater risk of side effects.

Our finding that 5-HT increases heart rate is in accordance with the demonstration of 5-HT<sub>3</sub> receptors in the human right atrium, mediating positive inotropic and chronotropic effects [34].

In conclusion, this study shows that 5-HT infusion stimulates the fasting motility with more frequent and rapidly propagating phase III of MMC. It is therefore suggested that 5-HT released locally, from neurons or enterochromaffin cells, may participate in the control of small intestinal interdigestive motility.

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