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Peripheral Effects of Rimonabant on Upper Gastrointestinal Motility

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Abstract

Background: Rimonabant (SR 141716A) is an antagonist-inverse agonist of cannabinoid receptor 1 (CB1), which was developed for the obesity treatment. The aim of this study was to investigate effects of rimonabant on gastric emptying, gastric tone, accommodation and compliance, antral contractions and small intestinal contractions in dogs.

Materials and Methods: Six dogs were equipped with a duodenal cannula for the measurements of gastric emptying, small bowel contractions and small bowel slow waves. Another six dogs were equipped with a gastric cannula for the measurements of gastric tone, accommodation and compliance, antral contractions and gastric slow waves. Each of the measurements was obtained in one control and two rimonabant sessions (different doses).

Results: 1) Rimonabant accelerated gastric emptying of liquids and the effect was more potent at a dose of 1 mg/kg than 0.5 mg/kg; 2) Rimonabant increased gastric tone and reduced gastric compliance and accommodation with the 1.0 mg/kg dose being more potent; 3) Rimonabant inhibited antral contractions; 4) Rimonabant increased small intestinal contractions. The small intestinal contraction index was 9.60 ± 2.44 in the control session and increased to 12.35 ± 1.45 with rimonabant 0.5mg/kg (p=0.018 vs. control) and 14.75 ± 2.46 with rimonabant 1 mg/kg (p=0.008 vs. control).

Conclusions: Rimonabant reduces gastric compliance and accommodation, inhibits antral contractions but increases intestinal motility. These findings suggest the peripheral mechanisms of rimonabant in reducing food intake and body weight.

Keywords: Gastrointestinal motility; Obesity; Rimonabant

Introduction

Drugs that interfere with cannabinoid CB1 receptor transmission suppress a number of food-related behaviours and these compounds are currently being assessed for their potential utility as appetite suppressants. Rimonabant (SR 141716A) is a cannabinoid receptor 1 (CB1) antagonist-inverse agonist which was developed for obesity treatment [1]. Clinical trials showed that rimonabant caused cumulative weight loss and a significant change of waist circumference, an increase of High-Density Lipoprotein (HDL) cholesterol level and a decrease in triglycerides and fasting insulin [2]. Further research showed that the effects of rimonabant on food intake and weight loss were associated with alteration of leptin expression in hypothalamus [3]. CB1 receptors, found in the endocannabinoid system are expressed in the brain, the adipocyte, the skeletal muscle and the enteric nervous system. CB1 pathway is believed to affect central and peripheral actions on lipid and glucose metabolism in adipose tissue [4] and helps to regulate food intake, energy balance and gastrointestinal motility [5]. Gastric motility is a key mediator of hunger, satiation and satiety. Alterations in GI motility have been observed in obese patients and these alterations could be important factors to the development of obesity and eating disorders [6]. Therapies aimed at regulating the observed changes in GI motility are being actively explored and applied clinically in the management of obese patients [7]. Rimonabant was reported to accelerate gastric emptying and small intestine transit in a number of rodent studies [5,8]. In some studies [9,10] rimonabant was found to increase electrically evoked, cholinergically mediated contractions in rat- and guinea-pig isolated myenteric plexus-longitudinal muscle preparations. One of recent human studies [11] showed that, rimonabant did not influence gastric compliance and sensitivity to distension, but the meal-induced gastric accommodation reflex was inhibited by rimonabant. However, there is no systematic study investigating the effects of rimonabant on GI motility, including gastric tone, accommodation, compliance, antral contraction and small intestinal transit in animals or humans. In this study, we aimed to determine the effects of rimonabant on upper GI motility in healthy dogs.

Material and Methods

Animal and surgical preparation

A total of 12 healthy female dogs (18-27 kg) were operated after an overnight fast under general anaesthesia as described earlier [12]. Under midline laparotomy, one pair of 28-gauge cardiac pacing wires (A and E Medical, Farmingdale, NJ, USA) were implanted on the gastric serosa along the great curvature 6 cm above the pylorus. Another pair of wires was implanted in the small-bowel serosa 35 cm below the pylorus. The two electrodes in each pair were arranged in a circumferential pattern with an interval of about 0.5-1.0 cm. The electrodes were affixed to the serosa by nonabsorbable sutures. The connecting wires of the electrodes were tunnelled through the anterior abdominal wall subcutaneously and placed outside the skin. In six of the dogs, a cannula was placed in the duodenum 20 cm beyond the pylorus. In the other six dogs, a cannula was placed in the stomach. At the end of the surgical procedure, the dogs were placed in a recovery cage after receiving medications for postoperative pain management. The study was initiated after the dogs had thoroughly recovered from

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the surgery (usually 2 weeks after the surgery). The study was approved by the Institutional Animal Care and Use Committees of the VA Medical Centre, Oklahoma City, OK (P#1102-002).

GI motility measurements

Gastric emptying: The animal was fed with a 237 ml liquid meal (240 kcal; Boost; Novartis Medical Nutrition) mixed with 100 mg of phenol red. The gastric effluent was collected from the duodenal cannula every 15 min for 90 min. For each collection of the gastric effluent, the volume was recorded and a 5 ml sample was taken and analyzed all together at the end of the study using a spectrophotometer [13].

Gastric and intestinal slow waves: Gastric and intestinal slow waves were recorded from the gastric and intestinal electrodes using a multichannel recorder (Acknowledge III, EOG 100A; Biopac Systems, Santa Barbara, CA, USA). A previously established spectral analysis method was used to evaluate the following slow wave parameters: a) the Dominant Frequency (DF) and Dominant Power (DP); b) the percentage of normal slow waves (4-6 cycles/min (cpm) for the stomach and 17-22 cpm for the small bowel) [14].

Gastric tone: Gastric tone was assessed by the measurement of gastric volume under an isobaric operating pressure. For each individual animal, one same operating pressure was used, defined as a pressure 2 mmHg above the minimal distending pressure. Gastric volume was calculated by averaging all values during a particular period excluding initial transient data.

Gastric compliance: A stepwise pressure distension procedure was applied to test gastric compliance. Isobaric distension was performed in 4 mmHg steps every 60 s from 2 mmHg to a maximum of 18 mmHg. The volume was averaged over the last 30 s of each pressure level. Gastric compliance was defined as the linear slope of the volume-pressure curve [15].

Gastric accommodation: Gastric accommodation was defined as the difference in gastric volume measured under the isobaric condition between the postprandial state and the preprandial state. It was computed as the averaged gastric volume after a liquid meal minus the average gastric volume in the pre-prandial state [16].

Intestinal and gastric antral contractions: Intestinal and gastric antral contractile activities were recorded from the four pressure sensors attached to a manometric catheter using a microcapillary infusion system (Medtronic Synectics, Stockholm, Sweden). The manometric catheter was inserted into the gastric antrum or the jejunum via the gastric or the duodenal cannula. Small-bowel or gastric antral contractions were recorded for 30 min before a solid meal (413 kcal; Pedigree; Master foods USA) and for 40 min immediately after the solid meal. The area under contractions, defined as the Contractile Index (CI) was computed using the Polygram function testing software (Medtronic, version 2.04; Synectics Medical) [17].

Experimental design

Four experiments were performed in each dog. Each experiment included 3 sessions: control (saline) and 2 rimonabant sessions (1 mg/kg or 0.5 mg/kg) in a randomized order on separate days at an interval of 3 days. The dose of rimonabant was determined based on a previous study performed by others [8]. The solvent of rimonabant is the solvent was saline. The protocol for the rimonabant sessions were the same as control session except that rimonabant was given one hour before the session was initiated.

Experiment 1: Experiment was performed to study the effects of rimonabant on gastric emptying and gastrointestinal myoelectrical activities in the dogs with a duodenal cannula. In the control session, preprandial gastrointestinal myoelectrical activity was recorded for 30 min. After the dogs were fed with a liquid meal (tell compositions of the meal), the gastric effluent from the duodenal cannula was collected and postprandial gastrointestinal myoelectrical activities were recorded for 60 min.

Experiment 2: Experiment was designed to study the effects of rimonabant on gastric tone, compliance and accommodation in the same six dogs with the gastric cannula. Each session included a 30 min recording of gastric volume under an isobaric operating pressure followed by gastric compliance test. Then gastric volume was recorded for 40 min immediately after a liquid meal (Ensure, 350 calories / bottle, Walmart, Oklahoma City, OK).

Experiments 3 and 4: Experiment was performed in the dogs with the gastric cannula and dogs with the duodenal cannula to investigate the effect of rimonabant on gastric antral contractions and small bowel contractions, respectively. The contractions were recorded before a solid meal (Pedigree Complete Nutrition Beef and Chicken, 450 calories/can, Walmart, Oklahoma City, OK) for 30 min and immediately after the solid meal for 40 min.

Statistical Analysis

All data are presented as the mean ± the standard error. One-way ANOVA was used to investigate the difference in any of the above mentioned parameters among different sessions. Statistical significance was assigned at $p<0.05$.

Results

Rimonabant accelerated gastric emptying of liquid

Rimonabant significantly accelerated gastric emptying of liquid at a dose of 1.0 mg/kg but not 0.5 mg/kg. Gastric emptying was 62.3 ± 7.7% at 75 min and 67.2 ± 7.7% at 90 min in the control session, and increased to 72.1 ± 5.1% at 75 min ($p=0.049$, vs. control) and 76.8 ± 5.3% at 90 min ($p=0.039$, vs. control) in the session with rimonabant of 1mg/kg (Figure 1).

Rimonabant increased gastric tone and impaired gastric accommodation

Rimonabant at both doses significantly increased gastric tone in the dogs. The typical tracings of gastric volume measured under the same isobaric condition in the control and rimonabant sessions are shown

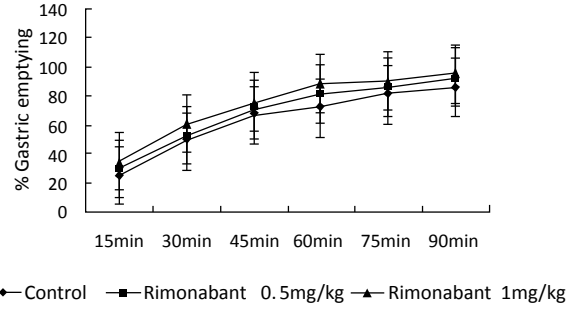


Figure 1: The effects of rimonabant on the percentage of gastric emptying of liquids. Gastric liquid emptying percent was significantly accelerated after rimonabant 1 mg/kg administrated.

in Figures 2A1-2A3. Gastric volume was significantly reduced in both rimonabant sessions and the effect was significantly more potent with the dose of 1.0 mg/kg than the lower dose of 0.5 mg/kg (Figure 2B). Rimonabant also significantly decreased gastric accommodation in a dose-dependent manner with the dose of 1.0 mg/kg being significantly more potent than the dose of 0.5 mg/kg (Figure 2C).

Rimonabant impaired gastric compliance

Rimonabant reduced gastric compliance (Figure 3) shows the pressure-volume curves in the control and rimonabant sessions. The gastric compliance expressed as the slope of the pressure-volume was reduced from 9.59 ± 0.72 ml/mmHg in the control session to 6.97 ± 1.15 ml/mmHg in the rimonabant of 1.0 mg/kg session (P=0.0002 vs. control) and 7.01 ± 0.58 ml/mmHg in the rimonabant of 0.5 mg/kg session (P=0.0002 vs. control).

Rimonabant inhibited gastric antral motility

Rimonabant significantly decreased gastric antral contractions in a dose-dependent manner (Figure 4A). The postprandial contractile index of the antrum was 10.1 ± 1.4 in the control session and decreased to 7.3 ± 1.5 in the session with rimonabant of 0.5 mg/kg and 5.8 ± 1.2 (p=0.014 vs. control) in the session with rimonabant of 1.0 mg/kg. Typical tracings of postprandial gastric antral contractions in the control session and the sessions with Rimonabant are presented in (Figure 4B).

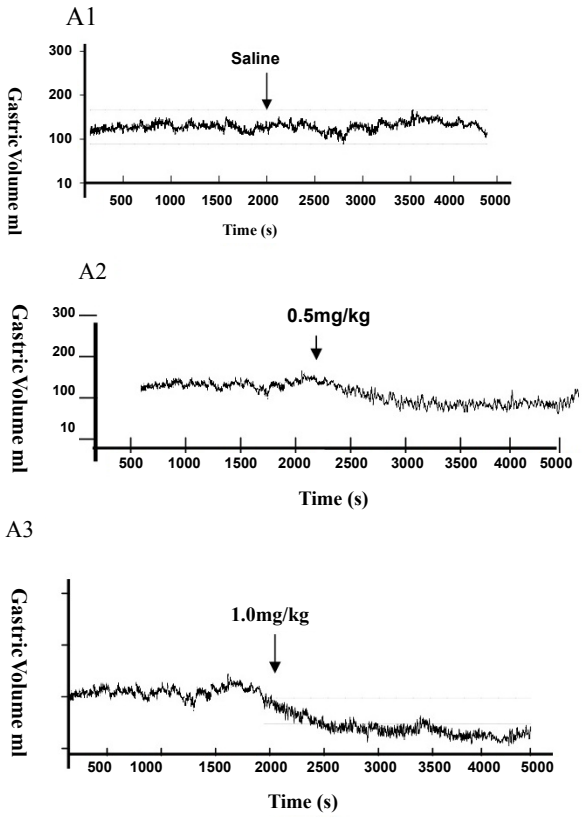
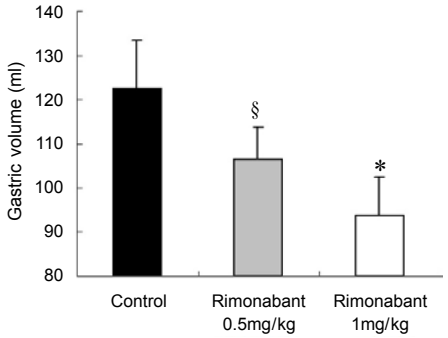
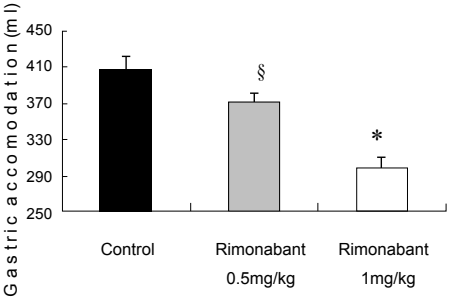


Figure 2A: A1: Rimonabant increased gastric tone dose-dependently (reflected as a decrease in gastric volume measured under isobaric condition: A1: control). **A2:** Rimonabant increased gastric tone dose-dependently (reflected as a decrease in gastric volume measured under isobaric condition, A2: rimonabant 0.5 mg/kg). **A3:** Rimonabant increased gastric tone dose-dependently (reflected as a decrease in gastric volume measured under isobaric condition: A3: rimonabant 1mg/kg).



*p <0.05, vs. the corresponding baseline **p<0.05, vs. the corresponding Rimonabant 0.5 mg/kg

Figure 2B: Rimonabant increased gastric tone and decreased gastric accommodation significantly and dose-dependently. The gastric volume decreased in fasting state after rimonabant administration.



*p < 0.05, vs. the corresponding baseline **p<0.05, vs. the corresponding Rimonabant 0.5 mg/kg

Figure 2C: Rimonabant increased gastric tone and decreased gastric accommodation significantly and dose-dependently. The gastric volume decreased postprandially after rimonabant administration.

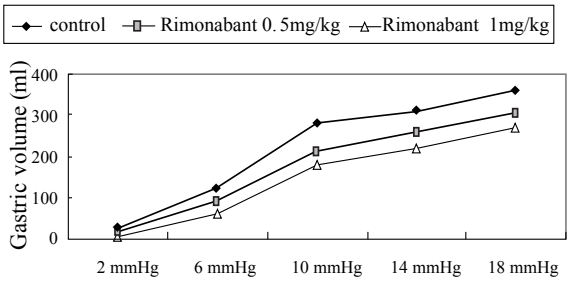


Figure 3: The volume–pressure curves represent the mean value of barostat intraballoon volume for each of the distension with or without rimonabant administration. Gastric compliance was significantly decreased after rimonabant administration (*p<0.01). These effects were dose-dependently.

Rimonabant increased small-bowel contractions

Rimonabant significantly increased postprandial small-bowel contractions in a dose-dependent manner (Figure 5A). The contraction index of the small bowel was 9.6 ± 2.4 in the control session and increased to 12.4 ± 1.5 (P=0.018 vs. control) in the session with rimonabant of 0.5 mg/kg and 14.8 ± 2.5 (P=0.008 vs. control) in the session with rimonabant of 1.0 mg/kg. Typical tracings of postprandial small-bowel contractions in the control and rimonabant sessions are presented in (Figure 5B).

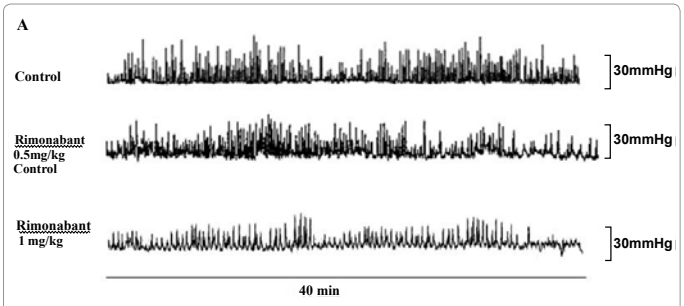


Figure 4A: The Antral contraction tracing with or without rimonabant.

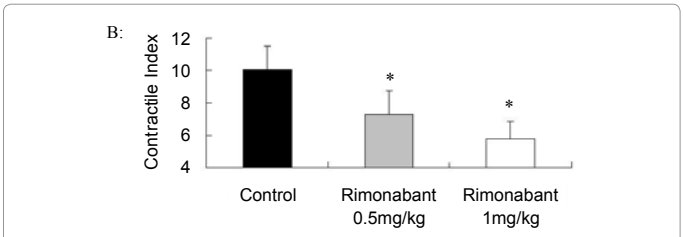


Figure 4B: Rimonabant decreased antral contraction significantly and dose-dependently. The antral CI present in different groups. *P<0.05 vs. Control.

Rimonabant had no effects on gastric and small intestinal slow waves

Rimonabant did not alter gastric and intestinal slow waves. In the control session, the DF of the gastric and intestinal slow waves was 5.01 ± 0.34 cycles/min (cpm) and 19.44 ± 0.54 cpm respectively in the fasting state 4.91 ± 0.32 and 19.63 ± 0.54 cpm, respectively in the postprandial state and 4.79 ± 0.29 cpm and 19.14 ± 0.61 cpm, respectively in the postprandial state in the session with rimonabant 1mg/kg ($p > 0.05$ vs. the corresponding control). Also, the dominant power was not changed with rimonabant. It was –4.05 ± 0.98 dB and –9.60 ± 3.9dB, respectively in the fasting state, –4.20 ± 0.76 and –6.89 ± 4.71dB, respectively in the postprandial state and –4.4 ± 1.12 dB and –6.37 ± 5.79 dB, respectively in the postprandial state in the session with rimonabant 1mg/kg ($p > 0.05$ vs. the corresponding control). In addition, the percentages of normal gastric and intestinal slow waves were not changed with rimonabant. It was 93.6 ± 6.0% and 99.4 ± 1.4%, respectively in the fasting state, 95.6 ± 2.4% and 95.5 ± 2.2%, respectively in the postprandial state, and 94.1 ± 2.12% and 95.71 ± 4.03% respectively in the postprandial state in the session with rimonabant 1mg/kg ($p>0.05$ vs. the corresponding control).

Discussion

In the current study, we have found 1) rimonabant accelerated gastric liquid emptying; 2) rimonabant increased gastric tone, impaired gastric accommodation and compliance; 3) rimonabant inhibited postprandial gastric antral contractions; 4) rimonabant increased postprandial small bowel contractions; and 5) gastric or small bowel slow waves were not affected by rimonabant. Gastric liquid emptying was accelerated with rimonabant in our current study, which was in agreement with a precious rodent study [8]. An initial acceleration of gastric liquid emptying may result in reduced symptoms of fullness arising in the stomach, but may lead to a higher rate of energy delivery into the duodenum, thus increasing volume load and distension of the proximal small intestine, which may cause a greater fullness or satiation after the meal [18]. That is, the accelerative effect of rimonabant on liquid gastric emptying may provide earlier and stronger satiety signals.

We also observed that rimonabant increased gastric tone and impaired gastric accommodation and compliance. Gastric tone is generated by sustained muscular contractions of the stomach wall. Gastric accommodation and compliance play an important role in the regulation of gastric distention and intestinal exposure of nutrients, hence it may also control satiation [19]. The increased gastric tone impairs gastric accommodation and compliance. Impaired accommodation and compliance are primarily responsible for the fullness sensation in dyspepsia [20]. The decrease in gastric accommodation and compliance with rimonabant observed in the present study suggests a peripheral role of rimonabant in limiting food intake. Other the other hand, it has been known that different mechanisms are involved in gastric emptying of solids and liquids, which cause different effects on food intake and appetite. Gastric emptying of liquid is driven mainly by the tone of the gastric fundus, whereas the emptying of solid is achieved by antral contraction and gastric peristalsis. Accordingly, the acceleration in liquid gastric emptying with rimonabant in our study may be attributed to the increase in gastric tone. While it enhances tone of the stomach, rimonabant inhibited antral contractions. The exact mechanisms involved in this inhibitory effect were not clear. However, as an anti-obesity agent, the suppression of antral contractions might have a synergistic effect on the reduction of food intake. As mentioned above, gastric emptying of solid is accomplished by antral contractions. The reduction in antral contractions may lead to delayed gastric emptying of solids, which results in prolonged feeling of abdominal fullness and postprandial satiety. We also found that the rimonabant increased small intestinal contractions, which may increase the small intestinal transit. The small bowel transit plays an important role in nutrient absorption that is related to the development of obesity. On one hand, increasing

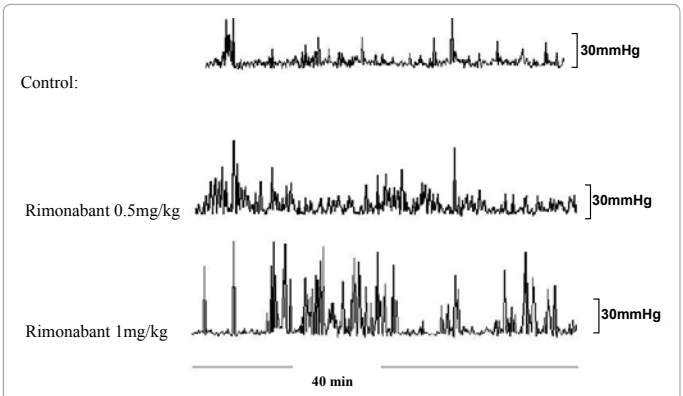


Figure 5A: Recording of small bowel contractions. A: Showed the small bowel contraction tracing with or without rimonabant.

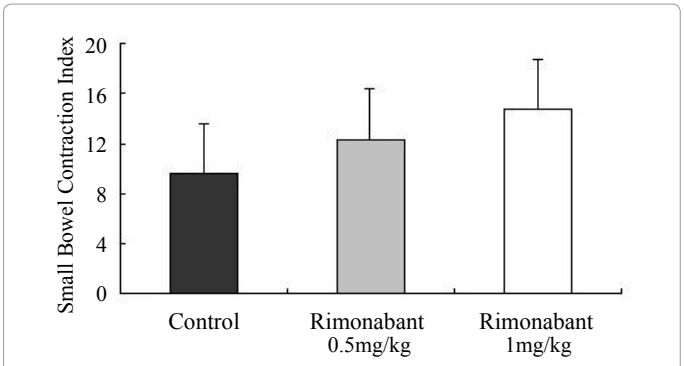


Figure 5B: Small-bowel contractions were significantly increased in the session with rimonabant dose-dependently.*P<0.05 vs. Control.

intestinal transit caused the reduction of fat absorption [21], suggesting the therapeutic potential for obesity. On the other hand, under normal physiological situations, undigested nutrients can reach the ileum, which activates the ileal brake. A reduction in small bowel transit time may diminish absorption of the components of that meal in the small bowel [22] and induce early triggering of ileal brake. The relevance of the ileal brake as a potential target for weight management is based on specific findings [23]: First, the ileal brake activation reduces food intake and increases satiety levels, which appeared to be maintained over time. Second, previous study proved that the increasing exposure of the ileum to nutrients under surgical procedures produced weight loss and improved glycemic control. These findings suggest that the actions of rimonabant on regulating energy balance and lipid metabolisms might be partially attributed to the enhancement in small bowel motility.

However, rimonabant has tolerance and some side effects. In a non-obese rodent study with repeated administration of rimonabant [24] tolerance to the anorectic effect of rimonabant was reported to develop over time. In a study investigating the effects of repeated administration of rimonabant on gastrointestinal propulsion in mice, the acute administration of rimonabant produced a marked stimulation of small intestinal peristalsis [25]. But, tolerance to this effect rapidly developed after repeated treatments and the stimulant effect of rimonabant on the transit of the non-absorbable marker through the small intestine vanished on the third day of treatment [25]. The prokinetic effect of CB1 receptor antagonists in animals is consistent with data from clinical trials that highlighted diarrhea as one of the initial adverse events associated with rimonabant. Van Gaal et al. reported that at 1 year, adverse events more frequently related to rimonabant were gastrointestinal, neurological and psychiatric in nature and serious adverse events were infrequent and almost equivalent to placebo [26]. Due to the central action of the CB1 receptor agonists, adverse events of severe depression and suicidal thoughts were frequently reported with the use of rimonabant [27-29]. On the other hand, recent studies have been undertaken to characterize the behavioral effects of CB1 receptor neutral antagonists such as AM4113 to determine if these drugs can reduce feeding and food-reinforced behaviors. Across a variety of different tests, AM4113 produces effects on food-motivated behavior that are very similar to those produced by CB1 antagonist-inverse agonists (such as rimonabant) [30]. Moreover, this drug did not induce conditioned gaping in rats or vomiting in ferrets [31]. These results suggest that CB1 receptor neutral antagonists may decrease appetite by blocking endogenous cannabinoid tone, and that these drugs may be less associated with nausea than is the case for CB1 antagonist-inverse agonists. Above all, the strengths of rimonabant are as follows: (1) In 4 well-designed studies with >6600 overweight and obese patients, rimonabant has demonstrated consistent efficacy with regard to weight reduction [1,2,32]; (2) Rimonabant offers a novel mechanism of action, which may make it well suited as an alternative for people who do not respond well to other agents and for combination treatment with other anti-obesity agents; (3) Weight loss achieved with rimonabant also appears to improve some features of metabolic syndrome [32]; (4) Its pharmacokinetic profile appears to be favorable in general; (5) Most side effects appear to be mild and transient; (6) No evidence of any significant cardiovascular adverse effects exists.

The limitations of rimonabant are the following: (1) Weight-reduction efficacy is not superior to the modest effects observed with currently approved anti-obesity drugs; (2) Although rimonabant appeared to be reasonably well tolerated in general, psychiatric symptoms (severe depression and suicidal thoughts) were the most common adverse effects [27] that led to suspension from the European market. (3) In a non-obese rodent study with repeated administration of rimonabant, tolerance to the anorectic effect of rimonabant was reported to develop over time [24,25].

(3) The sample of subjects enrolled in the RIO trials had limited racial diversity. According to the discussion above, this compound has limitation in clinic application. However, since the EC system plays a very important role in energy metabolism and food intake, the CB receptor antagonists still have potentials in obesity treatment. One of the mechanisms may be mediated via the GI motility modulation effects. Our current research helped to understand anti-obesity effects of rimonabant, the CB1 receptor antagonist. Future works should be devoted to develop CB1 antagonists that do not cross the blood-brain barrier or improving the chronic use of low dose rimonabant.

Conclusion

In conclusion, rimonabant increases gastric tone and impaired gastric compliance and accommodation; it also inhibits antral contractions but increases intestinal motility. These findings suggest the peripheral mechanisms of rimonabant in reducing food intake and body weight loss in obesity patients.

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