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Endocannabinoid control of gastric sensorimotor function in man

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SUMMARY

Background
Little is known about the physiological role of the endocannabinoid system in the regulation of the motility and the sensitivity of the stomach. Endocannabinoid system dysfunction has been hypothesized to contribute to the control of food intake and the pathogenesis of functional dyspepsia.

Aim
To study the influence of rimonabant, the endocannabinoid 1 (CB1) receptor antagonist, on gastric sensorimotor function in healthy controls.

Methods
After 4 days of pre-treatment with rimonabant 20 mg/day or placebo, 12 healthy volunteers (mean age 34 ± 12 years, six men) participated in a placebo-controlled, double-blind, randomized, crossover study with a gastric barostat assessment of gastric sensitivity to distension, gastric compliance, gastric accommodation and phasic motility on day 3 and a liquid nutrient challenge test on day 4.

Results
Rimonabant did not influence gastric compliance and sensitivity to distension. The meal-induced gastric accommodation reflex was significantly inhibited by rimonabant (154.3 ± 30.9 vs. 64.3 ± 32.4 mL, $P = 0.02$). Rimonabant did not affect maximal nutrient tolerance or meal-related symptoms during the satiety drinking test.

Conclusion
Endocannabinoids acting on the CB1 receptor are involved in the control of gastric accommodation in man.

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INTRODUCTION

It is well established that cannabinoids have a number of gastrointestinal effects, such as stimulation of appetite, inhibition of emesis and inhibition of motility.[1–3] These effects are attributable to actions of cannabinoids act on two specific G-protein coupled cannabinoid (CB) receptors termed CB1 and CB2, which are expressed at many sites within the brain-gut axis. The CB1 receptor is mainly expressed by neurons, while the CB2 receptor is mainly localized on immune cells.[1–3] Besides both CB receptors, the endocannabinoid system (ECS) comprises endogenous cannabinoid ligands such as anandamide and 2-arachidonylglycerol and the enzymes involved in the biosynthetic and degradative pathways of these ligands.[1–3] In the enteric nervous system, the ECS is involved in the control of activity of the enteric nervous system, which coordinates gastrointestinal sensorimotor function.[4]

Little is known about the role of the ECS in the control of gastric and sensory motor function. Delta-9-tetrahydrocannabinol, a natural CB1 agonist, was shown to decrease the rate of gastric emptying in man.[5] In rats, the synthetic CB1 antagonist rimonabant increases gastric emptying.[6, 7] The role of the ECS in the control of gastric accommodation and sensitivity has not been directly addressed. Related to gastric sensitivity, it has been postulated that descending anti-nociceptive pathways originating in the central nervous system, with endocannabinoids as one of the main neurotransmitters, may act to inhibit perception of visceral discomfort or pain under physiological conditions.[8] Therefore, suppression of endocannabinoid action by rimonabant could be hypothesized to result in visceral hypersensitivity.

Rimonabant was commercially available as a drug in the treatment of obesity, until being expelled from the market because of an increased prevalence of depression. In a Cochrane review, mean weight loss was estimated to be 4.6% after 1 year of treatment, which was associated with beneficial effects on different metabolic parameters and cardiovascular risk factors linked to overweight.[9–11] This has been attributed to two mechanisms: first, by decreasing food intake through actions on the hypothalamus and the limbic system and second, by increasing energy expenditure, related to increased lipolysis and thermogenesis.[10, 11]

It remains unclear whether inhibition of ECS actions in the enteric nervous system, through changes in gastric sensorimotor function, may also contribute to the effects of rimonabant on food intake. Inhibition of gastric accommodation or increased gastric sensitivity may also decrease food intake, as these have been associated with early satiation and weight loss in patients with functional dyspepsia (FD).[12–14] The objective of the present study therefore was to investigate whether suppression of endocannabinoid action by rimonabant affects sensitivity and motor function of the proximal stomach and tolerance of a nutrient challenge test in healthy volunteers.

MATERIALS AND METHODS

Subjects

Twelve healthy volunteers (six males, mean age 34 ± 12 years, body mass index 22.9 ± 0.6 kg/m^2) participated in the study. None of them had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. In addition, volunteers with a history of depression were excluded. Written informed consent was obtained from each participant. The ethics committee of the University Hospital had previously approved the protocol.

Study design

Volunteers were treated with rimonabant or placebo in a double blind, randomized, crossover fashion. After 3 days of pre-treatment, a gastric barostat study was performed on day 4 and a satiety drinking test on day 5. All subjects were studied twice with at least 1-week wash-out between treatment periods.

Drugs

Rimonabant was available as a drug for clinical use, through oral administration. The dose chosen (20 mg) was derived from the clinically applied dose for obesity treatment. Similar placebo capsules were obtained from the pharmacy.

Gastric barostat study

The gastric barostat study was performed according to a standard protocol.[12, 13] After an overnight fast, a double lumen polyvinyl tube (Salem sump tube 14 Ch; Sherwood Medical, Petit Rechain, Belgium) with an adherent polyethylene bag (maximal volume 1200 mL; 17 cm maximal diameter) was introduced through the

mouth and secured to the subject's chin with adhesive tape. The correct position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a programmable barostat device (PC polygraph and Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed volume of 300 mL for 2 min with the subject in a recumbent position and again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk upright in a specifically designed bed. After a 30-min adaptation period, the minimal distending pressure (MDP) was determined by increasing the intra-bag pressure with 1 mmHg every 3 min, until a volume of 30 mL or more was reached. This pressure level matches the intra-abdominal pressure. The study protocol is summarized in Figure 1.

Gastric sensitivity, compliance and fasting gastric tone

Graded isobaric distensions (each lasting for 2 min) were performed in stepwise increments of 2 mmHg starting from MDP, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step. They used both a global graphic rating scale that combined verbal descriptors on a graded scale (0–6) and a 10-cm visual analogue scale (VAS) to indicate the intensity of 10 epigastric symptoms (discomfort, pain, fullness, bloating, satiety, nausea, epigastric burning, belching and heartburn). The end point of this distension sequence was established when subjects reported discomfort (score 5). Afterwards, the pressure level was set at MDP + 2 mmHg for 45 min and drug was administrated after 15 min. Thereafter, two identical sequences of stepwise distensions were performed separated by the administration of a liquid meal (see below). The three series of isobaric stepwise distensions will be termed in chronological order: 'basal', 'post drug' and 'postprandial'.

Gastric accommodation and phasic motility

Between the second and third series of stepwise distensions, pressure level was again set at MDP + 2 mmHg for 90 min with administration of a liquid meal (200 mL, 300 kcal, 13% proteins, 48% carbohydrates, 39% lipids, Nutridrink; Nutricia, Bornem, Belgium) after 30 min.

Nutrient tolerance and meal-related symptoms

After an overnight fast, volunteers underwent a drinking test to quantify nutrient tolerance and the occurrence of meal-induced satiety. A peristaltic pump (MINIpuls2; Gilson, Villiers-Le-Bel, France) filled one of two beakers at a rate of 15 mL/min with a liquid meal (Nutridrink, Nutricia, Bornem, Belgium). Subjects were requested to maintain intake at the filling rate, thereby alternating the beakers as they were filled and emptied. At 5-min intervals, they were asked to fill out VAS scores for 10 epigastric symptoms (hunger, satiety, fullness, bloating, nausea, belching, burning, cramps, pain and appetite) and to score their satiety on a scale graded 0–5 (1 = threshold, 5 = maximum satiety). Meal intake was stopped when a score of 5 was reached. The postprandial evolution was followed by VAS scores every 15 min for 2 h.

Data analysis

In the barostat study, for each 2-min isobaric distending period, the intragastric volume was calculated by

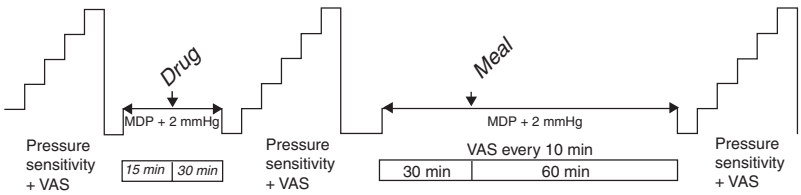

Figure 1. Schematic outline of the study protocol. Stepwise isobaric distensions with assessment of sensations were performed before and after drug administration. The intra-bag volume at MDP + 2 mmHg was recorded before and after drug administration and before and after the meal. MDP, minimal distending pressure; VAS, Visual Analogue Scale.

averaging the recording. The perception threshold was defined as the lowest pressure relative to MDP, and the corresponding volume, that evoked a perception score of 1 or more. The discomfort threshold was defined as the lowest pressure relative to MDP, and the corresponding volume, that evoked a score of 5 or more. Pressure-volume and pressure-perception curves were obtained from the stepwise distensions and fitted with a linear regression model as previously described.[12, 13] Gastric compliance was calculated as the slope and the intercept of the pressure-volume curve obtained during the isobaric distensions. The analysis of stepwise distensions was limited to the pressure range for which a value was obtained in at least 75% of the subjects.

To evaluate gastric tone before and after administration of the drug, the mean intra-balloon volume was calculated over consecutive 5-min intervals. Drug-induced changes in gastric tone were quantified by calculating the difference between the average intragastric volume during 15 min before and 30 min after drug administration.

To assess gastric accommodation, the mean volume of the stomach over consecutive 5-min intervals was calculated 30 min before the meal and 60 min after the meal. Gastric accommodation was quantified by subtracting the mean preprandial from the mean postprandial volume.

To evaluate the effect of rimonabant on phasic contractile activity of the fundus, which corresponds to slow changes in baseline volume after filtering out respiratory artefacts, a baseline reconstruction was performed using a computerized algorithm. Consecutively, a motility index was calculated as the area between the curve and the baseline. Phasic contractility was quantified during three 30-min periods: the preprandial period and the first and second postprandial periods.

For the nutrient tolerance test, the meal volume and corresponding amount of kilo-calories (kcal) ingested until the occurrence of maximum satiety (score of 5) was calculated.[12]

Statistical analysis

Based on previous studies, the study was powered to detect 30% changes in relevant parameters. All data are presented as mean ± standard error of the mean (S.E.M.). Paired student's *t*-tests were used to compare mean values between both treatments. Gastric accommodation results were compared using a two-way ANOVA for repeated measurements. A *P*-value <0.05 was considered statistically significant.

RESULTS

Conduct of the study

All participants completed the studies as planned. The study protocol was well tolerated by all subjects. No side effect was reported during administration of rimonabant or placebo.

Gastric sensitivity

The pressures needed to induce first perception or discomfort and the corresponding intra-balloon volumes did not differ between placebo and rimonabant during any of three series of stepwise distensions (Figure 2). The area under the pressure-perception curve for the same distending steps did also not differ between placebo and rimonabant (*AUC* 19.8 ± 0.3 vs. 22.7 ± 0.5 mmHg, N.S.) (Figure 3a). VAS scoring also did not reveal any altered intensities of pain or other epigastric symptoms between rimonabant and placebo during the three series of stepwise distensions (details not shown).

Gastric motility

The mean MDP was not altered by rimonabant (8.2 ± 0.4 vs. 7.9 ± 0.4, N.S.). During the three series of stepwise distensions, progressively higher intragastric pressures produced progressively larger intragastric volumes (Figure 3b). Rimonabant did not alter gastric compliance (34.9 ± 3.9 vs. 39.0 ± 5.2 mL /mmHg, N.S.). The average intra-balloon volume at MDP + 2 mmHg did not differ between placebo and rimonabant prior to drug administration (218.0 ± 23.7 vs. 221.3 ± 23.1 mL, NS) or thereafter (165.8 ± 18.0 vs. 171.3 ± 18.3 mL, N.S.). The mean volume change in intra-balloon volume at MDP + 2 mm HG after drug administration was 52.2 ± 12.9 mL after placebo and 50.0 ± 18.8 mL after rimonabant (N.S.).

The average intra-balloon volume did not differ significantly between placebo and rimonabant before the meal (216.5 ± 27.5 vs. 267.4 ± 30.5 mL, N.S.) or after the meal (370.7 ± 39.0 vs. 331.7 ± 52.4 mL, N.S.). Ingestion of the meal caused an immediate relaxation of the proximal stomach in all subjects, reflected by

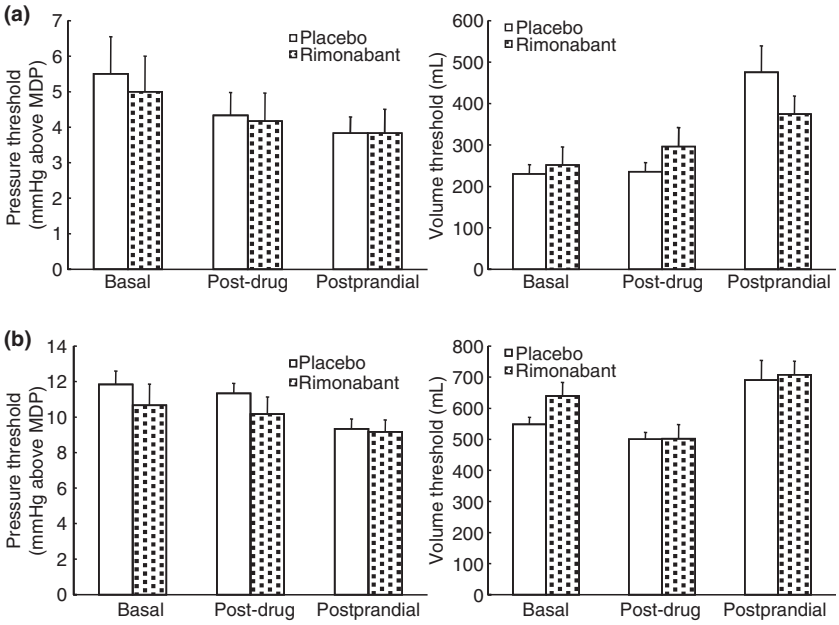

Figure 2. Gastric sensitivity: Pressure (left panel) and volume (right panel) thresholds for first perception (a) and discomfort (b) during three series of stepwise distensions. Rimonabant did not affect gastric sensitivity as pressure thresholds and corresponding volumes were not altered compared with placebo during three series of stepwise distension (basal, post drug, postprandial). MDP, minimal distending pressure.

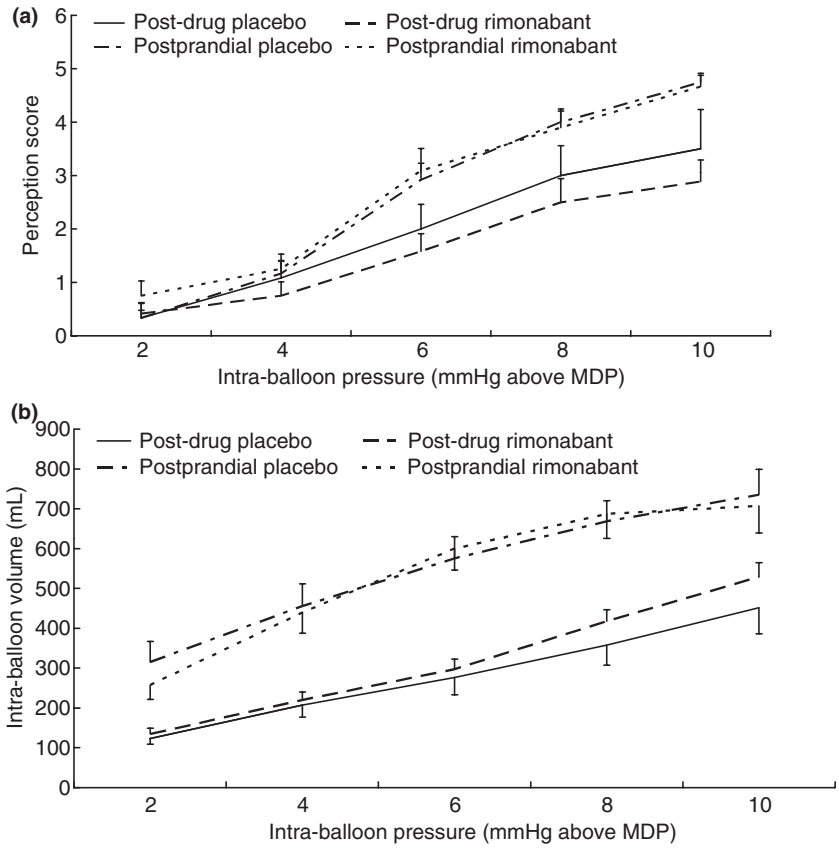

Figure 3. (a) Pressure-perception curves obtained by gradually increasing isobaric gastric distensions. Post-drug and postprandial curves are shown for placebo and rimonabant for all pressure levels where at least 80% of subjects had not reached the discomfort threshold. The area under the pressure-perception curves did not differ between placebo and rimonabant. (b) Pressure volume curves obtained by gradually increasing isobaric gastric distensions. Post-drug and postprandial curves are shown for placebo and rimonabant for all pressure levels where at least 80% of subjects had not reached the discomfort threshold. Gastric compliance, calculated as the slope of the pressure-volume curves, was not altered by rimonabant. MDP, minimal distending pressure.

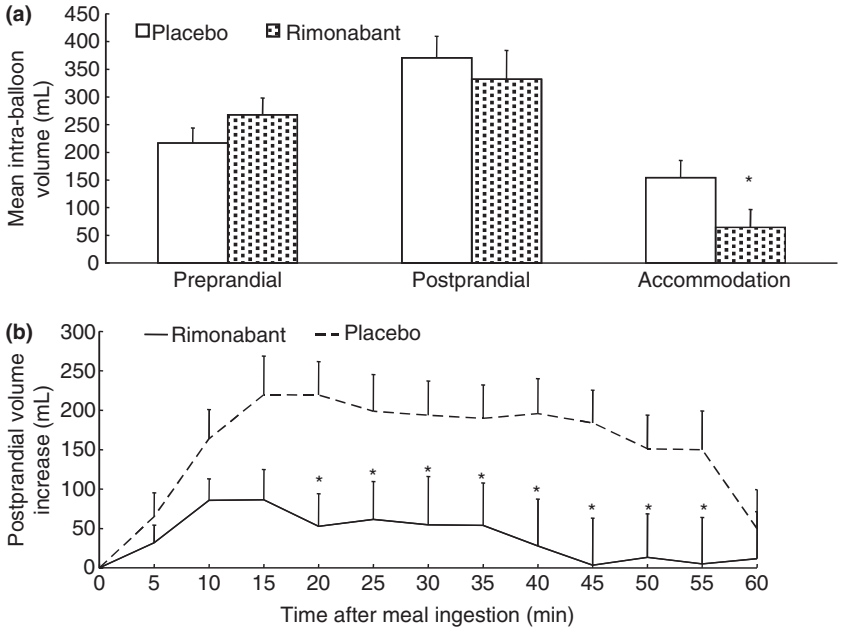

Figure 4. (a) Mean preprandial and mean postprandial volumes were not altered by rimonabant. Gastric accommodation was significantly suppresed by rimonabant ($P = 0.02$). (b) Increase in intra-balloon volume at 5-min intervals after meal administration. After rimonabant, meal-induced gastric relaxation was significantly suppressed, indicated by the smaller volume increase of the barostat balloon. (*:$P < 0.05$ compared to placebo).

an increase in the balloon volume (Figure 4a). Meal-induced accommodation was significantly suppressed by rimonabant (154.3 ± 30.9 vs. 64.3 ± 32.4 mL, $P = 0.02$) (Figure 4b). Phasic gastric motility was not significantly altered by rimonabant (details not shown).

Nutrient tolerance and meal-related symptoms

The amount of liquid nutrient meal ingested at maximum satiety was not significantly different after placebo compared to rimonabant (831.3 ± 89.2 vs. 781.2 ± 61.6 mL, N.S.). Visual analogue scores for epigastric symptoms were not significantly altered by rimonabant during the drink test or during the 3-h postprandial follow-up period (Figure 5).

DISCUSSION

The aim of the present study was to investigate how suppression of endocannabinoid action by rimonabant would influence sensitivity to gastric distension and gastric response to meal ingestion in healthy volunteers.

It has been postulated that descending inhibitory pain pathways originating in the central nervous system, with endocannabinoids as one of the main candidate neurotransmitters, inhibit perception of visceral

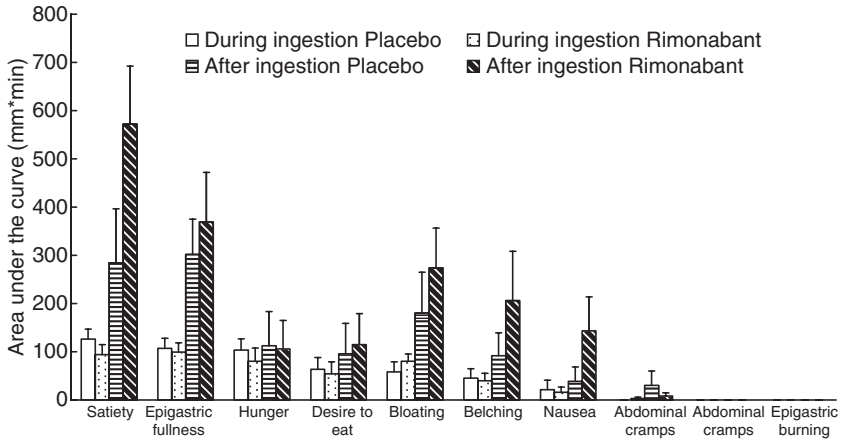

Figure 5. Symptom intensity ratings on VAS during and after a nutrient challenge test. No significant differences between rimonabant and placebo were found.

discomfort or pain under physiological conditions.[8] Moreover, in rats, it has been shown that both the delta-9-tetrahydrocannabinol-induced increase in gastric volume as well as the hypophagic effect of rimonabant can be abolished by capsaicin deafferentiation.[15, 16] These observations suggests that CB1 receptors located on sensory terminals are important for the modulation of gastric volume and food intake. In the present study, we found that suppression of endocannabinoid action by rimonabant had no significant influence on gastric sensitivity to balloon distension as quantified by perception and discomfort thresholds, by area under the pressure-perception curve and by VAS scoring during stepwise distensions. These data therefore argue against a major role for the ECS in the control of mechanosensitivity of the proximal stomach in healthy subjects. One limitation of the current study is that, in line with ethical recommendations, a sensation of discomfort was the endpoint of each series of stepwise distensions. We cannot exclude that the ECS only becomes activated when truly painful sensations are elicited.[8] In addition, it remains conceivable that the ECS is activated in patients with enhanced sensitivity of the stomach to distension, for instance in FD,[13] and that suppression of endocannabinoid action might further enhance gastric sensitivity under such conditions. Finally, our data do not exclude efficacy of exogenously applied CB1 agonists in pain control of hypersensitive patients.

When assessing effects on proximal stomach motility, we found that inhibition of endocannabinoid action by rimonabant did not influence fasting gastric fundic tone and gastric compliance, but significantly inhibited meal-induced gastric accommodation. It remains unclear whether this effect of rimonabant is attributable to its actions in the brain or in the enteric nervous system. Indeed, we and others previously provided evidence for a continuous ECS tone in the enteric nervous system.[1–4] On the other hand, gastric accommodation is a vago-vagally mediated reflex which is integrated in the brain stem.[17] Endocannabinoids can potentially control this vago-vagal reflex pathway at many points as CB1 receptors are expressed on vagal afferents, in the brain stem, on interneurons in the stomach wall and on postganglionic fibres innervating gastric smooth muscle.[1, 2] Further clarifying the site of action where rimonabant inhibits the accommodation reflex would require studies with a peripherally acting CB1 antagonist, and no such drug is presently available for human studies. However, a number of arguments in favour of a peripheral site of action of the ECS related to gastric motility can be found. First, the observation in the present study that rimonabant inhibited gastric accommodation reflex without an increase in VAS scores for satiety or other epigastric symptoms, is supportive of a peripheral effect. Second, delayed gastric emptying in rats after intraperitoneal injection of a CB1 agonist was reversed by oral administration, but not by intracerebroventricular administration of rimonabant.[18] Furthermore, delayed gastric emptying after intraperitoneal injection of a CB1 agonist in rats could not be prevented by ganglionic blockade with intraperitoneal hexamethonium.[7] Other animal studies showed conflicting results as the inhibitory effect of delta-9-tetrahydrocannabinol on gastric emptying in rats was abolished by bilateral vagotomy and as the ED_{50} in rats for decreasing gastric emptying was lower with cerebroventricular compared with intraperitoneal administration of CB1 agonists.[7, 19] The hypothesis that impaired function of the ECS contributes to impaired gastric accommodation in FD deserves further studies, for instance, by assessing the influence of rimonabant on gastric accommodation in these patients.[12]

Gastric accommodation results from a relaxation of gastric smooth muscle cells by an inhibitory NANC input in the postprandial state, with an important nitrergic component, although an inhibition of cholinergic pathways may also contribute.[12, 17, 20, 21] In contrast, fasting gastric fundic tone is caused by a continuous state of tonic contraction that is maintained by a vagally mediated cholinergic input.[17] ECS control of accommodation by altered NANC neurotransmission is plausible as fasting gastric fundic tone was not influenced by rimonabant. An alternative explanation for this finding could be that the ECS is activated on demand upon meal ingestion. However, it has been shown that postprandial concentrations of endocannabinoids in the enteric nervous system are decreased 7-fold compared to the fasting state.[16] *In vitro* studies in animals provide evidence that both the excitatory as well as inhibitory gastric innervation are prone to ECS regulation.[22, 23] It is conceivable that the ECS controls the action of interneurons that are responsible for coupling of vagal efferents to inhibitory motor neurons, as, at least in rodents, CB1 receptor immunoreactivity in the stomach wall is completely co-localized with choline acetyltransferase positive neurons.[1, 2, 6]

Drink test results also argue against an important role for the ECS in the control of gastric sensitivity as VAS scores for 10 epigastric symptoms were not altered by rimonabant. In addition, we did not find a significant inhibition of nutrient tolerance after rimonabant pre-treatment in the present study. This is surprising as previous studies have shown associations between impaired gastric accommodation and early satiation in functional dyspepsia and in a number of pharmacological studies in healthy volunteers.[17, 20, 24] Moreover, in laboratory animals, the ECS was shown to stimulate appetite and food intake in a rimonabant-reversible manner.[10, 11] A number of factors may have contributed to this apparent contradiction. First, the numbers of subjects studied were relatively low, but significant effects have been obtained in previous studies with similar numbers of subjects.[20, 24, 25] Second, the accommodation reflex relaxes the proximal stomach during food intake, thereby allowing storage of the meal without a rise in intra-gastric pressure. It remains unclear whether inhibition of the gastric accommodation reflex by rimonabant is associated with a rise in intragastric pressure necessary to activate mechanoreceptors responsible for early satiety and other symptoms.[26] Indeed, in rats, rimonabant was shown to decrease intragastric pressure.[19] Furthermore, rimonabant has been shown to decrease mainly the intake and palatability of sweet foods while it was much less effective in decreasing the intake of a standard meal as used in the present study.[10] Finally, it has been shown that the ECS becomes upregulated in obesity, while the present study included lean healthy subjects.[27]

In summary, in this placebo-controlled, double-blind, randomized, crossover study, we found that endocannabinoids acting on CB1 receptors are involved in the control of the gastric accommodation reflex. Rimonabant inhibits meal-induced accommodation, but does not affect fasting gastric compliance or sensitivity to gastric distension. Further studies will be needed to address whether rimonabant inhibits accommodation through a central or a peripheral site of action.

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REFERENCES

1 Pertwee RG. Cannabinoids and the gastrointestinal tract. *Gut* 2001; **48**: 859–67.
2 Duncan M, Davison JS, Sharkey KA. Review article: endocannabinoids and their receptors in the enteric nervous system. *Aliment Pharmacol Ther* 2005; **22**: 667–83.
3 Hornby PJ, Prouty SM. Involvement of cannabinoid receptors in gut motility and visceral perception. *Br J Pharmacol* 2004; **141**: 1335–45.
4 Boesmans W, Ameloot K, van den Abbeel V, Tack J, Vanden Berghe P. Cannabinoid receptor 1 signalling dampens activity and mitochondrial transport in networks of enteric neurones. *Neurogastroenterol Motil* 2009; **21**: 958–e77.
5 McCallum RW, Soykan I, Plankey W, *et al.* Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double blind, randomized study. *Aliment Pharmacol Ther* 1999; **13**: 77–80.
6 Casu MA, Porcella A, Ruiu S, *et al.* Differential distribution of functional cannabinoid CB1 receptors in the mouse gastroenteric tract. *Eur J Pharmacol* 2003; **459**: 97–105.
7 Izzo A, Pinto L, Borrelli F, *et al.* Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil. *B Jour Pharmacol* 2000; **129**: 1627–32.
8 Walker JM, Huang SM. Endocannabinoids and pain modulation. *Prostaglandin Leukot Essent fatty acids* 2002; **66**: 235–42.
9 Currioni C, Andre C. Rimonabant for overweight or obesity. *Cochrane Database Syst Rev* 2006; **CD006162**: 1–56.
10 Carai M, Colombo G, Maccioni P, *et al.* Efficacy of rimonabant and other cannabinoid CB1 receptor antagonists in reducing food intake and body weight : preclinical and clinical data. *CNS drug reviews* 2006; **12**: 91–9.
11 Akbas F, Gasteyger C, Larsen M, *et al.* A critical review of the cannabinoid receptor as a drug target for obesity management. *Obesity reviews* 2008; **10**: 58–67.
12 Tack J, Piessevaux H, Coulie B, *et al.* Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; **115**: 1346–52.
13 Tack J, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Hypersensitivity to gastric distention is associated with symptoms in functional dyspepsia. *Gastroenterology* 2001; **121**: 526–35.
14 Tack J, Jones MP, Karamanolis G, Coulie B, Dubois D. Symptom pattern and pathophysiological correlates of weight loss in tertiary-referred functional dyspepsia. *Neurogastroenterol Motil* 2010; **22**: 29–e5.
15 Ball AJ, Moerschbaecher JM, Hornby PJ. Delta-9-tetrahydrocannabinol effects on gastric motility are mediated by a

capsacin-sensitive vagal pathway. *Digestion* 2001; **63**: 269.
16 Gomez R, Navarro M, Ferrer B. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *J Neurosci* 2002; **22**: 9612–7.
17 Kindt S, Tack J. Impaired gastric accommodation and its role in dyspepsia. *Gut* 2006; **55**: 1685–91.
18 Landi M, Croci T, Manara L. Modulation of gastric emptying and gastrointestinal transit in rats through intestinal cannabinoid CB1 receptors. *Eur Jour Pharmacol* 2002; **450**: 77–83.
19 Krowicki ZK, Moerschbaecher JM, Winsauer PJ, *et al.* ΔTHC inhibits gastric motility in the rat through cannabinoid CB1 receptors. *Eur J Pharmacol* 1999; **371**: 187–96.
20 Tack J, Demedts I, Meulemans A, *et al.* Role of nitric oxide in the gastric accommodation reflex and in meal induced satiety in humans. *Gut* 2002; **51**: 219–24.
21 Van Oudenhove L, Kindt S, Vos R, Coulie B, Tack J. Influence of buspirone on gastric sensorimotor function in man. *Aliment Pharmacol Ther* 2008; **28**: 1326–33.
22 Storr M, Gaffal E, Allescher HD, *et al.* Effects of cannabinoids on neural transmission in rat gastric fundus. *Can J Physiol Pharmacol* 2002; **80**: 67–76.
23 Hienemann A, Shahbazian A, Holzer P. Cannabinoid inhibition of guinea-pig intestinal peristalsis via inhibition of excitatory and activation of inhibitory neural pathways. *Neuropharmacology* 1999; **38**: 1289–97.
24 Cuomo R, Vandaele P, Coulie B, *et al.* Influence of motilin on gastric fundus tone and on meal-induced satiety in man: role of cholinergic pathways. *Am J Gastroenterol* 2006; **101**: 804–11.
25 Tack J, Caenepeel P, Piessevaux H, Cuomo R, Janssens J. Assessment of meal-induced gastric accommodation by a satiety drinking test in health and in functional dyspepsia. *Gut* 2003; **52**: 1271–7.
26 Tack J, Caenepeel P, Corsetti M, *et al.* Role of tension receptors in dyspeptic patients with hypersensitivity to gastric distention. *Gastroenterology* 2004; **127**: 1058–66.
27 Engeli S, Bohnke J, Jordan J, *et al.* Activation of the peripheral endocannabinoid system in human obesity. *Diabetes* 2005; **54**: 2838–43.