Neurogastroenterol Motil (2004) **16,** 439–446 doi: 10.1111/j.1365-2982.2004.00564.x

Effect of ghrelin and growth hormone-releasing peptide 6 on septic ileus in mice

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Abstract *Ghrelin is an orexigenic peptide with prokinetic effects in the rat. We investigated the effect of ghrelin and growth hormone-releasing hormone 6 (GHRP-6) on gastric emptying and transit in control and septic mice. Mice were injected i.p. with lipopolysaccharides (LPS) or saline (control). After 16–17 h mice were pretreated with saline, ghrelin or GHRP-6 1 h before intragastric administration of Evans blue. Fifteen minutes later, after assessment of the behaviour scale, mice were killed and gastric emptying, transit and rectal temperature were measured. In control mice, ghrelin (100 μg kg^{-1}) and GHRP-6 (20–100 μg kg^{-1}) accelerated gastric emptying, whereas ghrelin and GHRP-6 failed to increase transit significantly. Septic mice developed a delay in gastric emptying and transit, hypothermia and a deterioration of the behaviour scale. In septic mice, ghrelin (20 μg kg^{-1}) accelerated gastric emptying without effect on transit while GHRP-6 significantly accelerated gastric emptying dose-dependently and failed to increase transit significantly. Ghrelin and GHRP-6 had no effect on the endotoxin-induced hypothermia or deterioration of behaviour scale. Therefore, the beneficial prokinetic effect of ghrelin but mainly of GHRP-6 offers potential therapeutic options in the treatment of septic gastric ileus.*

Keywords *endotoxin, gastric emptying, ghrelin, GHRP-6, ileus, sepsis.*

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Received: 18 November 2003
Accepted for publication: 20 January 2004

INTRODUCTION

Ghrelin, a 28 amino acid octanoylated peptide, is the endogenous ligand for the growth hormone secretagogue-receptor (GHS-R) first isolated from rat and human stomach.[1] Meanwhile, ghrelin structures have been determined in mouse, pig, cow, sheep and dog.[2,3] The highest number of ghrelin-producing cells is found in the stomach where ghrelin is produced by the enteroendocrine X/A-like cells in the oxyntic mucosa of rats and humans.[4,5] Ghrelin not only stimulates growth hormone secretion but also has a number of other regulatory functions in the brain and the periphery.[6–8] Ghrelin has important orexigenic and adipogenic effects, stimulating food intake and reducing fat utilization in rodents [9,10] and enhancing appetite and food intake in humans.[11] In the gastrointestinal tract, ghrelin stimulates gastric acid secretion and gastric motility in rats.[12,13] The receptor for ghrelin, the GHS-R, has been identified prior to the discovery of ghrelin by the use of enkephalin analogues that stimulated the release of growth hormone secretagogues.[14] One such peptide is growth hormone-releasing peptide 6 (GHRP-6), a hexapeptide shown to actively release growth hormone *in vivo* in humans and animals.[6]

Sepsis is the leading cause of death in critically ill patients.[15] During the onset of sepsis, the inflammatory system becomes hyperactive, with the production of chemokines, cytokines and reactive oxygen species. In later stages of sepsis, anti-inflammatory mediators are produced and various innate functions are suppressed. This might lead to a hyporeactive host defence system rendering the patients more susceptible to bacterial translocation and secondary infections.[15,16] During sepsis, the most frequent gastrointestinal complications are ileus and mucosal barrier dysfunction.[17] In the pathogenesis of ileus, the involvement of both neuronal and local inflammatory responses within the bowel wall is postulated.[18] Afferent neurones in

the bowel wall are activated by different mediators, produced by the local inflammatory cells, such as NO (nitric oxide), prostaglandins and monocyte chemoattractant protein (MCP-1).[18–20] Stimulation of afferent neurones activates a neuronal reflex pathway resulting in the activation of inhibitory adrenergic and nitrergic motor neurones.[21,22] Ileus is involved in the pathophysiology of sepsis by promoting bacterial stasis, overgrowth and translocation.[23] Theoretically, ileus could be overcome by stimulation of excitatory pathways to increase the gastrointestinal motility thereby interrupting the occurrence and/or maintenance of bacterial translocation and the activation of inflammatory cascades. Previously we showed that prokinetic therapy with cisapride had a beneficial effect in postoperative ileus in rats.[24] However, clinical trials have met with limited success and patients experienced unwanted side-effects.[25,26] Ghrelin has prokinetic effects on postoperative ileus in the rat,[13] suggesting that ghrelin and other synthetic GHS-R agonists may have a therapeutical potential in this condition. However, little is known about the effect of ghrelin on the murine gastrointestinal tract. Therefore, the aim of our study was to investigate the effect of ghrelin and GHRP-6 on gastric emptying and small intestinal transit in mice in control conditions and during sepsis.

MATERIALS AND METHODS

Set-up experimental procedure

All procedures received approval from the Committee for Medical Ethics and the use of Experimental Animals at the University of Antwerp. Sepsis was induced after intraperitoneal injection of lipopolysaccharides (LPS), a commonly used model for sepsis in animals.[27,28] However, as there are considerable differences between different animal species in sensitivity to bacterial factors, it is important to develop a reproducible experimental set-up limiting confounding variables such as the animal species (including strain and gender), the time schedule and the serotype and dose of LPS.[27,28] Preliminary results learned that intraperitoneal injection of LPS from *Escherichia coli* (serotype 055:B5) in a dose of 20 mg kg^{-1} in male Swiss OF1 mice induced a reproducible delay in gastric emptying, small intestinal transit and rectal temperature after 16–18 h without induction of diarrhoea or intussusception and with an acceptable mortality rate less than 10%. We reproduced these findings in previous experiments investigating the role of inducible nitric oxide synthase in septic ileus.[29]

Swiss OF1 mice (30–38 g) were fasted at 9 AM for 24 h with free access to water. They received an intraperitoneal (i.p.) injection with saline (control) or LPS (*E. coli* 055:B5; 20 mg kg^{-1}) at 5 PM. The next morning, i.e. 16–17 h after LPS or saline injection, drugs or saline were injected i.p. once. We injected the drugs well after induction of sepsis to investigate their potential therapeutic benefit in septic ileus. One hour after injection of saline or the drug under study, the mice received an intragastric injection of 0.1 mL Evans blue, a non-nutrient semi-liquid solution (50 mg mL^{-1} 0.9% NaCl with 0.5% methylcellulose).[30] Fifteen minutes later, after assessing the general sickness behaviour of the mice (for details see next paragraph), the mice were anaesthetized with ether inhalation, rectal temperature was measured (°C) as an indicator of the severity of the sepsis induced and a laparotomy was performed. The stomach was clamped above the lower oesophageal sphincter and beneath the pylorus to prevent leakage of Evans blue. The gastrointestinal tract was resected (stomach to caecum) and intestinal transit of Evans blue was measured from the pylorus to the most distal point of migration. Total length of the small intestine was measured and transit was expressed in percentage (migration of Evans blue compared with the total length).[22] Thereafter, the stomach was cut beneath the lower oesophageal sphincter clamp and above the pyloric clamp. Gastric emptying was determined spectrophotometrically as previously described.[29] Briefly, the stomach and its contents were put in 15 mL 0.1 N NaOH. The stomach was minced and homogenized (PRO 200; Pro Scientific Inc., Monroe, CT, USA) during 30 s. The suspension was diluted with 0.1 N NaOH to 20 mL and kept for 1 h at room temperature. Five millilitres of the supernatant were then centrifuged at 1356 g for 20 min at 4 °C. Samples were further diluted 1/5 with 0.1 N NaOH and absorbance of the sample was read at a wavelength of 565 nm (A565) with a Cary 4E UV-visible spectrophotometer (Varian, Mulgrave, Victoria, Australia). The stomach and its contents obtained from a mouse killed immediately after orogastric administration of Evans blue served as standard (reference stomach). Percentage gastric emptying was calculated by the formula [(A565 reference−A565 sample)/A565 reference] × 100.

Behaviour scale

We also used a subjective scale to validate the sickness behaviour of the mice and signs of toxicity as previously described.[29] A global scale between 1 and 5 was given to each mouse. Systemic toxicity was monitored

by several characteristic parameters such as a ruffled fur, piloerection, immobility, lethargy and conjunctivitis. Mice were monitored before injection of Evans blue. A score of 1 indicates normal active, exploring behaviour with a normal appearance of the fur and eyes, a score of 2 indicates mild symptomatology (mild piloerection, mild conjunctivitis, less explorative behaviour), score of 3 moderate symptomatology (ruffled fur, piloerection, severe conjunctivitis, only moving around after tactile stimulation), a score of 4 serious symptomatology (severe conjunctivitis, piloerection, ruffled fur and lethargic) and a score of 5 indicates a severely ill mouse that is nearly dying.

Experimental protocol

In a first series of experiments we investigated the effect of ghrelin treatment. Therefore, the mice were randomly (Latin square) divided into two groups: one control group receiving an i.p. injection of saline and the other group receiving an i.p. injection with LPS (20 mg kg^{-1}). Both groups were subdivided into three subgroups that received an i.p. injection of saline, ghrelin 20 μg kg^{-1} or ghrelin 100 μg kg^{-1} 1 h before Evans blue. Doses were chosen in accordance with literature data in rodents.[10,12,13,31] In these six subgroups (each $n = 8$–9) gastric emptying, small intestinal transit, rectal temperature and behaviour scale were measured.

In a second series of experiments we investigated the effect of GHRP-6. Therefore, the mice were randomly (Latin square) divided into two groups: one control group receiving an i.p. injection of saline and the other group receiving an i.p. injection with LPS (20 mg kg^{-1}). Both groups were subdivided into three subgroups receiving an i.p. injection of saline, GHRP-6 20 μg kg^{-1} or GHRP-6 100 μg kg^{-1} 1 h before Evans blue. Doses were chosen in accordance with literature data in rodents.[10] In these six subgroups (each $n = 10$) we measured gastric emptying, small intestinal transit, rectal temperature and behaviour scale.

Drugs used

We used diethyl ether (Merck, Darmstadt, Germany) and NaCl 0.9% (Baxter, Lessines, Belgium). Evans blue and LPS (*E. coli* serotype 055:B5) were purchased from Sigma (St Louis, MO, USA). Ghrelin (rat) was purchased from Tocris (Bristol, UK), GHRP-6 was purchased from Bachem (St Helens, UK).

Presentation of results and statistical analysis

Throughout the manuscript, mice that did not receive LPS, are referred to as 'control' mice. Mice that were injected with saline instead of the drug under study are referred to as 'saline-treated.'

Parametric values are shown as mean ± SEM for n indicating the number of mice used. For statistical analysis we used two-way ANOVA. The first factor concerned the presence or absence of LPS, the second parameter the drug under study. For post hoc testing we used a one-way ANOVA followed by a Dunnett post hoc test (drug effect, three groups) or a non-paired Student's t-test (LPS effect, two groups) as appropriate. $P \leq 0.05$ was considered to be significant. The behaviour scale values are nonparametric and shown as median with their 25th and 75th percentiles. Nonparametric analysis was performed using Kruskal–Wallis testing for three groups and Mann–Whitney U-test when only two groups were involved. $P \leq 0.05$ was considered to be significant. All data were analysed with the SPSS for Windows software (SPSS Inc., Chicago, IL, USA).

RESULTS

Effect of ghrelin on gastric emptying and small intestinal transit

Gastric emptying In saline-treated control mice gastric emptying was 55.8 ± 3.5%. Gastric emptying was not altered by ghrelin 20 μg kg^{-1} (54.5 ± 4.8%) but was significantly enhanced to 73.7 ± 2.8% in control mice treated with 100 μg kg^{-1} ghrelin (Fig. 1A). LPS significantly delayed gastric emptying to 32.9 ± 5.7% in saline-treated LPS mice (Fig. 1A). Treatment with either 20 or 100 μg kg^{-1} ghrelin in LPS mice did not induce a significant change when compared with saline-treated LPS mice (Fig. 1A). However, the effect of LPS on gastric emptying was no longer significant in mice treated with ghrelin 20 μg kg^{-1}: gastric emptying after treatment with ghrelin 20 μg kg^{-1} was 54.5 ± 4.8% in control mice and 51.6 ± 5.1% in LPS mice (Fig. 1A).

Small intestinal transit In saline-treated control mice small intestinal transit was 37.8 ± 4.2%. Ghrelin at a dose of 20 and 100 μg kg^{-1} had no significant effect on the small intestinal transit in control mice: transit was, respectively, 36.5 ± 4.2% and 45.4 ± 3.4% (Fig. 1B). LPS significantly delayed small intestinal transit to 19.3 ± 1.7% in saline-treated LPS mice (Fig. 1B). After treatment with ghrelin 20 and 100 μg kg^{-1} in LPS mice, transit was not significantly altered: transit was 22.6 ± 2.7% and 19.3 ± 2.8%, respectively (Fig. 1B). The effect of LPS on transit remained significant in the three groups of mice (saline-treated and both doses of ghrelin) (Fig. 1B).

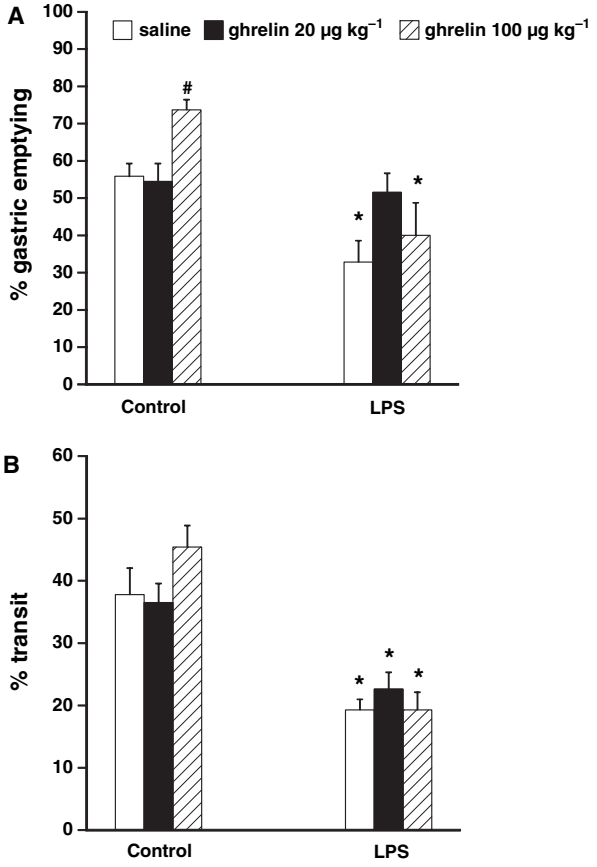

Figure 1 Effect of lipopolysaccharides (LPS) in saline-treated mice (open bars, $n = 8$–9), in ghrelin 20 μg kg^{-1}-treated mice (solid bars, $n = 9$) and in ghrelin 100 μg kg^{-1}-treated mice (hatched bars, $n = 8$) (A) on percentage gastric emptying and (B) on percentage transit. Results are expressed in percentage gastric emptying and percentage transit and shown as mean ± SEM. Two-way ANOVA was used followed by post hoc testing: one-way ANOVA followed by Dunnett test (drug effect) or non-paired Student's *t*-test (LPS effect). $P \leq 0.05$, significant drug effect within control group compared with saline-treated mice; *, $P \leq 0.05$, significant effect of LPS in mice treated with the same drug regimen.

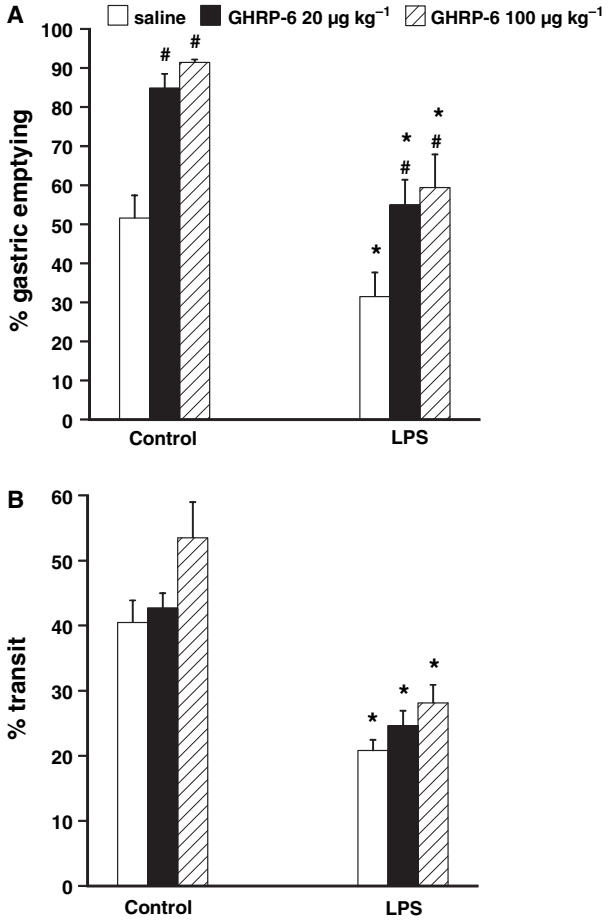

Figure 2 Effect of lipopolysaccharides (LPS) in saline-treated mice (open bars, $n = 10$), in GHRP-6 20 μg kg^{-1}-treated mice (solid bars, $n = 10$) and in GHRP-6 100 μg kg^{-1}-treated mice (hatched bars, $n = 10$) (A) on percentage gastric emptying and (B) on percentage transit. Results are expressed in percentage gastric emptying and percentage transit and shown as mean ± SEM. Two-way ANOVA was used followed by post hoc testing: one-way ANOVA followed by Dunnett test (drug effect) or non-paired Student's *t*-test (LPS effect). $P \leq 0.05$, significant drug effect within control or LPS group compared with saline-treated mice; *, $P \leq 0.05$, significant effect of LPS in mice treated with the same drug regimen.

Effect of GHRP-6 on gastric emptying and small intestinal transit

Gastric emptying In saline-treated control mice gastric emptying was 51.6 ± 5.8%. Gastric emptying was significantly and dose-dependently increased by GHRP-6 20 and 100 μg kg^{-1} in control mice to respectively 84.8 ± 3.7% and 91.4 ± 0.7% (Fig. 2A). LPS significantly delayed gastric emptying to 31.5 ± 6.2% in saline-treated LPS mice (Fig. 2A). After treatment with GHRP-6 20 and 100 μg kg^{-1} in LPS mice, gastric emptying significantly and dose-dependently increased to respectively 55.0 ± 6.5% and 59.4 ± 8.5% (Fig. 2A). The effect of LPS on gastric emptying remained significant in all three groups (saline-treated and both doses of GHRP-6) (Fig. 2A).

Small intestinal transit In saline-treated control mice small intestinal transit was 40.5 ± 3.4%. GHRP-6 20 μg kg^{-1} had no significant effect on the small intestinal transit in control mice. After treatment with GHRP-6 100 μg kg^{-1}, small intestinal transit was 53.5 ± 5.5%; however, no significance was reached ($P = 0.052$; Fig. 2B). LPS significantly delayed small intestinal transit to 20.8 ± 1.6% in saline-treated LPS

mice (Fig. 2B). After treatment with GHRP-6 20 and 100 μg kg^{-1} in LPS mice, transit did not increase significantly: transit was respectively 24.7 ± 2.3% ($P = 0.396$) and 28.1 ± 2.8% ($P = 0.059$) (Fig. 2B). The effect of LPS on transit remained significant in the three groups of mice (saline-treated and both doses of GHRP-6) (Fig. 2B).

Effect of ghrelin and GHRP-6 on rectal temperature and behaviour scale

Lipopolysaccharides induced a significant decrease in rectal temperature in saline-treated mice both in the ghrelin and GHRP-6 experiments from respectively 36.3 ± 0.1 °C and 36.3 ± 0.2 °C in control mice to 30.3 ± 0.9 °C and 31.0 ± 0.6 °C in LPS mice. Ghrelin 20 and 100 μg kg^{-1} had no effect on rectal temperature in control mice (36.2 ± 0.3 °C and 36.4 ± 0.2 °C, respectively) or LPS mice (31.5 ± 0.8 °C and 32.4 ± 0.7 °C, respectively). In addition, GHRP-6 20 and 100 μg kg^{-1} had no effect on rectal temperature in control mice (36.1 ± 0.3 °C and 36.1 ± 0.2 °C, respectively) or LPS mice (31.2 ± 0.6 °C and 31.6 ± 0.4 °C, respectively).

Lipopolysaccharides induced a significant increase in behaviour scale in saline-treated mice in both the ghrelin and GHRP-6 experiments from 1 (1–1) in control mice to respectively 3 (3–3) and 3 (3–4) in LPS mice. Ghrelin and GHRP-6 in both doses had no effect on the behaviour scale in control mice [1 (1–1) and 1(1–1), respectively] and LPS mice [3 (3–3) and 3(3–3.25), respectively]. There was no mortality in the LPS-treated mice in the ghrelin experiments, whereas three of 33 mice (9%) died during the night after LPS injection but before injection of saline or GHRP-6.

DISCUSSION

This study provides evidence for a prokinetic role of ghrelin and GHRP-6 on gastric emptying in control mice without a significant effect on small intestinal transit. In septic mice, GHRP-6 significantly and dose-dependently accelerated gastric emptying. Only the lower dose of ghrelin had prokinetic effects on gastric emptying in septic mice. Both ghrelin and GHRP-6 had no significant effect on small intestinal transit in septic mice.

Effects of ghrelin and GHRP-6 in control mice

Our results illustrating the prokinetic effect of ghrelin on gastric emptying in control mice are in accordance with previous literature studies most of which were performed in rats. In our study, ghrelin and GHRP-6 were unable to significantly accelerate small intestinal transit in control mice. This is in contrast to our results in rats where we found an increase in small intestinal transit after administration of both ghrelin and GHRP-6.[32] Trudel *et al.* previously showed that ghrelin was able to accelerate gastric emptying and small intestinal transit in conscious rats without effect on colonic transit.[13] Masuda *et al.* described an increase in the amplitude of gastric motility after administration of ghrelin in anaesthetized rats.[12] In mice, ghrelin increased food intake and gastric emptying rate.[31] The estimated half-life of exogenous ghrelin in rat plasma is 30 min.[33] Both our study and the study of Asakawa *et al.* [31] showed the potency of ghrelin 100 μg kg^{-1} to accelerate gastric emptying 1 h after i.p. injection in control mice.

In our study, GHRP-6 accelerated gastric emptying more potently than ghrelin in control mice: GHRP-6 20 μg kg^{-1} accelerated gastric emptying, whereas a dose of 100 μg kg^{-1} ghrelin was needed to accelerate gastric emptying in control mice. However, the molecular mass of GHRP-6 is 873, compared with 3315 for ghrelin, this means that a dose of 20 μg kg^{-1} GHRP-6 corresponds to a dose of 75 μg kg^{-1} ghrelin and indeed a dose of 100 μg kg^{-1} ghrelin was able to accelerate gastric emptying in control mice. Therefore, more extensive dose–response studies are needed to clarify whether there is indeed a difference in potency. On the contrary, a difference in potency may result from a different action of the agonists on different GHS-R. Both ghrelin and GHRP-6 bind to the GHS1a receptor.[6] However specific binding sites have been identified for GHRP-2 and GHRP-6 that are presumably different from the GHS1a receptor as the binding sites show a very low affinity for ghrelin.[6] In the rabbit antrum, it has been shown that GHRP-6 has a higher affinity than ghrelin for the motilin receptor, and GHRP-6 increases the response to electrical field stimulation via activation of motilin receptors on tachykinergic nerves and activation of other GHS-R subtypes on cholinergic nerves while ghrelin is unable to do so.[34] These results illustrate the potential different mechanisms of action of ghrelin and GHRP-6 in different animal species.

Both ghrelin and GHRP-6 have more effect on motility in the stomach than in the small intestine. This could be related to differences in receptor density in the stomach and small intestine or to different mechanisms of action in the stomach and small intestine. In previous work, we and others also found evidence for differential control mechanisms for gastric emptying and small intestinal transit.[21,29] GHS-R are

widely expressed in central and peripheral tissues while circulating ghrelin is mainly produced in the stomach. In the rat, GHS-R are present in the stomach, the small and large intestine [4,35] and in the afferent nerves of the ganglion nodosum projecting to the stomach.[36] In humans, Gnanapavan *et al.* showed that the type 1a GHS-R was predominantly expressed in the pituitary and absent in most gastrointestinal tissues whereas the type 1b GHS-R, a non-functional receptor, was expressed widely in the gastrointestinal tract.[37] On the contrary, Dass *et al.* showed the presence of GHS-R in human stomach and colon without specifying the GHS-R subtype.[35]

The exact mechanism of action by which ghrelin and GHRP-6 stimulate gastric motor activity remains to be elucidated. The effect of ghrelin is, at least partially, mediated by vagal nerve signalling to the brain as the motor effects of ghrelin were blocked by vagotomy in anaesthetized rats.[12] However, a recent study in conscious rats showed that after vagotomy, i.c.v. administration of ghrelin was without effect on the motor activity in stomach and duodenum whereas i.v. ghrelin still exerted its effect on duodenal motility.[38] There is supportive evidence for both pathways. The expression of the ghrelin receptor (GHS-R) is demonstrated in stomach-projected vagal afferent neurones and in neuronal cell bodies in the vagal ganglion nodosum [36,39] and in electrophysiological studies, i.v. ghrelin is shown to suppress gastric vagal afferent discharge.[31,39] However, ghrelin can also exert its effects via peripheral receptors in the enteric nervous system: GHS-R immunoreactivity is shown within the enteric nervous system of both rat and human stomach and distal colon, in addition to cells associated with gastric glands, putative entero-endocrine and/or mast cells. There are no GHS-R found in smooth muscle cells or epithelia of rat and human stomach and distal colon.[35]

Effects of ghrelin and GHRP-6 in septic mice

Septic ileus remains an important issue in the clinical setting facilitating the occurrence of bacterial translocation and the development or maintenance of multiple organ failure leading to increased morbidity and mortality.[15,16] Treatment remains often empirical and suboptimal. Previously we demonstrated the beneficial effect of cisapride on postoperative ileus in rats.[24] However, clinical trials with cisapride had mixed results: its effectiveness may depend on the route of administration and cisapride also had some major adverse effects, rendering it less favourable for clinical use.[25,26] Trudel *et al.* showed the beneficial effect of ghrelin on postoperative ileus in rats.[13] Therefore, we investigated the therapeutic effects of ghrelin and GHRP-6 in septic mice. In our study, ghrelin 20 μg kg^{-1} reversed the endotoxin-induced delay in gastric emptying without any effect on the endotoxin-induced delay in small intestinal transit. Ghrelin 100 μg kg^{-1} did not have this beneficial effect on gastric emptying in septic mice. Surprisingly, ghrelin showed a different potency in control and septic mice: in control mice a dose of 100 μg kg^{-1} was needed to accelerate gastric emptying whereas a dose of 20 μg kg^{-1} was beneficial in septic mice. Possibly, the bioavailability of ghrelin is changed during sepsis. This may be due to a more effective uptake of i.p. injected ghrelin related to changes in permeability during sepsis, to less breakdown of ghrelin by proteases in sepsis or to a change in the ratio octanoylated (biologically active) *vs* non-octanoylated (biologically inactive) ghrelin during sepsis. If the bioavailability of ghrelin is changed during sepsis, it is possible that the higher dose of ghrelin loses its beneficial effects due to the development of desensitization. Alternatively, during sepsis the vagal pathways may become sensitized and more readily affected by lower concentrations of ghrelin. More detailed studies are needed to unravel this mechanism.

GHRP-6 was able to significantly and dose-dependently accelerate gastric emptying in septic mice to gastric emptying values comparable with saline-treated control mice. In addition, there was a tendency to increase small intestinal transit in septic mice. The GHRP-6-induced increase in gastric emptying is comparable in control and septic mice and also the effect of LPS on gastric emptying is comparable in saline-treated mice and in GHRP-6-treated mice. These results suggest that GHRP-6 did not interfere with the pathogenic mechanisms of septic ileus. This is also supported by the fact that ghrelin and GHRP-6 were not able to influence the endotoxin-induced hypothermia or the endotoxin-induced increase in behaviour scale. These findings indicate that their beneficial effect on motility is not related to the amelioration of the general health state. Nevertheless, the beneficial effect of ghrelin but mainly of GHRP-6 on gastric ileus in septic mice offers potential therapeutic options in the treatment of septic ileus.

CONCLUSION

Our results support a prokinetic role for ghrelin and GHRP-6 on gastric emptying in control mice. In septic mice, the beneficial effect of ghrelin on gastric emptying was not dose-related in contrast to the prokinetic effects of GHRP-6, illuminating the differences

between the endogenous ligand and the synthetic GHS-R agonist. Ghrelin and GHRP-6 had no significant effect on small intestinal transit in control and septic mice. The beneficial prokinetic effect of ghrelin – but, mainly of GHRP-6 – offers potential therapeutical options in the treatment of disorders related to delayed gastric emptying such as sepsis-induced gastric ileus.

ACKNOWLEDGMENTS

Benedicte De Winter is a postdoctoral assistant of the Interuniversity Poles of Attraction (IUPA) Program (P5/20) – Belgian State, Prime Minister's Office – Federal Office for Scientific, Technical and Cultural Affairs. This work was financially supported by the IUPA program P5/20.

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