Effect of Serotonin on Small Intestinal Contractility

In Healthy Volunteers

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Part of the data has been presented at meetings and published in connection with these as abstracts in Neurogastroenterol & Motility, 15 (5), 581, 2003 and in Acta Physiol Scand, 181 (1), 1-163, 2004.

Short title: Serotonin and intestinal contractility

Key words

Blood levels, human, intestines, motility, 5-hydroxytryptamine, migrating motor complex, physiology, and serotonin.

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Summary

The physiological significance of serotonin released into the intestinal lumen for the regulation of motility is unknown in humans. The aim of this study was to evaluate the effect of serotonin infused into the lumen of the gastric antrum, duodenum or the jejunum, on antro-duodeno-jejunal contractility in healthy human volunteers. Manometric recordings were obtained and the effects of either a standard meal, continuous intravenous infusion of serotonin (20 nmol/kg/min) or intraluminal bolus infusions of graded doses of serotonin (2.5, 25 or 250 nmol) were compared. In addition platelet-depleted plasma levels of serotonin, blood pressure, heart rate and electrocardiogram were evaluated. All subjects showed similar results. Intravenous serotonin increased migrating motor complex phase III frequency 3-fold and migrating velocity 2-fold. Intraluminal infusion of serotonin did not change contractile activity. Platelet-depleted-plasma levels of serotonin increased 2-fold following both intravenous and high doses of intraluminal infusions of serotonin. All subjects reported minor short-lived adverse effects following intravenous serotonin stimulation, while only half of the subjects reported minor short-lived adverse effects following intraluminal serotonin stimulations. We conclude that exogenous serotonin in the lumen of the upper part of the small intestine does not seem to change antro-duodeno-jejunal contractility significantly in healthy adult volunteers.

Introduction

Large amounts of serotonin (5-hydroxytryptamine, 5-HT) are contained within the intestines, in particular in the duodenum and rectum (Ahlman & Nilsson 2001). 5-HT is a paracrine neuro-endocrine transmitter released to a wide range of stimuli in health and in various disease states (Gershon, 2002).

5-HT is released in both fasting and post-prandial conditions from sensory cells of the intestinal mucosal lining by several mechanisms (mechanical, chemical, and osmotic) (Kellum & Jaffe 1976; Bertrand 2004**)**. 5-HT is released intramurally and intraluminally (Gershon 2002; Gronstad et al 1987; Gronstad et al 1986; Kojima et al 1999; Tanaka et al 2004), and studies in dogs indicate a role for intraluminal (IL) 5-HT for intestinal contraction (Kellum et al 1986**)**. However the effect of IL 5-HT on intestinal contraction in humans is unknown.

Once released, 5-HT plays a critical physiological role by preparing the intestines for optimal handling of food and pathogenic substances by activating 5-HT receptors on various types of cells including neurones in the enteric nervous system, epithelial cells and smooth muscle cells, causing local hyperaemia, secretion for absorptive and digestive purposes, and motility (Gronstad et al 1986; Hansen 2003; Hansen et al 1998; Hansen & Skadhauge 1997). Furthermore, abnormal levels of 5-HT in the circulating blood plasma and in intestinal tissues preparations have been associated with diarrhoea, dysmotility, and inflammation. Hence 5-HT is also believed to play a significant pathophysiological role in some of the functional gastrointestinal disorders (Gershon 2003).

The intestines are quantitatively the most important sites for 5-HT synthesis. Mucosal enterochromaffin (EC) cells are the dominating storage site for 5-HT and are believed to act as mechanosensory elements, which subsequently activate intrinsic sensory neurones that initiate the peristaltic reflex by releasing 5-HT (Hansen 2003). 5-HT is released into the lumen as well as into the portal circulation via exocytose and the release is regulated by a complex pattern of neuronal and endocrine inputs (Racke et al 1996). Once released, 5-HT activates at least 5-HT_3, 5-HT_4, and

5-HT_7 receptors located on neuronal and muscular structures in the gut wall, for the control of small intestinal motor activity (Hansen 2003; Tonini 2005).

Small intestinal contractility can be subdivided into fasting and post-prandial periods. The post-prandial period is initiated by the intake of a caloric meal and by definition terminates by the recurrence of phase III of the migrating motor complex (MMC). The MMC cleanse the small intestine and has as such been termed the "gut housekeeper". One MMC period (cycle) comprises phases I, II and III of which phase III is the most distinctive and easily recognized. The phase III of MMC is characterized by frequency, migration (propagation) velocity, and duration (Hansen 2002). Initiation of these organized complexes involves an intricate interaction of the extrinsic (vagal) and intrinsic primary afferent innervation and the endocrine factors (Hansen 2002; Hansen 2003). Increase in circulating blood levels of 5-HT increases phase III frequency and migration velocity in healthy humans (Lordal & Hellstrom 1995; Lordal et al 1998), while the effect of increased levels of IL 5-HT remains to be determined.

The primary aim of the study was to investigate how exogenous IL 5-HT affects small intestinal contractility in healthy humans. We used antro-duodeno-jejunal manometry to assess this.

Material and methods

Subjects

Four healthy volunteers participated in the study (table 1). Due to the potential risk by infusion of serotonin and since all the studied subjects experienced adverse effects and showed similar patterns of manometric and other responses, we did not include more than 4 subjects. The fertile female subject was examined in the luteal phase of her menstrual cycle. No subjects were taking any kind of medication and none reported symptoms or a history of gastrointestinal or cardiovascular disease. All subjects drank below the recommended safe alcohol limit (<14 and 21 units/week for females and males, respectively) and did not smoke on a daily basis. Intake of acetaminophen, tryptophan-rich foods (e.g. invertebrate, banana, kiwi fruit, chocolate, tomato, and nuts) and cigarette smoking, all of which might influence 5-HT body content, was prohibited 24 hours prior to examinations. Subjects had a normal clinical examination, body mass index (less than 30), electrocardiogram, and haemodynamic parameters (blood pressure and heart rate) prior to examinations. None of the subjects had participated in a clinical trial of any drug within the previous month.

Ethics

The subjects gave written informed consent for participation in this study, which was approved by the Research Ethics Committee of Copenhagen (KA 97170) and The Danish Medicines Agency (2612-1501). Subjects received a minor financial compensation for participation.

Protocol

Each subject was examined in the morning on three separate days (day 1-3) after fasting overnight. The manometry catheter was placed (see details below) and veins on both arms were cannulated: one for infusion and the other for obtaining blood samples. The recordings started (time = 0 min) with the subjects at rest in the supine position. During all examinations the subjects received intravenous saline 0.9% (1 ml/min). Subjects were initially examined for a basal resting period of

180 min in the fasting condition. Due to the recognized inter-individual (but not intra-individual) variability in the cyclic pattern of contractile activity of the small intestine (Hansen 2002), the fasting period for each subject served as its own control to the subsequent meal or 5-HT stimulation. All examinations ended after 300 min.

On **day 1**, meal stimulation was performed at time = 180 min with the intake of a mixed liquid meal (Nutridrink®, 25 ^{0}C, 4 ml/kg=630 kJ/kg, 390 mOsm/l, composed as a % of energy: proteins 13%, carbohydrates 48% and fat 39%, multiple vitamins and minerals, and kindly donated by Nutricia A/S, DK).

On **day 2**, intravenous **(IV)** 5-HT stimulation was performed at time = 180 min with continuous infusion for 60 minutes of 5-HT (5-hydroxytryptamine creatinine sulphate, 20 nmol/kg/min, purchased at Sigma Chemicals, DK, and prepared for infusion at Herlev University Hospital Pharmacy of Copenhagen, DK). The dose of 5-HT was selected based on pilot studies. Higher doses than 20 nmol/kg/min 5-HT was unacceptable due to high incidence of severe adverse effects (e.g. heat of the head, redness, burning, tenderness, strong heart beat, and heat sensation).

*On **day 3**,* intraluminal **(IL)** 5-HT stimulation was performed. Bolus infusions (16 in total, with 15 min intervals) were started at time = 60 min. Bolus infusions consisted of 10 ml saline 0.9% alone (4 in total) or 10 ml saline 0.9% containing increasing graded doses of 5-HT (5-hydroxytryptamine creatinine sulphate, 2.5, 5 and 250 nmol, purchased at Sigma Chemicals, DK, and prepared for infusion in our laboratory) (12 in total) (see tables 2 and 3). The dose of 5-HT was selected based on reports from the literature (Kellum et al 1976; Gronstad et al 1986; Gronstad et al 1987; Hansen & Jaffe 1994; Zhu et al 2001; Ferrara et al 1986; Tanaka et al 2004). The bolus infusions were given subsequently, first in channel 7 (J3), which was the channel with the most aborally located sensors/side holes in the jejunum, subsequently in channel 5 (J1), in channel 3 (D1) and finally in channel 1 (A1) located in the antrum of the stomach (see table 2 and fig.). Bolus infusions of saline alone were followed by bolus infusions of saline added accumulating graded doses of 5-HT (fig.).

Venous blood samples were obtained for measurement of 5-HT levels. Blood samples were collected at the end of the fasting period in all examinations on day 2 and day 3 (time = 170 min), at the end of the period with **IV** infusion of 5-HT (time = 240 min) on day 2, and at the end of the periods with **IL** infusion of 25 nmol 5-HT (time = 240 min) and 250 nmol 5-HT (time = 300 min) on day 3.

Blood pressure, heart rate and electrocardiogram were monitored every 15 min throughout all examinations. Symptoms reported by the subjects during the examinations were recorded. The subject was blinded to what was infused on day 3 (**IL** 5-HT stimulation), but it was not possible to blind the subject during examinations on day 1 (meal stimulation) or day 2 (**IV** 5-HT stimulation).

Manometric recordings

The contractility pattern was monitored by manometry. A 250 cm long and 7-channel (lumen/sensor) polyvinyl catheter was introduced via the nose and fluoroscopy was used to position the catheter in such a way that two channels with side holes were located in the antrum of the stomach (A1 and A2), two in the duodenum (D1 and D2) and the three remaining in the jejunum (J1, J2 and J3) (table 2). Each channel was connected to an external pressure transducer and a low-compliance pneumohydraulic water-perfused system. Pressure transducers were coupled to an AD-converter and a computer for data sampling and analysis (GMC Aps, Denmark). The channels and side-holes served as the route for IL bolus infusions of saline and 5-HT.

Analysis of manometry recordings

Two blinded observers, who worked together and agreed upon the presence or the absence of specific motor patterns, evaluated the manometric recordings. They analysed visually the start and the end of phase III of the MMC. Phase III was identified according to the criteria of Vantrappen and co-workers (Vantrappen et al 1977)**:** (a) appearance of uninterrupted bursts of rhythmic pressure waves with a frequency of 11-12 contractions per min and lasting for at least 2 min in each

segment, (b) aboral migration of activity passing at least the distal two registration points (3 recording sites in total), and (c) a period of complete quiescence after phase III activity. Antral phase III had to be followed by duodenal phase III and the site of origin of each phase III was noted. Total MMC cycle length was calculated from the end of phase III to the end of the next phase III. Pressure wave frequency and amplitude were calculated for 10-min periods, from 10 min before infusion until 30 min after the start of infusion. Phase III propagation in each segment (duodenum and jejunum) was calculated form the start of phase III. The time-interval between the start of saline/5-HT infusion to the appearance of phase III was calculated for each segment separately. The second antral (A2), second duodenal (D2) and third jejunal channel (J3) was used to describe the MMC and pressure wave characteristics.

Analysis of 5-HT levels

Two and a half ml venous blood samples were collected into a cold (2-8^0 C) polystyrene tube containing sodium EDTA (5 mmol/l), mixed gently by inversion and immediately cooled on ice. Within 10 min, samples were centrifuged at 4000 rpm/1700 g for 30 min at 4^0 C. The upper two-thirds of the platelet-depleted plasma (PDP) was transferred to polystyrene tubes and stored at –20^0 C. 5-HT levels in PDP samples were measured using an enzyme immunoassay (Immunotech, Marseille, France).

Data and statistical analysis

Data are expressed as means ± standard deviation (SD) or medians (range). Effects of 5-HT on phase III characteristics, PDP levels of 5-HT, and haemodynamics were examined. Statistical analysis was done with the SigmaStat 3.2. package (SPSS Incl., Chicago, IL, USA). The statistical significance was evaluated using Wilcoxon's test for paired data of two groups, Mann-Whitney test for unpaired data of two groups, and analysis of variance (ANOVA) for comparison of more than two groups. Differences resulting in a p value less than 0.05 were regarded statistically significant.

Results

Manometric recordings during fasting conditions and under meal stimulation

All subjects demonstrated normal fasting patterns in all examinations (see table 3). Phase III characteristics varied somewhat between subjects and almost all phase IIIs originated in the duodenum and migrated all to the jejunum. All subject demonstrated normal post-prandial patterns (data not shown) and the MMC returned within 180 min.

5-HT stimulation

All subjects responded with an increase in phase III occurrence frequency and migration velocity within 10 min following stimulation with **IV** 5-HT (see table 3). IV 5-HT did not change however the duration of phase III's. **IL** infusion of 5-HT did not change any of the phase III characteristics (see table 3). Specifically, the frequency (and the interval time between phase IIIs), migration velocity and duration of phase III's did not change. There was no change in the contraction pattern of phase I and phase II and the amplitude of contractions in phase I, phase II and phase III was within normal values and did not change during examinations (data not shown).

Platelet-depleted-plasma levels of 5-HT

Intravenous 5-HT stimulation

The PDP levels of 5-HT in the fasting period (time = 170 min) varied considerably between subjects but increased significantly from 40±22 to 81±35 nmol/l (p=0.032) following IV infusion of 5-HT (time = 240 min).

Intraluminal 5-HT stimulation

The PDP levels of 5-HT in the fasting period (time = 60 min) varied considerably between subjects (72 ± 76 nmol/l). The PDP levels were unchanged (61 ± 56 nmol/l) at the end of the stimulation period with bolus infusions of saline alone (time = 120 min). Nor did the PDP levels change at the end of periods with infusions of 25 nmol 5-HT (32 ± 18 nmol/l, time = 240 min). However, PDP-levels of 5-HT increased significantly to 67±18 nmol/l (p=0.035) following periods with infusion of 250 nmol 5-HT (time = 300 min).

Haemodynamic parameters

Meal stimulation

The haemodynamic parameters were within normal values in the fasting period (systolic blood pressure, 126 ± 6 mmHg; diastolic blood pressure, 76 ± 8 mmHg; and heart rate, 62 ± 14 beats/min). No significant changes in blood pressure, heart rate or electrocardiography were observed following meal stimulation (data not shown).

Intravenous 5-HT stimulation

The haemodynamic parameters were within normal values in the fasting period. During stimulation with **IV** 5-HT, there was a trend but no statistically significant change in blood pressure, heart rate (see table 4) or electrocardiography (data not shown).

Intraluminal 5-HT stimulation

The haemodynamic parameters were within normal values in the fasting condition. During stimulation with **IL** 5-HT, there was no statistically significant change in blood pressure, heart rate (see table5) or electrocardiography (data not shown).

Adverse effects

Meal stimulation

No adverse effects were reported during fasting or following meal stimulation.

Intravenous 5-HT stimulation

During periods with **IV** infusion of 5-HT, all the subjects reported one or more of the following symptoms: tenderness (3 subjects), heat sensation (3 subjects), redness (1 subject), and burning sensation (1 subject) in the infused arm, sensation of strong heartbeat (1 subject) and heat of the head (1 subject). All symptoms disappeared completely within 10 min after ending 5-HT infusion. None of the subjects wanted to stop the examination and none of subjects has reported late adverse effects.

Intraluminal 5-HT stimulation

During periods with **IL** infusion of 250 nmol 5-HT, 2 of the 4 subjects reported one or more of the following symptoms: tenderness (2 subjects), heat sensation (2 subjects), sensation of strong heartbeat (1 subject) and heat of the head (1 subject). Adverse effects were not observed following infusion of 2.5 nmol and 25 nmol doses of 5-HT. All symptoms disappeared completely within 10 min after ending 5-HT infusion. None of the subjects asked to stop the examination and none of subjects has reported late adverse effects.

Discussion

A distinctive feature of physiological regulation of the intestines is that stimuli of hormonal release and neural activation arise within the lumen from the mechanical and chemical properties of food and digestive secretions. One of these neuro-endocrine substances is 5-HT and data suggest a pivotal role for 5-HT in modulating intestinal functions including secretions, blood flow and peristaltic motor activity (Hansen 2003; Hansen et al 1998; Hansen & Skadhauge 1997; Ormsbee et al 1984). Furthermore change in 5-HT metabolism has been demonstrated in some disorders of intestinal function. Consequently there is a rationale for using serotonergic agents for treatment of functional gastrointestinal disorders such as irritable bowel syndrome (Baker 2005; Kilkens et al 2004).

When exogenous 5-HT is applied into the intestinal lumen in doses comparable to those released by physiological stimuli (0.016 mg/ml, about 40 nmol/ml), a localized vasodilatation occurs in the intestinal mucosal and submucosal layers (Gronstad et al 1986; Hansen et al 1998). Exogenous 5-HT also stimulates intestinal secretions. However, it acts with less potency when exposed to luminale side as compared to the serosal side of the epithelia (Hansen & Skadhauge 1997). Hence we hypothesized that both IV and IL stimulation with 5-HT would have similar effects on intestinal contractility but with different potencies.

The present study suggests that selective local increase in IL levels of 5-HT, in contrary to circulating (i.e. IV) plasma levels, does not alter small intestinal contractility significantly in healthy volunteers. In the following the results from our study is discussed with relation to related findings reported in the literature and keeping in mind the small number of subjects studied and the associated potential risk of misinterpretations due to type II statistical error.

Manometric recordings

In this study we used manometry to assess small intestinal contractility. Manometry provides detailed information on the functional neuromuscular integrity and myopathy and neuropathy can

be diagnosed accordingly (Hansen 2002). However, manometry does allow us to identify the underlying specific disease in case of neuromuscular dysfunction. Accordingly small intestinal motility can be impaired as a consequence of disease processes (e.g. some inflammatory, connective tissue and vascular diseases) that primarily do not affect neuromuscular function (Husebye et al 1999).

All subjects in this study demonstrated normal fasting and post-prandial patterns of contractility with the expected biological variations in phase III characteristic (Hansen 2003). Hence all subjects were considered to be healthy with respect to the intestinal neuromuscular function and continued to examinations with 5-HT stimulation.

Serotonin and the migrating motor complex

Ormsbee and co-workers presented the evidence for a role of endogenous 5-HT in the regulation of the MMC (Ormsbee et al 1984). Depleting the endogenous 5-HT stores in dogs reduced the phase III activity. Other animal studies have supported these findings: the MMC cycling frequency is increased following inhibition of 5-HT reuptake mechanisms (Gorard et al 1994) and following supplementing the diet with the 5-HT precursor 5-hydroxytryptophan, whereas selective destruction of 5-HT neurones in the myenteric plexus results in a decrease in MMC cycling frequency (Sagrada et al 1990). Furthermore the concentrations of circulating and luminale 5-HT have been demonstrated to cycle in close temporal association with the MMC in dogs (Haga et al 1996; Tanaka et al 2004) with peak concentrations at the end of phase II (Tanaka et al 2004).

All subjects responded to stimulation with IV 5-HT with an increase in phase III frequency and migration velocity. This is consistent with previous studies in dogs (Ormsbee et al 1984) and humans (Lordal et al 1998). IL infusions of 5-HT did not change any of the phase III characteristics. These results are consistent with studies in dogs, where the release of 5-HT in Thiery-Vella loops or intraduodenal infusion of low doses of 5-HT (20-400 ng/min, about 0.05-1 nmol/min) did not change the MMC characteristics (Ferrara et al 1986; Tanaka et al 2004).

We do not know why stimulation with the highest dose of IL 5-HT did not induce similar manometric changes as IV 5-HT despite PDP 5-HT levels increased to similar levels as those following IV 5-HT. As intrinsic primary neuronal activity is only altered by mucosal and luminal stimulators (mechanical, chemical, etc.), but not by circulating substances, we speculate that IL 5-HT induces compensatory mechanisms by which the contracting effects of circulating 5-HT is counteracted (Hansen 2003).

Platelet-depleted-plasma levels of 5-HT

Only PDP concentrations of 5-HT were measured as PDP levels more accurately reflect acute changes whereas those in platelet-rich-plasma and platelets alone are more indicative of any change over time (Houghton et al 2003).

As expected the PDP levels of 5-HT varied significantly between subjects during both fasting and post-stimulatory conditions. PDP levels of 5-HT double following meal stimulation (Hansen et al 2006), following stimulation with IV 5-HT and high doses of IL 5-HT but not following stimulation with low doses of IL 5-HT (this study). Inactivation of 5-HT is accomplished by reuptake of the amine by mucosal EC cells, mast cells, epithelial cells, neurones and platelets, and by enzymatic degradation by monoamine oxidase in the liver and lungs. This is followed by excretion in the urine as the main metabolite, 5-hydroxyindole-3-acetic acid (Wade et al 1996). We speculate that the differences in PDP levels of 5-HT following stimulation with low doses of IL 5-

HT as compared to the high dose of IL 5-HT and IV 5-HT were due to saturation of the elimination capacity.

Haemodynamic parameters

In healthy humans intravenous infusion of 60 nmol/min/kg, but not 15 nmol/min/kg, of 5-HT over 30 min has been reported to cause positive inotropic but no chronotropic cardiac effect (Lordal et al 1998). In animals sustained high blood levels of 5-HT, cause positive inotropic, chronotropic and proarrhythmic effects (Kaumann 1991; Zinner et al 1983). In particular prolongation of the QT-segment is potentially lethal and the reason for why some 5-HT_4 receptor agonists never will be used in clinics. Despite significant increases in PDP levels of 5-HT in our study neither IV, nor IL 5-HT stimulation changed the haemodynamic parameters statistically significant. Stimulations with 5-HT were also devoid of arrhythmic side effects. Thus our results are consistent with previous reports and together they suggest that IV doses of 5-HT higher than 20 nmol/kg/min are needed in order to cause significant inotropic effects and even higher doses are needed in order to cause chronotropic and proarrhytmic effects in healthy humans.

Adverse effects

The incidence of adverse effects seemed to correspond well with PDP levels. However, the profile of adverse effects was different from another similar study, where subjects received up to 60 nmol/min/kg of IV 5-HT in a stepwise design (Lordal et al 1998). In specific and to our surprise none of the subjects in our study complained about nausea, vomiting, mental discomfort or abdominal cramps, which could result from increased intestinal contractility and phase III activity. Another unanswered question is why not all of the subject's experienced adverse effects following IL infusion of the highest dose of 5-HT, although PDP levels increased to similar levels as following IV infusion of 5-HT. We speculate that increasing the infused doses of 5-HT in a

stepwise manner alters receptor sensitivity to 5-HT on neuronal structures in the peripheral and central nervous system and thereby changes the experience of adverse effects.

Conclusion

The present study suggest that exogenous intraluminal 5-HT, in contrast to exogenous intravenous 5-HT, does not affect contractility of the small intestine in healthy humans.

Acknowledgements

This work was kindly supported by Sofus Carl Emil Friis and his wife Olga Friis Foundation, The Carlsberg Foundation, The Enid Ingemann Foundation, Else and Mogens Wedell-Wedellsborg Foundation, Dagmar Marshall Foundation, The Lundbeck Foundation, The Novo Nordisk Foundation, C.C. Klestrup and his wife Henriette Klestrup Foundation, The Danish Medical Association Research Foundation, The Danish Hospital Foundation for Medical Research in Region of Copenhagen, The Faeroe Islands and Greenland, and The Gangsted Foundation. We thank Lene Appelt and Trine Schnoor for their assistance with experiments.

Figure

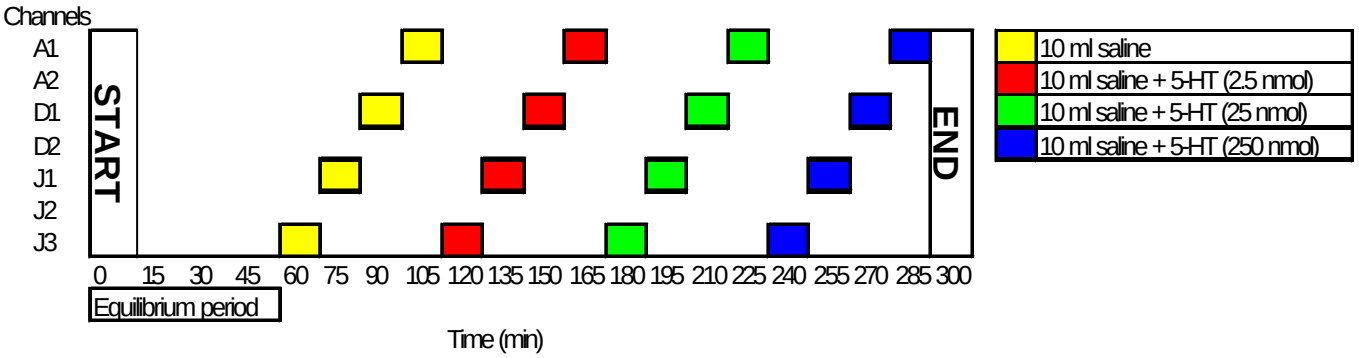
Channels
A1
A2
D1
D2
J1
J2
J3
START
END
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240 255 270 285 300
Equilibrium period
Time (min)
10 ml saline
10 ml saline + 5-HT (2.5 nmol)
10 ml saline + 5-HT (25 nmol)
10 ml saline + 5-HT (250 nmol)

Table 1

	Subjects			
	AB	LZ	MM	VA
Age (years)	24	23	57	51
Gender	M	F	M	F
BMI	23	26	27	28

Table 2

Channel	A1	A2	D1	D2	J1	J2	J3	
Start	Stomach	Stomach	Duodenum	Duodenum	Jejunum	Jejunum	Jejunum	**End**
0 cm	180 cm	185 cm	195 cm	205 cm	225 cm	235 cm	245 cm	250 cm

Table 3

Characteristics of phase III	Fasting	**IV** 5-HT	**IL** 5-HT
Frequency (number/hr)	0.2 (0-1)	**3.3 (2-5)***	0.2 (0-1)
Migration velocity (cm/min)	10.2 ± 9.1	**20.3 ± 7.4****	7.4 ± 2.3
Duration (min)	8.3 ± 2.2	7.1 ± 4.4	8.3 ± 4.1

Table 4

Haemodynamics following IV 5-HT	Saline	Saline + 5-HT
Systolic blood pressure (mmHg)	116 ± 6	119 ± 20 (p=0.80)
Diastolic blood pressure (mmHg)	68 ± 9	79 ± 16 (p=0.45)
Heart rate (beats per minute)	57 ± 9	64 ± 18 (p=0.66)

Table 5

Haemodynamics following IL 5-HT	Saline	Saline + 5-HT 2.5 nmol	Saline + 5-HT 25 nmol	Saline + 5-HT 250 nmol
Systolic blood pressure (mmHg)	128 ± 5	129 ± 12	125 ± 10	130 ± 25 (p=0.70)
Diastolic blood pressure (mmHg)	75 ± 10	74 ± 19	75 ± 19	91 ± 21 (p=0.33)
Heart rate (beats per minute)	60 ± 13	61 ± 10	61 ± 14	63 ± 19 (p=0.44)

Legends for figure and tables

Figure

Study design for examination with intraluminal (IL) stimulation. After an equilibrium period of 60 min, IL bolus infusions of saline alone or saline added graded doses of 5-HT (2.5, 25 or 250 nmol) were injected directly through the recording channels (side holes) of the catheter into the stomach (A1 and A2), duodenum (D1 and D2), and jejunum (J1, J2, and J3) with 15 min intervals. Injections started aborally in order to reduce "down-stream-flow" bias effects. Examination ended at time = 300 min.

Table 1

Characteristics for subjects are presented. Initials of names, age, gender (M = male, F= female) and body mass index (BMI).

Table 2

Design of the manometric catheter (total length of 250 cm). The tip of the catheter was located in jejunum. 7 channels with side holes recorded pressure changes: channel 1 and 2 (A1 and A2) were placed 5 cm apart in the antrum of the stomach. Channel 3 and 4 (D1 and D2) were placed 10 cm apart in duodenum and the distance between channel 2 and 3 was 10 cm. Channel 5, 6 and 7 (J1, J2 and J3) were placed 10 cm apart the jejunum and the distance between channel 4 and 5 was 20 cm. The final part of catheter to the tip was 5 cm long.

Table 3

Phase III of the migrating motor complex (MMC) is a band of regular pressure waves at the slow wave frequency that migrates down through the proximal small bowel to terminate between the midpoint of the small bowel and the terminal ileum. It recurs and is characterized by various parameters such as occurrence frequency, migration velocity, and duration (Hansen 2002). Data

presents phase III characteristics for the duodeno-jejunal (sensor D2-J1) segment: fasting (for 3 hrs, pre-stimulatory) and post-stimulatory after either intravenous (**IV**) continuous infusion of 5-HT (20 nmol/kg/min for 1 hr) or intraluminal (**IL**) bolus infusions of 5-HT (250 nmol for 1 hr). Data are presented for all 4 subjects as medians (range) for occurrence frequency and as mean values ± SD for migration velocity and duration. * $p = 0.036$, ** $p = 0.041$.

Table 4

Data presents haemodynamics characteristics at the end of the examinations periods with IL bolus infusion with saline alone or saline added 5-HT in accumulating graded doses (2.5, 25 and 250 nmol). Data are presented as mean values ± SD in 4 subjects. P is compared to saline alone.

Table 5

Data presents haemodynamics characteristics at the end of examinations periods with IV infusion with saline alone or saline added 5-HT (20 nmol/kg/min). Data are presented as mean values ± SD in 4 subjects. P is compared to saline alone.

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