

Basic Study

Correlation between colonic secretion and colonic motility in rats: Role of ghrelin

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Author contributions: Huang HH and Chen CY contributed to the conception and design of the study; Huang HH, Ting CH, Syu YF, and Chen CY contributed to the acquisition, analysis and interpretation of data; all authors drafted the article, made critical revisions related to the intellectual content of the manuscript, and approved the final version of the article to be published.

Supported by the Taiwan Ministry of Science and Technology No. NSC 95-2314-B-075-013-MY2 and No. NSC 95-2314-B-010-098-MY2 to Chih-Yen Chen.

Institutional animal care and use committee statement: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC), Taipei Veterans General Hospital.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: The statistical code and dataset are available from the corresponding author at chency@vghtpe.gov.tw.

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Manuscript source: Invited manuscript

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Received: June 28, 2016

Peer-review started: July 2, 2016

First decision: October 11, 2016

Revised: October 24, 2016

Accepted: November 14, 2016

Article in press: November 16, 2016

Published online: December 14, 2016

Abstract

AIM

To explore the relationship between colonic secretory function and colonic motility.

METHODS

Using a rat model chronically implanted with intracere-

broventricular (ICV) and cecal catheters, we validated the correlation between colonic secretion and colonic motor functions, as well as the role of ICV injection volume.

RESULTS

Compared to saline controls (5 μ L/rat), ICV acyl ghrelin at 1 nmol/5 μ L enhanced the total fecal weight, accelerated the colonic transit time, and increased the fecal pellet output during the first hour post-injection, while ICV des-acyl ghrelin at 1 nmol/5 μ L only accelerated the colonic transit time. These stimulatory effects on colonic motility and/or secretion from acyl ghrelin and des-acyl ghrelin disappeared when the ICV injection volume increased to 10 μ L compared with saline controls (10 μ L/rat). Additionally, the ICV injection of 10 μ L of saline significantly shortened the colonic transit time compared with the ICV injection of 5 μ L of saline. The total fecal weight during the first hour post-injection correlated with the colonic transit time and fecal pellet output after the ICV injection of acyl ghrelin (1 nmol/5 μ L), whereas the total fecal weight during the first hour post-injection correlated with the fecal pellet output but not the colonic transit time after the ICV injection of des-acyl ghrelin (1 nmol/5 μ L).

CONCLUSION

Colonic secretion does not always correlate with colonic motility in response to different colonic stimulations. Acyl ghrelin stimulates colonic secretion.

Key words: Colonic transit time; Fecal pellet output; Ghrelin; Intracerebroventricular injection; Secretion; Transit

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Core tip: The colokinetic effects of acyl ghrelin and des-acyl ghrelin depend on the intracerebroventricular (ICV) injection volume, and the acute increase of the ICV volume accelerates the colonic transit time. In addition, acyl ghrelin, rather than des-acyl ghrelin, stimulates colonic secretion. Colonic secretion does not always correlate with colonic motility in response to different colonic stimulations.

Huang HH, Ting CH, Syu YF, Chang SC, Chen CY. Correlation between colonic secretion and colonic motility in rats: Role of ghrelin. *World J Gastroenterol* 2016; 22(46): 10140-10147 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i46/10140.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i46.10140>

INTRODUCTION

The colonic motor function is assessed by the colonic

transit time (CTT), geometric center of colonic motility, and fecal pellet output. The fecal pellet output is a simple and easy method to measure colonic motor function^[1,2]. Recently, the geometric center method has been validated as a good measure to evaluate colonic transit; however, it requires the use of radiochromium which limits its application. The CTT using trypan blue dye is another option to measure the entire colonic motor function. This method has the advantage of no radioactivity. Our recent study showed that human/rat corticotropin releasing factor (h/r CRF)^[3,4], in addition to ghrelin as demonstrated by other studies, accelerated the CTT in conscious fed rats, using the trypan blue dye method. Peripheral CRF injection was also shown to increase the fecal output and secretion^[5].

Ghrelin is a 28-amino acid peptide that is mainly synthesized in the gastric oxyntic glands^[6,7]. Acyl ghrelin and des-acyl ghrelin are the two major molecular forms of ghrelin found in the stomach and plasma. Acyl ghrelin is a ghrelin peptide acylated by ghrelin *O*-acyl transferase^[8,9], and des-acyl ghrelin is produced with lacking *O*-*n*-octanoylation at serine 3^[10,11]. Acyl ghrelin is well known as an orexigenic gut-brain peptide^[12] and has the ability to regulate the gastrointestinal motility^[13] and energy balance^[14,15]. In contrast, des-acyl ghrelin is known to decrease food intake and disrupt the gastric motility^[16,17]. Intracerebroventricular (ICV) injection of acyl ghrelin has been reported to speed the CTT^[18], but the impact of des-acyl ghrelin through ICV injection on the colonic motor function is still unexplored.

In the current study, first, we aimed to investigate the effects of des-acyl ghrelin on colonic secretory and motor functions, as well as to validate the relationship between colonic secretion and motility. Second, we aimed to investigate the role of ICV injection volume in our unique rat model which can simultaneously measure the colonic motility and secretion in conscious rats.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (National Laboratory Animal Center, Taipei, Taiwan) weighing 250-320 g at the initial period of the experiment were used and housed in group cages under controlled illumination (light cycle: 08:00-20:00), humidity and temperature of 22.5 \pm 1.5 $^{\circ}$ C, and free access to water and laboratory chow pellets (LabDiet®, Brentwood, MO, United States). All experiments were performed starting at 9 a.m. in freely moving conscious rats, in accordance to guidelines which have been approved by the Institutional Animal Care and Use Committee, Taipei Veterans General Hospital.

Surgery

Implantation of the ICV catheter: For ICV implan-

tation, the rats were anesthetized with sodium pentobarbital (50 mg/kg, Nembutal; Abbott Laboratories, Abbott Park, IL, United States) by intraperitoneal injection, placed in a stereotaxic apparatus (Benchmark™, myNeuroLab, St. Louis, MO, United States), and implanted with a guide cannula (25-gauge; Eicom, Kyoto, Japan), which reached the right lateral ventricle. The stereotaxic apparatus was placed 0.8 mm posterior to the bregma, 1.4 mm right lateral to the midline, and 4.5 mm below the outer surface of the skull using a stereotaxic frame with the incisor bar set at the horizontal plane passing through the bregma and lambda^[19,20]. The guide cannula was secured, a dummy cannula (Eicom) was inserted into the guide cannula, and a screw cap (Eicom) was placed as described in our previous study^[19,20]. The rats were allowed 7 d for full recovery before food intake measurement after the implantation of the ICV catheters. If the rats did not increase their body weight 7 d after the operation, they were considered to have been injured during the operation and were excluded. All ICV injections with a total volume of 10 μ L were administered over 60 s *via* the AMI-5 (Eicom).

Implantation of the colonic catheter: The rats were anesthetized with sodium pentobarbital (50 mg/kg, Nembutal; Abbott) by intraperitoneal injection. After laparotomy of the lower abdomen, the proximal colon was exposed and a catheter (3 Fr, 1-mm diameter; ATOM) was implanted into the proximal colon, 2 cm distal from the cecocolonic junction^[3,4,21]. The catheter was fixed with a purse-string suture at the colonic wall and routed subcutaneously to the interscapular region, exteriorized through the skin, and secured together with an intravenous catheter for intracolonic administration of the dye marker^[3,4,21]. The animals were allowed to recover for 7 d before simultaneous measurement of colonic motor and secretory functions.

Preparation of drugs

Rat *O*-*n*-octanoylated ghrelin (Peptides International, Inc., Louisville, KY, United States) and rat des-acyl ghrelin (Peptides International) were kept in powder form at -20 °C, and dissolved in sterile, pyrogen-free 0.9% saline (Otsuka, Tokyo, Japan) immediately before use.

Colonic motor and secretory function tests

Measurement of the CTT: The measurement of colonic motor and secretory function was modified from our previous studies^[3,4,21]. The CTT was calculated using an enteral non-absorbable dye marker, trypan blue (Sigma Chemical Co., St. Louis, MO, United States). The dye (0.2 mL) was injected through the catheter positioned in the proximal colon, followed by a 0.2 mL saline flush 10 min after the ICV injection of acyl ghrelin and des-acyl ghrelin (1.0 nmol/rat). The

CTT was defined as the time interval between the dye injection and the discharge of the first blue pellet.

Measurements of fecal pellet output and total fecal weight:

The rats were accustomed to single housing for 7 d before the experiment. The total number of pellets was recorded every hour for 2 h following an intracolonic injection of trypan blue. The total fecal material was collected every hour for 2 h following the intracolonic injection of trypan blue, and its content was weighed as the total fecal weight^[3,4,21].

Statistical analysis

All the results are expressed as mean \pm standard error of the mean. One-way analysis of variance followed by the Student-Newman-Keuls post-hoc test was used to detect the differences among groups. The relationship between total fecal weight, CTT, and the fecal pellet output in response to the ICV injection of either saline, acyl ghrelin, or des-acyl ghrelin was analyzed by Spearman's nonparametric correlation. Differences were considered statistically significant when $P < 0.05$.

RESULTS

The ICV injection of acyl ghrelin (1 nmol/5 μ L/rat) significantly accelerated the CTT, and increased the fecal pellet output and total fecal weight during the first hour post-injection, but des-acyl ghrelin (1 nmol/5 μ L/rat) only significantly accelerated the CTT

As compared with saline controls (5 μ L/rat), ICV acyl ghrelin (1 nmol/5 μ L/rat) and des-acyl ghrelin (1 nmol/5 μ L/rat) significantly accelerated the mean CTT from 292 to 236 and 234 min, respectively ($P < 0.05$, Figure 1A). During the first hour post-injection, ICV acyl ghrelin (1 nmol/5 μ L/rat) also significantly increased the fecal pellet output and total fecal weight ($P < 0.05$, Figure 1B and D). ICV acyl ghrelin (1 nmol/5 μ L/rat) did not affect the fecal pellet output and total fecal weight during the second hour post-injection ($P > 0.05$, Figure 1C and E). ICV des-acyl ghrelin (1 nmol/5 μ L/rat) did not affect either the fecal pellet output or total fecal weight during first and second hour post-injection ($P > 0.05$, Figure 1C and E).

An increased ICV injection volume shortened the CTT, which led to the disappearance of the colokinetic effects of acyl ghrelin and des-acyl ghrelin (1 nmol/10 μ L/rat)

An ICV injection of 10 μ L of saline significantly shortened the mean CTT from 292 to 191 min compared to the ICV injection of 5 μ L of saline ($P < 0.05$, Figure 1A and F). Moreover, the ICV injection of acyl ghrelin (1 nmol/10 μ L/rat) and des-acyl ghrelin (1 nmol/10 μ L/rat) did not have any effects on the CTT, fecal pellet output, and total fecal weight, compared to saline controls (10 μ L/rat, Figure 1F-J).

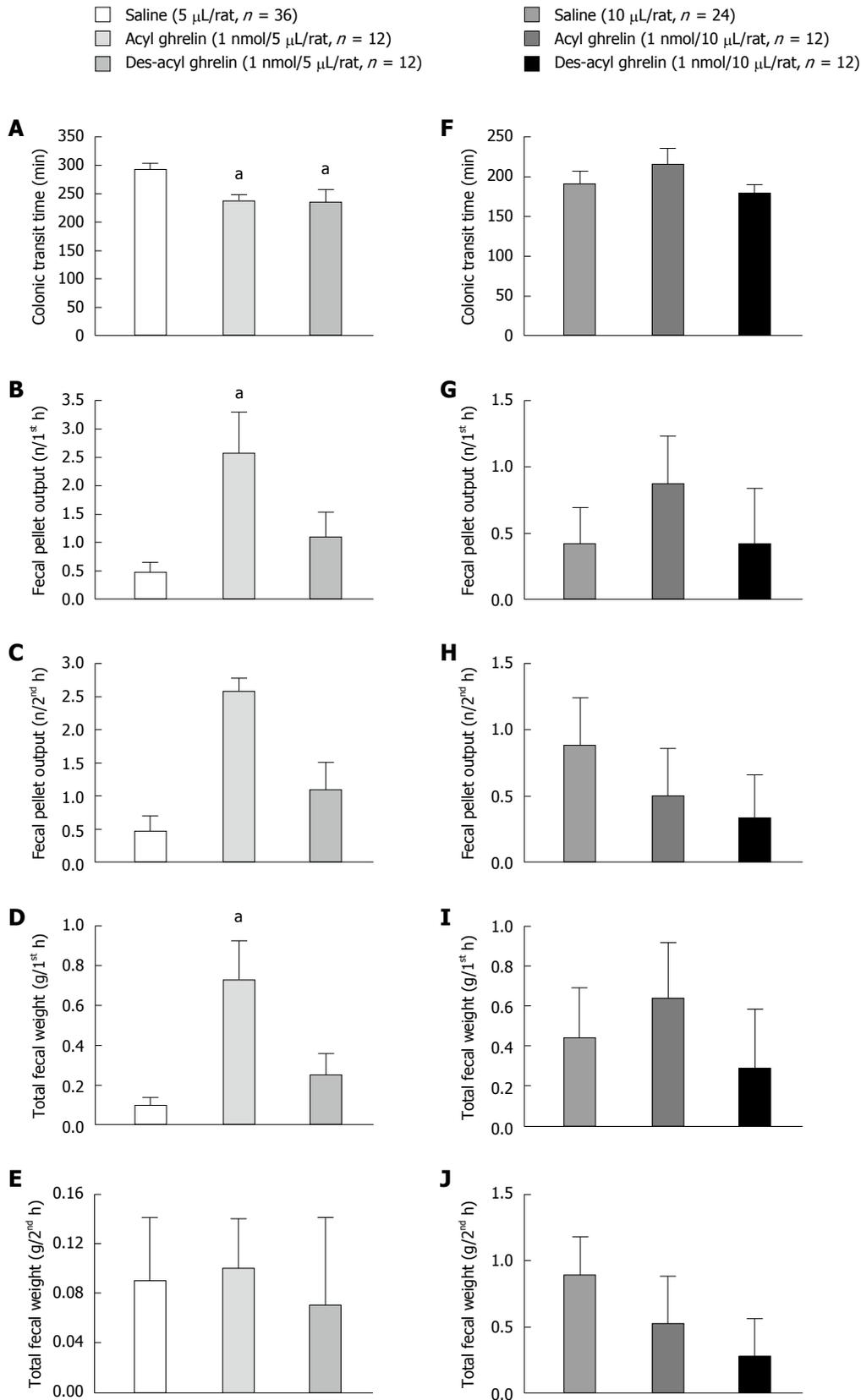


Figure 1 Effects of acyl ghrelin and des-acyl ghrelin on the colonic transit time (A and F), fecal pellet output (B, C, G, and H), and total fecal weight (D, E, I, and J) during the first and second hour post-injection at different intracerebroventricular injection volumes (5 $\mu\text{L}/\text{rat}$: A-E vs 10 $\mu\text{L}/\text{rat}$: F-J). Data are presented as mean \pm standard error of the mean. ^a $P < 0.05$, vs saline controls.

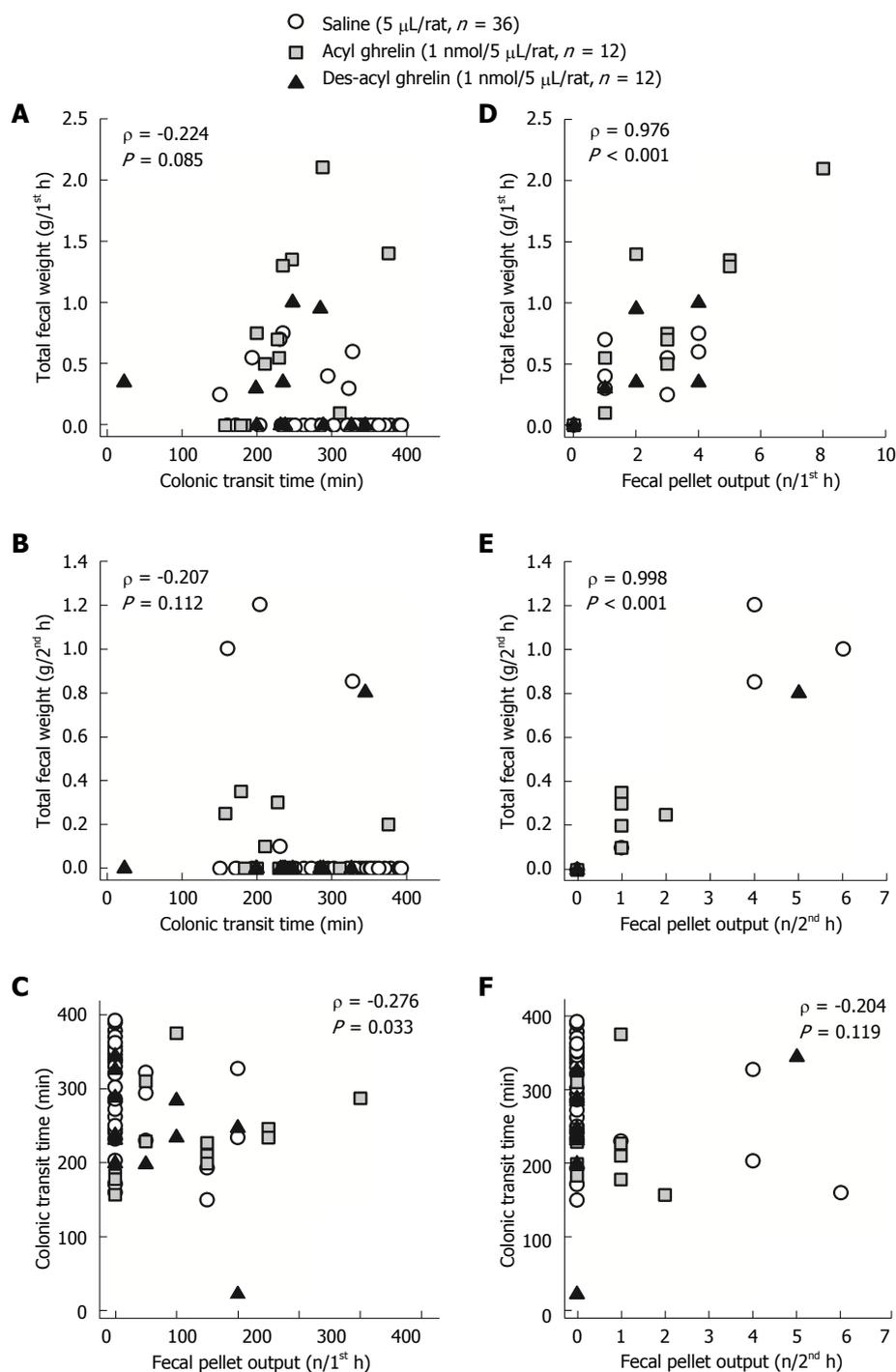


Figure 2 Pooled data demonstrating the relationships among total fecal weight (A-D), colonic transit time (A, B, C, and F), and fecal pellet output (C-F) stimulated by saline, acyl ghrelin, and des-acyl ghrelin with the intracerebroventricular injection volume at 5 μ L.

Relationships between total fecal weight, CTT, and fecal pellet output with an ICV injection volume of 5 μ L

We pooled the data from the ICV injection of saline, acyl ghrelin, and des-acyl ghrelin at 5 μ L, and analyzed the correlations among total fecal weight, CTT, and fecal pellet output. The total fecal weight did not correlate with the CTT during the first hour and second hour

post-injection ($P > 0.05$, Figure 2A and B), whereas the total fecal weight exhibited a significantly positive correlation with the fecal pellet output ($P < 0.001$, Figure 2D and E). The CTT had a negative correlation with the fecal pellet output during the first hour ($P < 0.05$, Figure 2C) but not the second hour post-injection ($P > 0.05$, Figure 2F).

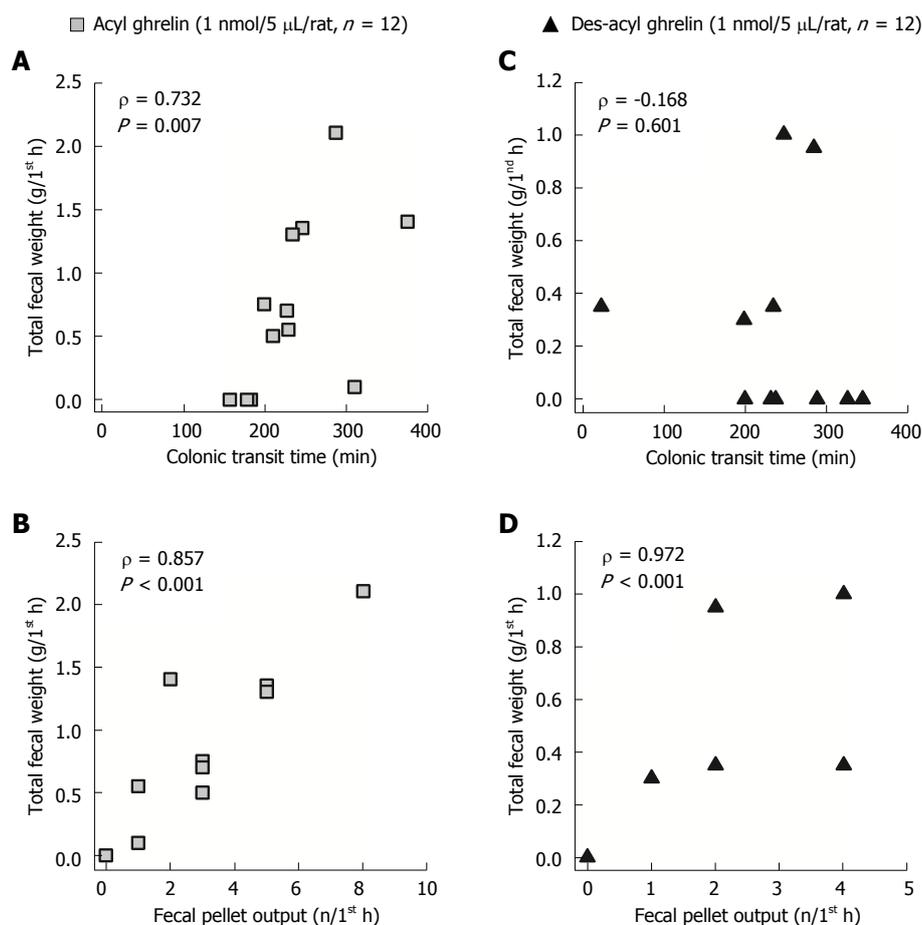


Figure 3 The relationships among total fecal weight, colonic transit time, and fecal pellet output during the first hour post-injection stimulated by either acyl ghrelin (A and B) or des-acyl ghrelin (C and D) with the intracerebroventricular injection volume at 5 μL .

Relationships between total fecal weight, CTT, and fecal pellet output during the first hour post-injection stimulated by acyl ghrelin and des-acyl ghrelin, respectively, with an ICV injection volume at 5 μL

We analyzed the correlations between total fecal weight, CTT, and fecal pellet output during the first hour post-injection, in response to ICV injection of either acyl ghrelin or des-acyl ghrelin with the volume at 5 μL . The total fecal weight significantly correlated with the CTT and fecal pellet output during the first hour after ICV acyl ghrelin (1 nmol/5 μL /rat) injection ($P < 0.01$, Figure 3A and B). The total fecal weight significantly correlated with the fecal pellet output, but not the CTT, during the first hour after ICV des-acyl ghrelin (1 nmol/5 μL /rat) injection ($P < 0.001$, Figure 3C and D).

DISCUSSION

In the present study, we first demonstrated the *in vivo* effects of ICV des-acyl ghrelin on colon motor and secretory functions. ICV injection of des-acyl ghrelin at 1 nmol/5 μL accelerated the CTT without altering the fecal pellet output and total fecal weight during the first hour and second hour post-injection. Acyl ghrelin and ghrelin mimetics have been previously shown to exhibit

colokinetic effects such as shortening the CTT^[22] and decreasing the time to the first bowel movement^[23], and may have the clinical implication in relieving diet-induced constipation in a rat model^[24]. In addition to accelerating the CTT and increasing the fecal pellet output during the first hour post-injection, we also showed that the ICV injection of acyl ghrelin at 1 nmol/5 μL enhanced the total fecal weight during the first hour post-injection, which is consistent with the results that intrathecal but not intravenous application of acyl ghrelin to the L6-S1 region of the spinal cord increased the fluid output through the anal cannula^[25]. Therefore, in our current study, the stimulatory properties of acyl ghrelin on the colonic secretion and motility are confirmed.

Although an acute increase of the ICV pressure has been reported to immediately suppress the amplitude of gastric and duodenal contractions in rabbits^[26], the effects of the ICV injection volume on colonic secretion and motility still remain obscure. Our study was the first to demonstrate that the increased ICV injection volume (from 5 μL to 10 μL) shortened the CTT in saline controls. Because the CTT has been shortened in the saline controls, the stimulating effects on colonic motility and/or secretion by either acyl ghrelin or des-acyl ghrelin disappeared when the ICV injection vol-

ume increased to 10 μ L at the same dose (1 nmol/rat). Acute moderate to severe head injury patients have been shown to have prolonged gastric emptying^[27]. An increased intracranial pressure is proposed to be the major cause of gastric motility dysfunction^[28]. The finding that an acutely increased ICV injection volume shortened the CTT may be explained by the increased intracranial pressure in a limited intracerebroventricular space, though we did not measure the increased intracranial pressure in our current study.

The CTT is considered a reflection of the motor function in the entire colon, while the fecal pellet output is the reflection of the distal colonic motor function^[29]. This means that the acceleration of the colonic transit is not always equal to the increase of fecal pellet output. A recent rodent study indicated that the central administration of CRF and restraint stress accelerate the colonic transit but do not always correlate with the increase of fecal pellet output^[28]. Our results are in accordance with this point (Figure 2B and C). We also showed that the ICV injection of acyl ghrelin enhanced the CTT, fecal pellet output, and total fecal weight, while the ICV injection of des-acyl ghrelin only accelerated the CTT. Therefore, we propose that acyl ghrelin accelerates the entire colon and distal colonic motor functions, whereas des-acyl ghrelin, lacking *O*-*n*-octanoylation at serine 3, may have greater effects in stimulating the proximal colon motor function without altering the distal colonic motility. In addition, our findings provide new information regarding the relationship between colonic secretion and motility. The finding that the total fecal weight during the first hour post-injection correlated with the CTT stimulated by the ICV injection of acyl ghrelin (Figure 3A) but not des-acyl ghrelin (Figure 3B) suggests that colonic secretion does not always correlate with colonic motility in response to different colonic stimulations.

In conclusion, the colokinetic effects of acyl ghrelin and des-acyl ghrelin depend on the ICV injection volume, and the acute increase of the ICV volume accelerates the CTT. In addition, acyl ghrelin, rather than des-acyl ghrelin, stimulates colonic secretion. Colonic secretion does not always correlate with colonic motility in response to different colonic stimulations.

ACKNOWLEDGMENTS

We would like to thank Miss Yu-Chi Lee for her secretarial assistance in manuscript editing, as well as the Clinical Research Core Laboratory of Taipei Veterans General Hospital for providing experimental space and facilities.

COMMENTS

Background

Acyl ghrelin is well known as an orexigenic gut-brain peptide and has the ability to regulate the gastrointestinal motility and energy balance. In contrast, des-acyl ghrelin is known to decrease food intake and disrupt the gastric motility.

Research frontiers

The intracerebroventricular (ICV) injection of acyl ghrelin has been reported to speed the colonic transit time (CTT), but the impact of des-acyl ghrelin through ICV injection on the colonic motor function is still unexplored.

Innovations and breakthroughs

This is the first study to investigate the effects of des-acyl ghrelin on colonic secretory and motor functions, as well as to validate the relationship between colonic secretion and motility. This is also the first study to evaluate the role of ICV injection volume on the colonic motility and secretion in conscious rats.

Applications

Using a rat model chronically implanted with ICV and cecal catheters, the authors validated the correlation between colonic secretion and colonic motor functions, as well as the role of ICV injection volume.

Terminology

The colokinetic effects of acyl ghrelin and des-acyl ghrelin depend on the ICV injection volume, and the acute increase in ICV volume accelerates the CTT. In addition, acyl ghrelin, rather than des-acyl ghrelin, stimulates colonic secretion. Colonic secretion does not always correlate with colonic motility in response to different colonic stimulations.

Peer-review

Colonic secretion does not always correlate with colonic motility in response to different colonic stimulations in rats: role of intracerebroventricular injection volume. The aims of this study were to investigate the influences of des-acyl ghrelin on colonic secretory and motor functions, as well as to validate the relationship between colonic secretion and motility. Also the authors aimed to appraise the role of ICV injection volume in our unique rat model which can simultaneously measure the colonic motility and secretion in conscious rats.

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P- Reviewer: Huerta-Franco MR S- Editor: Yu J

L- Editor: A E- Editor: Liu WX





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