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Short title Citalopram, gastric motor function and nutrient intake

Abbreviations

MDP = Minimal distending pressure

5-HT = 5-hydroxytryptamine

HV = Healthy Volunteer

Key words citalopram, serotonin, 5-HT, gastric barostat, gastric accommodation, gastric emptying

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For Peer Review

ABSTRACT

Background It is unclear whether endogenous serotonin release is involved in the regulation of gastric motility and food intake

Aim We aimed to study the effect of acute administration of the selective serotonin reuptake inhibitor citalopram on gastric motor function in man.

Methods 19 healthy volunteers underwent a gastric barostat, gastric emptying and/or a drinking test after treatment with either placebo or citalopram (20 mg intravenously). In the barostat protocol a flaccid bag was introduced in the stomach and inflated at intra-abdominal pressure +2 mmHg, volume was recorded before and after administration of a liquid meal (300 kcal). Gastric emptying for solids and liquids was simultaneously assessed using the ¹⁴C-octanoic acid/¹³C-Glycine breath test. During the drink test volunteers drank at a rate of 15 ml min⁻¹ until maximal satiation. Citalopram was compared to placebo using t-tests and mixed model analysis.

Results Citalopram induced a significant preprandial gastric relaxation (volume increase of 154±55 ml vs. -38±33 ml after placebo treatment; p<0.05) while the postprandial volume increase was significantly decreased after citalopram treatment (F_{12,80}=4.78, p<0.0001; maximum volume increase was 304±40 vs. 201±54 ml after placebo and citalopram treatment respectively). Citalopram enhanced solid (123±17 vs. 77±6 min, p<0.05) but not liquid emptying (62±6 vs. 57±4 min). Satiation scores during the drinktest were lower after citalopram (F_{19,153}=2.02, p=0.01; volunteers drank 998±129 vs. 765±79 ml after citalopram and placebo treatment respectively).

Conclusions The observed effects indicate a role for serotonin in the control of gastric motility and food intake.

INTRODUCTION

Serotonin (5-HydroxyTryptamine; 5-HT), a neurotransmitter in the enteric nervous system, is considered to play a key role in the control of gastrointestinal motility^{1,2}. Numerous studies have investigated the role of 5-HT in the control of gastric motility. Several 5-HT receptor agonists were shown to affect gastric motility in health: the 5-HT₁ receptor agonists sumatriptan and buspirone for example enhanced accommodation to meal and slowed gastric emptying^{3,4}, the 5-HT₃ receptor agonist MKC-733 delayed liquid gastric emptying in association with relaxation of the proximal stomach⁵ and the 5-HT₄ receptor agonists tegaserod and cisapride are known to accelerate gastric emptying, and enhanced gastric accommodation¹. Although 5-HT₃ receptor antagonism is known to abolish spontaneous phase III contractions in the antrum, the 5-HT₃ receptor antagonists tropisetron and ondansetron did not significantly affect gastric tone, gastric volumes after a meal or gastric emptying⁶⁻⁹. Also the 5-HT₄ receptor antagonist R216073 did not affect fundic relaxation or drinking capacity¹⁰. These observations question whether endogenous 5-HT release is involved in the control of gastric accommodation and emptying in man.

Selective serotonin reuptake inhibitors (SSRIs) enhance the availability of physiologically-released 5-HT both centrally and peripherally and effects of these drugs could thus indicate whether endogenously released 5-HT is involved in physiological processes. We previously showed that 7 days pretreatment with the SSRI paroxetine increased meal-induced gastric accommodation to a meal¹¹. In a similar treatment regimen however sertraline, paroxetine, or venlafaxine-XR

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(selective serotonin and norepinephrine reuptake inhibitor) were shown not to affect gastric compliance, sensitivity or gastric emptying^{12,13}. It is difficult to understand the role of 5-HT in gastric motility from these experiments as the observed effects, or lack of effect, could be mediated by the enhanced availability of 5-HT or desensitization of the 5-HT receptors given the relatively long treatment period. Indeed, the presumed working mechanism of SSRI drugs in depression is desensitization of 5-HT receptors because of the enhanced availability of physiologically released 5-HT¹⁴⁻¹⁶. In order to avoid desensitization of 5-HT receptors and to observe the role of acutely enhanced availability of 5-HT we aimed to study the effect of acute intravenous administration of the SSRI citalopram on gastric motor function in man.

METHODS

Ethical approval

All study procedures were approved by the Ethics Committee of the Leuven University Hospital, Belgium. Written, informed consent was obtained from all subjects, and studies conformed to the *Declaration of Helsinki*.

General study design and study subjects

This study used a randomized, placebo-controlled, single-blind, crossover design in which healthy volunteers (HVs) participated in a barostat study, a gastric emptying study and/or a nutrient challenge test. Between 2 visits a period of at least 1 week was respected. A pool of 19 HVs (10 men, age: 23 ± 1 years) with normal body mass index (22.7 ± 0.7 kg m⁻²) was included in the studies. Six HVs participated in both the barostat and gastric emptying protocol, 1 HV participated in both the gastric emptying and drinking test protocol and 4 HVs participated in both the drinking test and the barostat protocol. Per protocol volunteers always participated in both the placebo and citalopram treatment arm, hence all comparisons could be performed in a paired-wise fashion. None of the HV's had symptoms or a history of gastrointestinal disease, other significant diseases, psychological disorders or drug allergies; none were taking any medication or had any drug history.

Barostat study protocol

A double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded, was introduced through the mouth and secured to the

patient's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). To initially unfold the gastric balloon, the HV's were asked to lay down on a bed while the balloon was inflated with a fixed-volume of 500 ml of air for two minutes, then the balloon was deflated completely. After a 10 minute equilibration period, the patients were positioned in a comfortable sitting position with the knees slightly bent (80°) in a bed, specifically designed for that purpose.

After a 30 minute equilibration period the minimal intra-balloon distending pressure (MDP) was determined as the lowest pressure level that provided an intra-balloon volume of 30 mL or more during a protocol in which the balloon pressure was increased stepwise by 1 mmHg every minute (10,11). The MDP represents the pressure level that equilibrates the intra-abdominal pressure. Subsequently, sequential ramp distentions were performed in stepwise increments of 2 mmHg starting from MDP, each lasting for 2 minutes, while the corresponding intra-balloon volume was being recorded. Patients were instructed to score their perception of upper abdominal sensations induced by each distending stimulus at the end of every distending step, using a graphic rating scale that combined verbal descriptors on a scale graded from 0 to 6 (10,11). The end point of each sequence of distentions was established at an intra-balloon volume of 1000 ml, or when the patients reported discomfort (score 5) or pain (score 6).

After another 30 minute equilibration period, the intra-balloon pressure level was set at MDP + 2 mmHg. 30 minutes hereafter, citalopram (20 mg) or placebo was

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intravenously infused over 20 minutes using saline as vehicle. Immediately after this treatment the volunteers were asked to drink a nutrient drink (200 ml; 300 kcal; 13% proteins, 48% carbohydrates, 39% lipids; Nutridrink®, Nutricia, Belgium). Intra-balloon volume measurements continued for 60 minutes.

Gastric emptying study protocol

Gastric emptying for solids and liquids was simultaneously assessed using the previously validated ^{14}C -octanoic acid/ ^{13}C -glycin breath test ^{17,18}. 20 minutes before meal intake saline or citalopram (20 mg) were administered over a 20-minute period. The test meal consisted of 60 g of white bread and one egg, the yolk of which was doped with 74 kBq of ^{14}C -octanoic acid sodium salt. The meal was ingested within 5 min, followed immediately by 150 ml of water dosed with 100 mg of ^{13}C -glycine. The total caloric value of the test meal was 250 kcal. Breath samples were taken before the meal and at 15-min intervals for a period of 240 minutes postprandially. Gastric half emptying time ($T_{1/2}$) was calculated as previously described ¹⁷.

Drink test protocol

After an overnight fast volunteers underwent a satiety drinking test to quantify nutrient tolerance and the occurrence of meal-induced satiation as previously described ¹⁹. 20 minutes before the start of the nutrient drink ingestion either saline or citalopram (20 mg) was administered over a 20-minute period. A peristaltic pump (MINIpuls2; Gilson, Villiers-Le-Bel, France) filled one of two beakers at a rate of 15 ml min^{-1} with a liquid meal (Nutridrink, Nutricia, Bornem, Belgium). Subjects were requested to

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maintain intake at the filling rate, thereby alternating the beakers as they were filled and emptied. At 5-minute intervals, they were asked to score their satiation on a scale graded 0-5 (1=threshold, 5=maximum satiety). Meal intake was stopped when a score of 5 was reached.

Statistical analysis

All analyses were done using SAS statistical software version 9.1.3. (SAS Institute, Cary, NC, USA). Data are presented as the mean±S.E.M. Differences were considered to be significant at the 5% level.

Barostat study: To evaluate gastric tone, the mean intra-balloon volume was calculated over consecutive 5-minute intervals. The first 6 intervals (30 minutes) constitute the baseline period, the following 4 intervals (20 minutes) the preprandial period (during which citalopram or placebo was infused) and the final 12 intervals (60 minutes) constitute the postprandial period (i.e. after nutrient drink ingestion) (Figure 1). Preprandial relaxation at each time interval of the preprandial period was quantified by subtracting the average baseline volume from the preprandial volume. Meal-induced gastric relaxation at each time interval of the postprandial period was quantified by subtracting the average preprandial volume from the postprandial volume. In order to compare pre- and postprandial relaxation over time between treatments, delta values ($\text{relaxation}_{\text{placebo}} - \text{relaxation}_{\text{citalopram}}$) were calculated at each time point; these delta values were used as the dependent variable in all analyses described below. Mixed model analysis (using 'proc mixed' in SAS) with time as a categorical fixed effect was used to test the hypothesis that this delta-relaxation curve was significantly different from zero over time, this corresponds to a treatment effect

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over time and will be referred to accordingly throughout this paper. Random and/or repeated effects were added to the model in order to account for the between- and within-subject variability structure of the data in the best possible way. The model that fitted the data best (based on Akaike's Information Criterion) will be reported.

In addition, in order to compare volumes at certain time points, a paired Student's t-test was applied.

Gastric emptying: gastric half emptying time for both solid and liquid emptying were compared using paired Student's t-tests.

Drinktest: Satiation scores were represented as the average satiation score per 5 minutes. The difference in satiation score over time between both treatments was analysed using mixed model analysis as described above. Furthermore, the volume at which HVs stopped drinking was compared using Student's t-tests.

RESULTS

Conduct of the studies

All volunteers completed the studies as planned and no side effects were observed or reported during or after treatment with placebo or citalopram.

Barostat study

Mean baseline volumes before drug administration were not different between both treatment groups (254±31 vs. 198±26 ml for placebo and citalopram respectively; n=9) (Figure 1). However, compared to placebo, administration of citalopram induced a significant preprandial relaxation (treatment effect over time $F_{4,16}=5.16$, $p=0.007$), which seemed to be transient (Figure 1): at time -5 the volume increase was 154±55 vs. -38±33 ml after citalopram and placebo treatment respectively ($p<0.05$ (paired t-test)), while at time 0, the volume increase after citalopram treatment was reduced to 91±59 (vs. -36±31 ml after placebo treatment (NS (paired t-test))). Also, when comparing the mean preprandial volumes no significant differences could be detected (273±40 vs. 223 ±28 ml after citalopram and placebo treatment respectively; paired t-test).

When comparing the mean postprandial volume after citalopram treatment (363±41 ml) with the mean postprandial volume after placebo treatment (439±42 ml) no significance could be detected (paired t-test). However, when time was taken into account, citalopram treatment significantly decreased postprandial relaxation compared to placebo (treatment effect over time $F_{12,80}=4.78$, $p<0.0001$).

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Significances of post-hoc tests at individual time points for both analyses are shown in Figure 1.

Gastric emptying

Citalopram significantly enhanced solid (123 ± 17 vs. 77 ± 6 min, $p < 0.05$; $n = 10$; Figure 2) but not liquid emptying (62 ± 6 vs. 57 ± 4 min, NS).

Drinking test

Satiations scores after citalopram were consistently lower compared to placebo treatment throughout the drinking test. Although differences were relatively small, the effect of treatment over time was significant ($F_{19,153} = 2.02$, $p = 0.01$; $n = 10$). Significances of post-hoc tests at individual time points for both analyses are shown in Figure 3. Moreover, citalopram treatment significantly increased the amount of liquid nutrient meal ingested at maximum satiation (765 ± 79 vs. 998 ± 129 ml, $p < 0.05$) (Figure 3).

DISCUSSION

To date, there is an ongoing controversy regarding the role of endogenous 5-HT release in the regulation of gastric motility in man: while different 5-HT receptor agonists have been shown to modify gastric motility^{1,3-5}, antagonists per se seem to lack effect⁶⁻¹⁰. We previously showed that the SSRI paroxetine enhanced gastric meal-induced accommodation¹¹. In the latter study however the observed effect could be mediated by enhanced availability of synaptically released 5-HT or by 5-HT receptor desensitization due to the long treatment duration¹⁶. In the present study, acute treatment with the SSRI citalopram transiently decreased gastric basal tone, decreased gastric accommodation, accelerated gastric emptying of solids and decreased feelings of satiation, indicating an important role for 5-HT release in the regulation of stomach motility and food intake.

Citalopram is considered a highly selectively 5-HT reuptake inhibitor²⁰. However, citalopram has also been shown to weakly inhibit noradrenalin reuptake^{20,21}, has some affinity for α_1 adrenoreceptors and can act as a mild antihistaminic²². Moreover, citalopram has very weak affinity for muscarinic cholinergic receptors^{20,21}. The therapeutic dose range of citalopram is between 10-60 mg per day. In order to avoid effects via non-serotonergic mechanisms we chose to dose 20 mg, and we assume that the observed effects of citalopram at this dose are mediated via enhanced release serotonin which activates 5-HT receptors.

During the infusion, citalopram decreased basal gastric tone. This finding indicates that 5-HT release is involved in the balancing of inhibitory and excitatory stimuli that

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regulate basal gastric muscle tone. Indeed, in between meals the proximal stomach muscle tone is elevated, partly due to the myoelectrical properties of the fundus²³, besides a constant cholinergic input mediated by the vagal nerves²⁴. Although contractile factors are dominant there is also an inhibitory component active in the regulation of gastric tone: inhibition of nitric oxide synthase has been shown to decrease basal gastric tone²⁵. Our present findings indicate that also 5-HT release is part of this balance. Possible receptors that could decrease gastric tone are 5-HT₁, 5-HT₄ and 5-HT₇ receptors^{4,26-28}. It has been shown that the 5-HT₄ receptor antagonist R216073 did not affect basal gastric volumes¹⁰ which indicates that 5-HT₁ and/or 5-HT₇ receptors could be more likely candidates.

Upon food intake the physiology of the stomach changes dramatically. A vago-vagal reflex pathway is activated that inhibits cholinergic contractile input and increases the release of nitric oxide, especially to the proximal stomach²⁹. This reflex, also referred to as gastric accommodation, enhances the storage capacity of the stomach. In the present study citalopram decreases gastric accommodation to the meal, indicating that during that gastric accommodation endogenous 5-HT release activates 5-HT receptors that inhibit the accommodation reflex. Although we found no study that could mimic this effect using a 5-HT receptor agonist in humans or other species, *in vitro* studies in the dog indicate that activation of 5-HT₂ receptors might be responsible for the observed effect³⁰. Our results are seemingly in contrast with our previous finding that long-term treatment with paroxetine enhanced meal-induced gastric accommodation¹¹. However, long-term enhanced release of 5-HT might lead to receptor desensitization¹⁶, which might indeed lead to opposite effects as

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compared to short term treatment and might explain the observed differences ^{14,15}.

This observation does suggest that the effects observed with 7 days paroxetine pretreatment reflect receptor desensitization rather than enhanced availability of synaptically released 5-HT ¹¹.

The present study furthermore indicates that citalopram accelerates gastric emptying of solids but not of liquids. This is seemingly in contrast with a previous finding that could not find any differences in gastric emptying after chronic treatment with paroxetine or venlafaxine-XR ¹². Once again the difference might be attributed by the treatment duration, but the noradrenaline reuptake inhibitory effects of venlafaxine may also account for this difference, as adrenergic receptor activation decreases gastric contractility and gastric emptying ^{31,32}. Gastric emptying is the result of a complex interplay between the major motor patterns of the stomach. Tonic contractions of the proximal stomach propel gastric content distally while peristaltic contractions emerging from the mid-corpus progress in the direction of the antrum. A third mechanical factor in the regulation of GE is opening and closure of the pylorus. The relative importance of each of these three mechanical functions depends on food consistency: for liquids the pressure elicited by the proximal stomach and opening of the pylorus will drive gastric emptying, while the peristaltic pump of the antrum is crucial for grinding and emptying of solid food ³³. 5-HT₄ receptor agonists like tegaserod ³⁴ and cisapride ³⁵ have been shown to accelerate gastric emptying of solids and also in the present study the enhanced availability of 5-HT could activate 5-HT₄ receptors. Despite the effect on solid gastric emptying and the marked effect on gastric accommodation, acute treatment with citalopram did not significantly

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enhance gastric emptying of liquids. Very few agents, with the exception of motilin receptor agonists such as erythromycin³⁶ are able to enhance liquid gastric emptying in health. It is conceivable that more significant effects could be observed in patients with delayed (liquid) gastric emptying.

Citalopram has been suggested for the treatment of obesity and binge eating disorder^{37,38}. In the latter studies however, the proposed mechanism of action implicated the antidepressive properties of citalopram, rather than a direct effect on food intake. In our study acute treatment with citalopram was associated with lower satiation scores during the drinking test and increased the volume of nutrient drink ingested before volunteers scored maximal satiation. We previously showed that treatments that decreased gastric accommodation to a meal, also enhanced meal-induced satiation^{29,39,40}. On the other hand, drugs like sumatriptan, buspirone and cisapride that increased meal-induced gastric accommodation also enhance food intake to maximum satiety^{39,41}. Since citalopram decreased gastric accommodation to a meal we expected a decreased nutrient tolerance. It is therefore likely that other effects mediated by 5-HT might be responsible for the observed effect on food intake. Central 5-HT is well-known to play a complex role in the regulation of satiation and satiety and influences neurons in the arcuate nucleus, the ventromedial nucleus and other parts of the hypothalamus⁴²⁻⁴⁴. Enhanced availability of 5-HT at the central level might provide an explanation for our findings. **Although the observed effect in the present study was significant, it was not observed in all volunteers, and future studies will have to address whether this acute effect might play a role in the**

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anorectic effect of long-term citalopram treatment that is suggested to be mediated via 5-HT receptor desensitisation^{37,38}.

In conclusion, acute treatment with the selective 5-HT reuptake inhibitor citalopram decreases basal gastric tone, impairs gastric accommodation to a meal, enhances gastric emptying of solids and increases the volume of nutrient drink ingested before volunteers scored maximal satiation. The observed effects are probably mediated via enhanced availability of 5-HT and indirectly indicate an important role for 5-HT in the control of gastric motility and food intake. This study warrants further short- and long-term studies with selective 5-HT receptor agonists and antagonists to further elucidate the underlying mechanisms and clinical implications.

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FIGURES

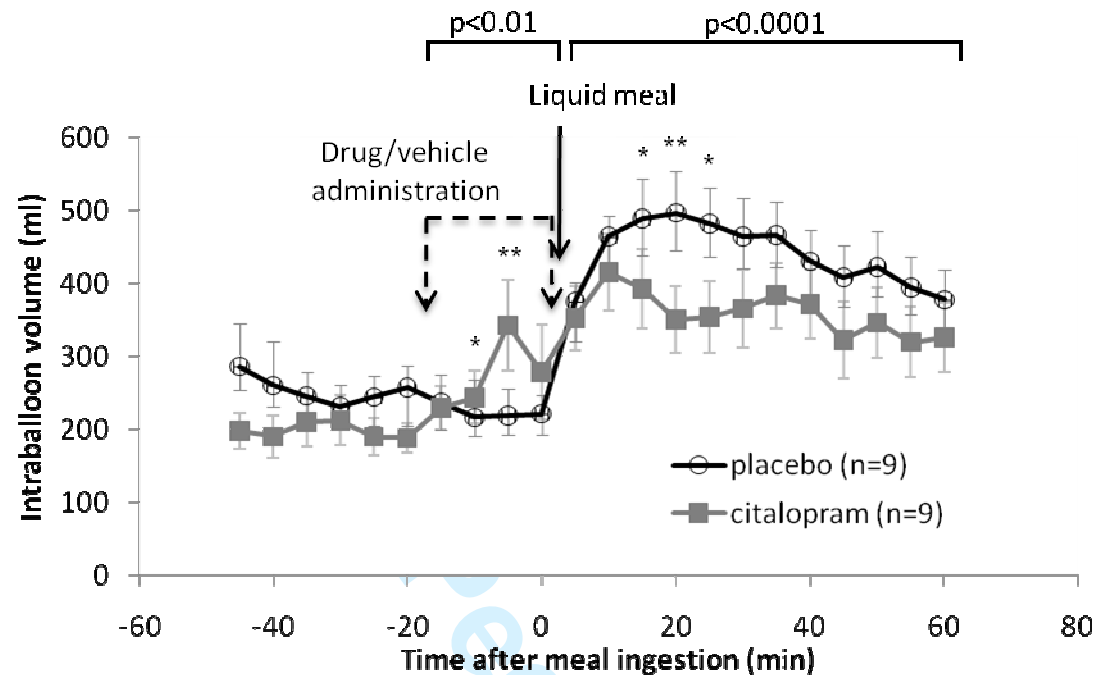


Figure 1 Mean intraballoon volumes at 5 min intervals, before treatment, during treatment and after treatment and consumption of a liquid nutrient drink. Citalopram (20mg) or vehicle (saline) was administered as an intravenous infusion over 20 minutes. During citalopram treatment a transient, significant relaxation was observed. After meal-intake the intraballoon volume increase was significantly inhibited after citalopram administration. Statistical differences at individual time points are indicated as follows: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

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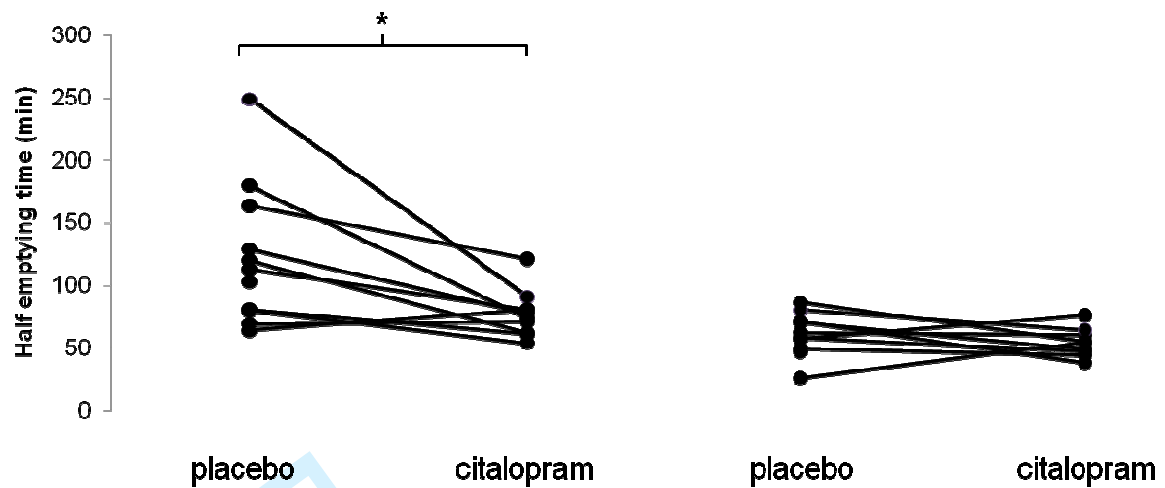


Figure 2 Solid and liquid half-emptying rates after administration of placebo or citalopram. Citalopram significantly enhanced solid emptying ($P < 0.05$).

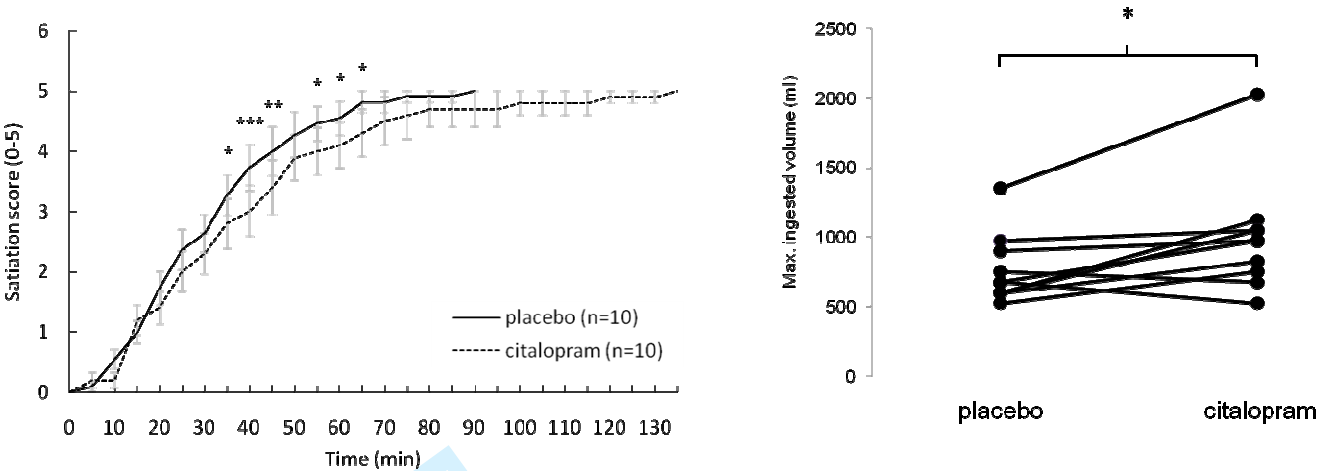


Figure 3 Satiation score over time during the drink test after treatment with citalopram was significantly lower compared to placebo (left panel; $p=0.01$). Statistical differences at individual time points are indicated as follows: * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Volunteers drank significantly more after citalopram treatment (right panel; $p<0.05$).

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