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INFLUENCE OF CITALOPRAM ON INTERDIGESTIVE GASTROINTESTINAL MOTILITY IN MAN.

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Running head: Citalopram and interdigestive motility

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ABSTRACT

Administration of 5-Hydroxytryptamine (5HT), and selective 5HT receptor ligands modify interdigestive motility in animals and in man. **Aim:** To study the effect of citalopram, a selective 5-HT reuptake inhibitor, on interdigestive motility in man. **Methods:** In 20 healthy subjects, antroduodenojejunal motor activity was studied manometrically. Basal interdigestive motor activity was recorded until the passage of two activity fronts. Ten minutes after the second activity front, placebo or 20 mg of citalopram were administered intravenously in a double-blind randomized fashion. Recording continued until the passage of two more activity fronts had occurred. **Results:** Administration of citalopram induced a premature small intestinal phase 3 after 35±6.4 min, compared to 120±17 min after placebo $p<0.01$. Citalopram shortened MMC cycle length at the expense of phase 1 and phase 2 and significantly increased the motility index during phase 2 in the antrum and the small intestine. **Conclusions:** In the interdigestive state in man, intravenous administration of the selective 5-HT reuptake inhibitor citalopram induces a premature intestinal phase 3 and suppresses gastric activity fronts. Phase 2 motility is stimulated both in the stomach and in the small bowel after citalopram. These data suggest 5HT is involved in the control of interdigestive motility.

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INTRODUCTION

The interdigestive state of the gastrointestinal tract in most mammalian species, including man, is characterized by the presence of a cyclical pattern of activity, called migrating motor complex (MMC) (1,2). The MMC is programmed by the enteric nervous system, but the oscillatory mechanism controlling its cyclical nature is poorly understood (3).

Serotonin or 5-Hydroxytryptamine (5HT) is a major neurotransmitter both in the brain and in the gastrointestinal tract, where it plays a key role in the regulation of sensory and motor functions (4). Evidence has accumulated that administration of 5HT, its precursor 5-hydroxytryptophane, and its selective 5HT receptor agonists and antagonists can modify interdigestive motility in animals and in man (5-13). However, the effect of 5HT on the MMC has not been studied directly in man, as the intravenous administration of 5-HT is associated with tachyphyllaxis and cardiovascular and pulmonary adverse effects (14). After its release, 5HT is inactivated by the serotonin reuptake transporter (SERT)-mediated uptake (4). The administration of a selective 5HT reuptake inhibitor has been proposed as an alternative approach to studying role of 5HT in the control of gastrointestinal motor function (4, 15-17). Selective serotonin reuptake inhibitors (SSRIs) act both centrally and peripherally to enhance the availability of physiologically released 5HT (18,19). During short term treatment, SSRIs enhance 5HT-mediated actions by prolonging the availability of physiologically released 5HT (17). In the treatment of depression and anxiety however, only long term treatment with citalopram lead to clinical improvement (20, 21), indicating that short and long term treatment have a different mechanism of action. A possible explanation is that long term treatment with citalopram leads to desensitisation, especially of 5HT inhibitory auto-receptors (20, 22).

One study reported a reduced periodicity of the MMC in the small bowel of healthy volunteers after 5 days pretreatment with the SSRI paroxetine (15).

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However, it is unclear whether this reflects enhanced availability of 5HT or whether auto-receptor desensitization is already involved. Moreover, there is evidence for differential involvement of 5HT in the control of gastric or small bowel interdigestive motility. It has previously been shown that gastric, but not small intestinal phase 3, is inhibited by the $5HT_3$ receptor antagonist ondansetron (10), and that administration of the $5HT_1$ receptor agonist sumatriptan induces a premature intestinal phase 3, while suppressing gastric phase 3 activity (9). So far, the influence of SSRIs on gastric interdigestive motility has not been studied in man.

The present study was undertaken to investigate the effects of acute inhibition of 5HT reuptake on interdigestive gastroduodenojejunal manometry in man. As longer-term use of SSRIs leads to receptor desensitisation, we focused on the effects of acute intravenous administration of citalopram, a selective SSRI which is used in the treatment of depression. Upon intravenous infusion peak plasma levels of citalopram are reached after 30 minutes and stable concentrations are maintained for at least 2 hours (23).

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MATERIAL AND METHODS

Study subjects

Twenty healthy volunteers (16 men; mean age: 24.9±1.0 years) participated in the study. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, and none were taking any medication. Informed consent was obtained from each participant. The protocol was approved by the Ethics Committee of the University Hospital.

Recording technique

Recordings of antroduodenojejunal intraluminal pressures were performed using an eight lumen polyvinyl catheter (outer diameter 6 mm) with a latex bag at its end that could be filled with mercury. The probe was introduced via the mouth and positioned under fluoroscopic control in such a way that the most distal of the three proximal sensors, which were 3 cm apart, was located in the antrum at the level of pylorus or just distal to it. The three other sensors were located in the horizontal part of the duodenum and in the proximal jejunum, respectively at 17, 42, and 67 cm distal to the antropyloric recording sites. The two remaining catheters were used for filling and emptying the mercury bag. This catheter assembly allowed at least one recording orifice to be kept in the distal antrum during the entire experiment and thus the migrating motor complex was adequately monitored simultaneously in the distal antrum, the duodenum, and the upper jejunum. The recording catheters were continuously perfused with water by means of a low compliance pneumohydraulic infusion pump (Arndorfer Medical Specialties Inc., Greendale, Wisconsin, USA) at a flow rate of 0.4 ml/min, and were connected to external pressure transducers (Siemens Elema 746, Siemens, Iselin, New Jersey, USA). Pressures were recorded on a polygraph (Elema Mingograph 82, Siemens) using a paper speed of 5 mm/s.

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Study design

Following an overnight fast of at least 12 hours, the recording probe was introduced as described above and secured to the subject's chin with adhesive tape. In all volunteers, gastrointestinal motility was recorded until the passage of two phases 3 of the MMC (either gastric or intestinal). Ten minutes after the second phase 3 passed at the most distal recording site, 20 mg of citalopram (Cipramil, Lundbeck, Belgium) or saline was administered intravenously over 20 minutes in a double-blind randomized controlled fashion. Motility was recorded until two consecutive phases 3 of the MMC had occurred after the administration of citalopram, or for up to two hours after the end of the infusion.

Study analysis

Analysis of the recordings of gastroduodenojejunal motor activity was performed by two of the authors independently. Visual inspection allowed continuous identification of the most distal antral recording site as the catheter that recorded up to three pressure waves per minute (antral waves) just proximal to the catheter that recorded up to 12 waves per minute (duodenal waves) or to the catheter that exhibited a mixture of antral and duodenal waves. The different phases of the migrating motor complex were identified as described previously (2,9,10). Whenever possible, the propagation velocity of phase 3 was assessed from the gastric to the duodenal sensor and from the first to the second jejunal sensor.

Comparisons were made for MMC characteristics after saline or citalopram. In addition, MMC characteristics before and after administration of saline or citalopram, where each subject served as his/her own control, were also compared. The Student's t test was used to determine significant difference between cycle lengths, duration of the different phases of the MMC, velocity of propagation of phase 3 and motility indices during phase 2. The Chi square test

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was used to compare the proportion of phase 3s of MMC starting in the stomach. All values are presented as median (SEM). Differences were considered to be significant at the 5% level.

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RESULTS

Conduct of the study

All subjects completed the study as planned. Ten subjects (8 men, 26±1.3 years) received saline and ten (8 men, 23.9±1.6 years) received citalopram. Administration of citalopram or saline was well tolerated and did not induce any specific sensations or adverse symptoms.

Phases of the migrating motor complex

In all volunteers, two phase 3 contractions before and at least one phase 3 contraction after the administration of saline or citalopram was readily identified. Table 1 summarizes the effects of citalopram and saline on different phases of the MMC. The interval to the first phase 3 was significantly shorter after citalopram compared to saline (35±6.4 vs. 120±17 min after the previous phase 3, $p<0.01$) (Figure1). Administration of citalopram significantly shortened MMC cycle length, and this was due to shortening of phase 1 and phase 2 of the MMC cycle.

Phase 3 motor activity

Of the activity fronts prior to drug administration, 14 (35%) activity fronts had a gastric origin and 26 (65%) had a small intestinal origin. After saline, the origin of phase 3 of the MMC was not significantly altered. In contrast, administration of citalopram caused a premature activity front with jejunal origin in the vast majority of subjects (Table 1). The duration of phase 3 of the MMC cycle, as well as the propagation velocity of the phase 3s at the jejunal level, were not affected by citalopram (Table 1). The lack of gastric phase 3 activity after administration of citalopram precludes meaningful analysis of gastric phase 3 characteristics.

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Phase 2 contractile activity

Phase 2 contractile activity was not significantly altered by saline administration. Citalopram on the other hand, increased the number of contractions per minute and the phase 2 motility index in the stomach (both p=0.05, Table 2). In the small intestine, citalopram increased the number of contractions per minute, their amplitude and mean area under the curve, and the phase 2 motility index (all p≤0.05, Table 2).

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DISCUSSION

The present study has shown that in the interdigestive state in man, acute intravenous administration of the selective 5HT reuptake inhibitor citalopram induces a premature phase 3 of MMC with jejunal onset. The MMC cycle length was significantly shortened by the administration of citalopram, at the expense of phase 1 and phase 2. Of all the phase 3s recorded preceding the administration of citalopram, 35% started in the stomach. After administration of citalopram, only 10% of phase 3s were observed to start in the stomach, which is a statistically significant decrease, and indicate that phase 3 motor activity in the stomach was suppressed. Except for the site of initiation, no differences in the duration and the velocity of migration of phase 3s were observed before and after citalopram. Citalopram stimulated phase 2 contractile activity, in the stomach as well as the small bowel.

Our observation that citalopram induced a premature jejunal phase 3 in man is consistent with a previous published study which showed shortened intestinal MMC cycles after a short period of oral treatment with paroxetine, a different selective 5HT reuptake inhibitor (15). According to that study, the release of 5HT, probably at the level of enteric nervous system, is involved in the control of interdigestive motility in man. Since then, the effects of 5HT on MMC had been only studied in animals. Administration of 5HT, or its precursor 5-hydrotryptophan, decreases MMC periodicity in animals (7,8), whereas administration of neural 5HT receptor antagonists increases MMC periodicity 5). Thus, our findings that citalopram reduced MMC periodicity strengthens the hypothesis that 5HT participates in the control of MMC in man.

Citalopram selectively and potently enhances inhibition of neuronal 5HT reuptake (17) and excessive 5HT would then activate 5HT receptors. It is unlikely that citalopram acts via a non-serotonergic mechanism on the MMC. The fact that citalopram demonstrates a very weak inhibition of noradrenaline reuptake argues

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against an action through an adrenergic mechanism (17,18). Moreover, its very weak affinity for muscarinic cholinergic receptors is unlikely to account for the effects seen in interdigestive motility (17,18). Although the mood-affecting central actions of citalopram only show after a long lag time (generally several weeks) we cannot exclude a central action of citalopram, further research is necessary to investigate the exact mechanisms involved (18-20).

A recent study in mice confirmed involvement of serotonergic nerves in the control of propagating contractile complexes (24). Assuming that citalopram acts on enteric nervous system to modify the inderdigestive motility, we cannot attribute its action to a certain 5HT receptor subtype. Several subtypes of 5HT receptors are known (4,25). Of these, $5HT_{1A}$, $5HT_{1P}$, $5HT_3$, and $5HT_4$ receptors have been identified in the enteric nervous system (25-30). In animals there is evidence that $5HT_3$ receptors participate in the control of the MMC (30), whereas $5HT_3$ and $5HT_1$ receptors seem to be involved in the control of interdigestive motility in man (9,10).

After citalopram treatment significantly less phase III contractions originated from the stomach which indicates that phase 3 motor activity in the stomach was suppressed. It is thought that the gastointestinal peptide motilin is involved in the induction of gastric phase 3 (10,28-30) whereas somatostatin elicits phase 3 with small intestinal origin, while abolishing gastric phase 3 (10,31-33). As we did not determine plasma motilin and somatostatin concentrations, it is unclear whether the effect of citalopram on gastric activity front is attributable to changes in plasma concentrations of these or other gastrointestinal hormones.

Except for the site of initiation, no differences in the duration and the velocity of migration of phase 3s were observed before and after citalopram. We also showed that the phase 2 motility index was significantly enhanced both in stomach and in small bowel after the administration of citalopram. On the other hand, increased propagation velocity of phase 3s and absence of influence on

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phase 2 motility index after paroxetine administration were demonstrated by Gorard et al (15). These discordances may reflect differences in the studies design. We used citalopram in a single intravenous dose, whereas Gorard et al used paroxitene for 5 days. Moreover, in our study motility was recorded until two consecutive phase 3s of the MMC had occurred before and after the administration of citalopram, whereas motility was recorded for 16-18 hours by Gorard et al (15). Finally, our catheter assembly allowed the adequate monitoring of the migrating motor complex simultaneously in the distal antrum, the duodenum, and the upper jejunum, whereas Gorard et al sited the transducers distal to the duodenojejunal flexure.

Mixed reports on the effect of citalopram for the treatment of irritable bowel syndrome (IBS) are found in literature: we recently reported that citalopram could improve symptoms in irritable bowel syndrome patients (34) while others could not find improvement over placebo (35). In diarrhea-predominant IBS however symptoms have been correlated to the shorter duration of the MMC (and especially phase 2; 36), while in constipation-predominant IBS frequency and amplitude of the MMC contractions are decreased (37). Should the findings of the present study on the short term effect of citalopram be confirmed in a study on the long term effects of citalopram we can speculate that citalopram could improve constipation-predominant IBS while it might not improve diarrhea-predominant IBS. Indeed, in the study of Talley et al 76% of all patients included had diarrhea-predominant IBS and no improvement with citalopram could be observed while in our study only 17% had diarrhea-predominant IBS, which could explain the differences found. As a matter of fact, in constipation-predominant IBS, another SSRI fluoxetine was found to significantly release abdominal discomfort and increase bowel movement (38), which could indicate that especially in constipation-predominant IBS citalopram could be an effective treatment.

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In conclusion, the present study showed that intravenous administration of the selective 5HT reuptake inhibitor citalopram induces a premature phase 3 with jejunal onset, while less phase III contractions have a gastric origin indicating that citalopram suppresses gastric activity fronts in the inderdigestive state in man. Moreover, phase 2 motility index was stimulated both in the stomach and in the small intestine after the administration of citalopram. These data suggest that release of 5HT, probably at the level of the enteric nervous system, is involved in the control of MMC in man.

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TABLES

TABLE 1. Characteristics of MMC activity before and after administration of citalopram or placebo.

Variable	Before administration	After administration	p Value
Saline			
MMC cycle duration (min)	83.8 (14.5)	104.4 (16.7)	NS
Phase 1 duration (min)	12.7 (3.5)	12.1 (3.7)	NS
Phase 2 duration (min)	64.2 (15.0)	86.7 (17.4)	NS
Phase 3 duration (min)	6.9 (0.6)	5.6 (0.7)	NS
Phase 3 propagation velocity (cm/min)	5.4 (0.4)	5.8 (0.8)	NS
Phase 3, percentage gastric onset	30% (6/20)	43% (6/14)	NS
Citalopram			
MMC cycle duration (min)	86.4 (12.5)	49.5 (3.5)*	<0.001
Phase 1 duration (min)	13.7 (2.4)	7.1 (1.6)	0.01
Phase 2 duration (min)	66.7 (14.2)	37.6 (6.5)*	0.04
Phase 3 duration (min)	6.0 (0.5)	5.8 (0.6)	NS
Phase 3 propagation velocity (cm/min)	5.8 (0.2)	5.3 (0.2)	NS
Phase 3, percentage gastric onset	40% (8/20)	10% (2/21)*	0.03

Results are expressed as median (SEM). * $p < 0.05$ for values after administration of citalopram compared to administration of saline.

The duration of the different phases of the MMC was measured during the cycle preceding the administration of citalopram and the first cycle after the administration of citalopram at the most distal jejunal channel; the propagation velocity of phase 3 was measured at the jejunal level.

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TABLE 2. Influence of citalopram and placebo on phase 2 contractility parameters.

Saline			
Phase 2 antral contraction frequency (n/min)	0.34±0.09	0.32±0.07	NS
Phase 2 antral contraction amplitude (mm Hg)	63.1±14.4	52.6±6.0	NS
Phase 2 antral contraction duration (sec)	5.3±0.7	5.1±0.3	NS
Phase 2 antral contraction area (mmHg*sec)	135.7±33.7	120.1±19.6	NS
Phase 2 antral motility index (mmHg*sec/min)	3.2±0.4	3.3±0.3	NS
Phase 2 small bowel contraction frequency (n/min)	1.2±0.2	1.4±0.2	NS
Phase 2 small bowel contraction amplitude (mm Hg)	29.1±1.1	29.0±2.0	NS
Phase 2 small bowel contraction duration (sec)	3.3±0.1	3.3±0.1	NS
Phase 2 small bowel contraction area (mmHg*sec)	58.9±5.2	57.0±3.6	NS
Phase 2 small bowel motility index (mmHg*sec/min)	4.1±0.2	4.2±0.2	NS
Citalopram			
Phase 2 antral contraction frequency (n/min)	0.78±0.09	1.03±0.09	0.05
Phase 2 antral contraction amplitude (mm Hg)	41.4±5.2	48.8±4.9	NS
Phase 2 antral contraction duration (sec)	4.1±0.2	4.4±0.2	NS
Phase 2 antral contraction area (mmHg*sec)	61.5±12.6	69.2±10.8	NS
Phase 2 antral motility index (mmHg*sec/min)	3.64±0.25	4.20±0.15	0.05
Phase 2 small bowel contraction frequency (n/min)	1.6±0.1	2.1±0.2	0.05
Phase 2 small bowel contraction amplitude (mm Hg)	25.1±2.3	28.5±1.7	0.03
Phase 2 small bowel contraction duration (sec)	3.1±0.1	3.3±0.1	NS
Phase 2 small bowel contraction area (mmHg*sec)	52.1±4.6	63.6±5.2	0.005
Phase 2 small bowel motility index (mmHg*sec/min)	4.4±0.1	4.8±0.2	0.02

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FIGURES

FIGURE 1. Effect of citalopram on inderdigestive gastrointestinal motility in healthy volunteer. A1, A2, A3, antral recording sites; D, duodenal recording site; J1, J2, jejunal recording sites.

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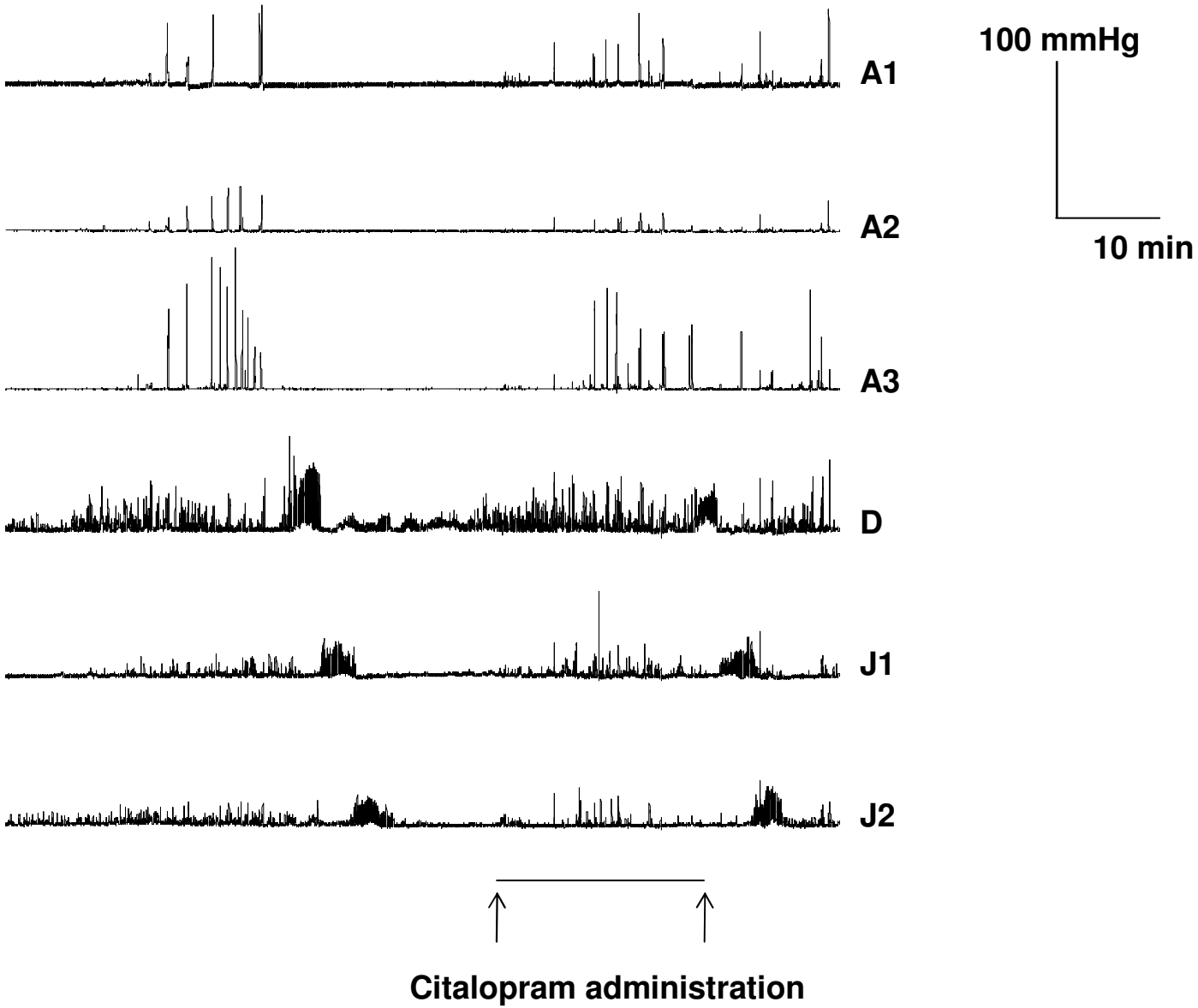

Dear Editor, Reviewers,

We appreciate the interest you had in our paper, and would like to discuss the comments by the reviewers point by point.

Reviewer 1

#1 The aim of this study was to examine the effect of acute inhibition of 5-HT reuptake. From literature we know that after intravenous administration of 20 mg citalopram peak plasma concentrations are reached within the hour and rapidly decrease afterwards (Lotrich *et al.*, 2005). We therefore chose to study the effect on interdigestive motility in a period of maximally 2 hours. Unfortunately, we could not determine plasma levels of citalopram and this is a weakness of the present study. To determine plasma citalopram concentrations HPLC analysis experience is necessarybut this was not available at the time we conducted the study.

#2 The aim of the study was to examine the effect of acute inhibition of 5-HT reuptake. Long term inhibition could induce compensation mechanisms that could act as an additional factor that makes interpretation of the data more difficult. Hence, although a longer study (e.g. to determine the frequency of phase III contractions) would indeed be very interesting this study would address another question, setup and discussion and thus be another study.

#3No crossover design was applied, mainly because this facilitates recruitment. It has to be noted though that despite the fact that the study was not a cross-over study the effect of citalopram on interdigestive motility was significant, indicating the relevance of our findings.

#4The reviewers comment is correct. Especially after saline administration it was not possible to detect 2 phases III in 2 hours. We apologize for the generalization of our statement and have adjusted the sentence in question to: 'In all volunteers, two phase 3 contractions before and at least one phase 3 contraction after the administration of saline or citalopram was readily identified.'

#5Indeed, we did not observe phase III contractions with a gastric origin in all volunteers after treatment with saline or citalopram, and therefore it is difficult to make a direct judgment whether or not gastric phase III contractions are suppressed. However we can make valid conclusions on the origin of the phase III contractions we observed and we found that after citalopram treatment significantly less phase III contractions had a gastric origin.We propose to formulate our findings more careful: in the first paragraph of the discussion we deleted the sentence in question and added that after Citalopram treatment significantly less phase IIIs originates in the stomach which indicates that phase 3 motor activity in the stomach was suppressed. Further on in the 3rd paragraph of p11 we adjusted the first sentence: 'After citalopram treatment significantly less phase III contractions originated from the stomach which indicates that phase 3 motor activity in the stomach was suppressed.'. Also in the conclusion we changed our formulation: 'while less phase III contractions have a gastric origin indicating that citalopram suppresses gastric activity fronts in the interdigestive state in man.'

#6 The sentence in question was adjusted accordingly: 'Although the mood-affecting central actions of citalopram only show after a long lag time (generally several weeks) we cannot exclude a central

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action of citalopram, further research is necessary to investigate the exact mechanisms involved (18-20).'

#7 has been adjusted in the text

Reviewer 2

1) The intention was merely to suggest that citalopram has different long term vs short term effects. This is of importance since in the present study we are interested in the short term effect and try to avoid long term effect. Our intention was not to discuss in full the possible differences in the mechanism of action on long and short term. We revised the sentence in question: 'In the treatment of depression and anxiety however, only long term treatment with citalopram lead to clinical improvement (20, 21), indicating that short and long term treatment have a different mechanism of action. A possible explanation is that long term treatment with citalopram leads to desensitisation, especially of 5HT inhibitory auto-receptors (20, 22).'

2) The sentence was adjusted accordingly: 'Upon intravenous infusion peak plasma levels of citalopram are reached after 30 minutes and stable concentrations are maintained for at least 2 hours (23).'

3) We agree with the reviewer, we cannot exclude involvement of the central nervous system. The text was changed accordingly: 'Although the mood-affecting central actions of citalopram only show after a long lag time (generally several weeks) we cannot exclude a central action of citalopram, further research is necessary to investigate the exact mechanisms involved (18-20).'

4) Due to its speculative nature we commented on the implications in the discussion only and added a paragraph before the discussion: 'Mixed reports on the effect of citalopram for the treatment of irritable bowel syndrome (IBS) are found in literature: we recently reported that citalopram could improve symptoms in irritable bowel syndrome patients (34) while others could not find improvement over placebo (35). In diarrhea-predominant IBS however symptoms have been correlated to the shorter duration of the MMC (and especially phase II; 36), while in constipation-predominant IBS frequency and amplitude of the MMC contractions are decreased (37). Should the findings of the present study on the short term effect of citalopram be confirmed in a study on the long term effects of citalopram we can speculate that citalopram could improve constipation-predominant IBS while it might not improve diarrhea-predominant IBS. Indeed, in the study of Talley et al 76% of all patients included had diarrhea-predominant IBS and no improvement with citalopram could be observed while in our study only 17% had diarrhea-predominant IBS, which could explain the differences found. As a matter of fact, in constipation-predominant IBS, another SSRI fluoxetine was found to significantly release abdominal discomfort and increase bowel movement (38), which could indicate that indeed in constipation-predominant IBS citalopram could be an effective treatment.'

Reference List

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1. Lotrich, FE, Bies, R, Muldoon, MF, Manuck, SB, Smith, GS & Pollock, BG. (2005). Neuroendocrine response to intravenous citalopram in healthy control subjects: pharmacokinetic influences. *Psychopharmacology*, **178**, 268-275.

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