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Original

GABAergic and glutamatergic neurons in the brain regulate phase II of migrating motor contractions in the *Suncus murinus*

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Abstract

Gastric contractions exhibit characteristic motor patterns in the fasted state, known as migrating motor contractions (MMC). MMC consist of three periodically repeated phases (phase I, II and III) and are known to be regulated by hormones and the autonomic and enteric nervous systems. However, the central regulation of gastric contractions in the fasted state is not completely understood. Here, we have examined the central effects of motilin, ghrelin, γ-aminobutyric acid (GABA) and L-glutamate signaling on gastric MMC by using suncus (*Suncus murinus*) as an animal model, because of their similar gastric motor patterns to those observed in humans and dogs. Intracerebroventricular (i.c.v.) administration of motilin and ghrelin had no effect on phase I and II contractions, respectively. Conversely, i.c.v. administration of $GABA_A$ receptor antagonist, during phase I of the MMC, evoked phase II-like contractions and significantly increased the motility index (MI). This was compared with the i.c.v. administration of GABA which inhibited spontaneous phase II contractions with a significantly decreased MI. In addition, i.c.v. administration of L-glutamate during phase I also induced phase II-like irregular contractions with a significant increase in the MI. Taken together with previous findings, these results suggest that central GABAergic and glutamatergic signaling, with the coordination of both peripheral motilin and ghrelin, regulate phase II contractions of MMC in the fasted state.

Key words: motilin, ghrelin, GABA, glutamate, *Suncus murinus*

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Introduction

In the fasting state, gastrointestinal contractions show characteristic motor patterns, designated as the migrating motor contractions (MMC) (1). MMC consist of three phases called as phase I (motor quiescent period), phase II (irregular and low amplitude contraction period) and phase III (regular and high amplitude contraction period) (2). It is considered that MMC play important functions in clearing the stomach, and that they are regulated by hormones, autonomic and enteric nervous system (3).

Rats and mice lack motilin and motilin receptor genes (4), and thus another small animal model, which produces motilin, had been explored to study MMC regulatory mechanisms. Suncus is a small laboratory animal that has a motilin signaling system, and it has now been considered that it is an animal model useful not only for basic research of GI functions but also for translational research on gastrointestinal motility. Using suncus as a model system, we elucidated the detailed mechanisms underlying the involvement of motilin, ghrelin and the vagus nerve on gastric contractions. Notably, we found that the gastric contractile patterns of suncus in the fasted state closely resemble those seen in humans and dogs (5), showing that the periodically repeated MMC cycle and its duration is the same as that in humans and dogs.

Ghrelin administration in phase II stimulated gastric contractions, and administration of ghrelin receptor antagonist significantly decreased the spontaneous phase II contractions in conscious suncus (6). In addition, vagotomy abolished the spontaneous phase II contraction while ghrelin administration into vagotomized shrews had no effect on phase II contractions (6). Moreover, it has been shown that the cognate ghrelin receptor (GHS-R) is expressed in the nodose ganglion of the vagus nerve, suggesting that ghrelin stimulates gastric phase II contractions via the vagus nerve (7). We also demonstrated that phase III contractions are coordinately regulated by motilin, ghrelin, and the enteric nervous system in suncus. Administration of motilin strongly evoked phase III contractions, but motilin had no effect under the blockade of endogenous ghrelin in conscious suncus (8). In addition, it has been shown that the GABAergic pathway is an essential mediator of ghrelin/motilin-induced gastric phase III contractions (8). Compared with gastric phase II contractions, the regulatory mechanisms of phase III of MMC have been well understood because the experimental effects of motilin and ghrelin with GABAergic neurons using conscious suncus is almost completely reproducible in *in vitro* organ bath experiments using resected stomach tissue.

Vago-vagal neuro-circuits are known to be important for regulating gastric function, and it has been shown that the peripheral sensory information is transmitted to the nucleus tractus solitarius (NTS) via the afferent vagus nerves (9). Then, the NTS neurons project to the dorsal motor nucleus of the vagus (DMV) and activated-DMV signals stimulate the efferent vagus nerves (10). In NTS-DMV synaptic contacts, GABA and L-glutamate are known to be the primary neurotransmitters (11, 12). These lead to the hypothesis that GABA and L-glutamate play an important role in regulating vagal efferent pathways related with gastric phase II motility.

In this study, we aimed to elucidate the mechanisms of phase II contraction of MMC. We first examined the central effect of ghrelin and motilin using conscious suncus because it has been reported that the motilin receptors (GPR38) and GHS-R are expressed not only in the gastrointestinal tract, but also in the brain, including the hypothalamus and medulla oblongata (7). Furthermore, the involvement of GABAergic and glutamatergic signaling within the brain in phase II gastric contractions in the fasted state was studied.

Materials and Methods

Animals

The experiments were performed using adult male *Suncus murinus* (7–39 weeks old, weighing 60–100 g) from an outbred KAT strain that was established from a wild population of in Kathmandu, Nepal. Suncus were housed individually in plastic cages equipped with an empty can as a nest box, under controlled conditions (23 °C ± 2 °C; lights on from 08:00 to 20:00), with free access to water and commercial trout pellets (No. 5P; Nippon Formula Feed Manufacturing, Yokohama, Japan). All procedures were approved and permitted in accordance with the guidelines of the Saitama University Committee on Animal Research.

Drugs used

Suncus motilin (Scrum Inc., Tokyo, Japan), human ghrelin (Asubio Pharma Co., Ltd., Hyogo, Japan), bicuculline (Sigma-Aldrich, St. Louis, MO, USA, CAS number:40709-69-1), GABA (Wako, Osaka, Japan, CAS number:010-02441), and L-glutamate (Sigma-Aldrich, CAS number:56-86-0) were dissolved in artificial cerebrospinal fluid (aCSF; 24 mM NaCl, 3.5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgSO{\cdot}7H_2O$, 1 mM NaH_2PO_4, 26 mM $NaHCO_3$, 10 mM glucose).

Animal surgery and measurement of gastric contraction

After fasting for 2–5 h, the animals were anesthetized via intraperitoneal injection (0.3 mg/kg medetomidine hydrochloride, 4 mg/kg midazolam and 5 mg/kg butorphanol tartrate), and placed on a stereotaxic apparatus (NARISHIGE Co., Ltd., Tokyo, Japan) for intracerebroventricular (i.c.v.) surgery. A guide cannula (model number: C317G/SPC, Plastics One Co., Ltd., Roanoke, VA, USA) was inserted into the lateral ventricle using the following coordinates (7.2 mm rostral to the posterior edge of the skull, 0.9 mm lateral from the midline and 1.7 mm ventral from the brain surface). Dental cement (Shofu Inc., Kyoto, Japan) was used for fixing the inserted guide cannula. A dummy cannula was inserted into the guide cannula (model number: C317DC/SPC, Plastics One Co., Ltd.) as a cap.

Around 4 days after i.c.v. surgery, the animals were anesthetized, and strain-gauge force transducers were implanted. The abdomen was opened via a midline incision and strain-gauge force transducer was sutured to the dorsal portion of the lower gastric body (3 cm distal from the pylorus) in order to measure circular muscle contraction. The strain-gauge force transducers used in this study were developed in our laboratory, using a smaller strain-gauge (KFG-02-120-C1-11N30C2; Kyowa Electronic Instruments, Tokyo, Japan). Waterproofing and response properties were checked in all transducers before implantation. The wires from the transducers were exteriorized through the abdominal wall and were run under the skin toward the back of the neck. For intravenous (i.v.) administration of motilin, a catheter consisting of silicone tubes (1.0 mm OD × 0.5 mm ID; Kaneka Medics, Osaka, Japan) was inserted into the right jugular vein, and another catheter was also exteriorized to the back of the neck. The animals were allowed to recover from the surgery for at least 2 days before the experiment and were used in several experiments. Amplified analog signals were converted with an analog digital converter (model ADC-24; Pico Technology Ltd., St. Neots, UK), after which the digital signals were recorded by the software (PicoLog; Pico Technology Ltd.) with a sampling interval of 100 milliseconds.

As we previously described (13), the definition of phase III contractions of the MMC in the conscious animals was based on that used for dogs and humans: clustered contractions with an amplitude of more than 8 g and lasting longer than 5 min. Similarly, phase I was defined as the period of motor quiescence with contractions of an amplitude of 0.5 g. Phase II was defined as the irregular contractions that followed phase I and

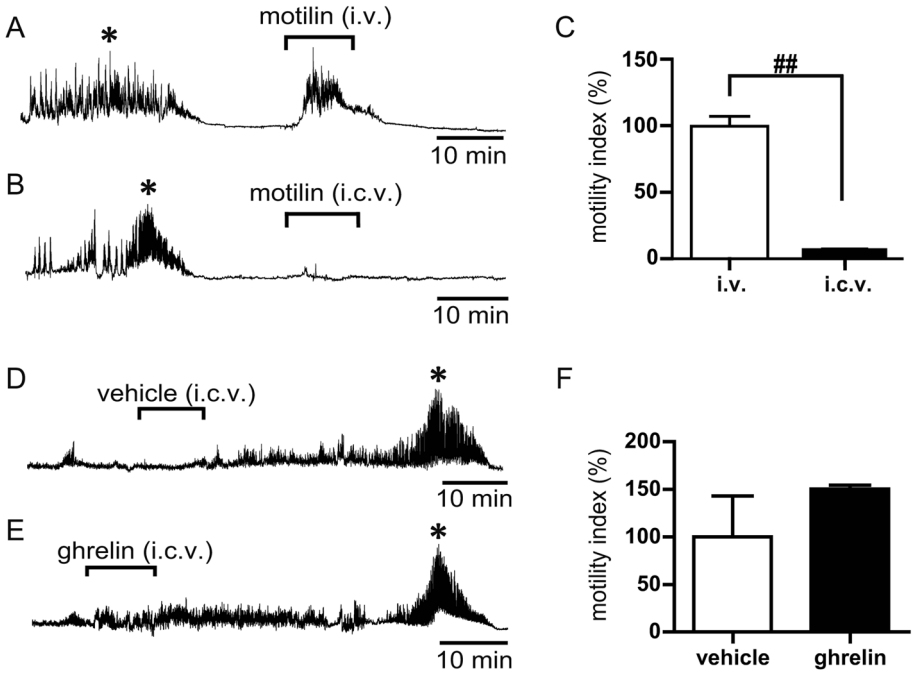

Fig. 1. The effect of i.v. or i.c.v. injection of motilin and ghrelin on phase I and phase II of MMC. The i.v. administration of motilin (50 ng/kg/min) induced phase III-like contractions in phase I (A), however, i.c.v. administration of motilin (50 ng/kg/min) did not stimulate gastric contractions in phase I (B). The motility index by i.c.v. motilin administration at phase I was significantly lower than that of i.v. administration of motilin (C). The i.c.v. administration of ghrelin (0.1 μg/kg/min) did not change phase II contractions (E) neither did vehicle administration (D). The motility index by ghrelin administration at phase II showed no significant differences (F). ##P<0.01 vs. i.c.v., n=3. *: phase III.

had an amplitude of >3-fold those in phase I.

i.v. and i.c.v. administration in MMC

The i.v. administration of motilin, and the i.c.v. administration of motilin, bicuculline and L-glutamate were initiated 10 min after the completion of spontaneous phase III with a rate of 1 μl/min for 10 min. Ghrelin or GABA was administered 10 min after the initiation of spontaneous phase II contractions.

Data and statistical analysis

Gastric motility was quantified using the motility index (MI) as the percentage of the area under the curve (AUC), which is equivalent to the integrated area between contractile wave and baseline. We measured the AUC of adjacent spontaneous phase II (Fig. 1D–F, Figs. 2–4), or III (Fig. 1A–C) contractions and its duration, followed by calculation of AUC/min (internal control). Following this, the AUC during 10 min drug infusion was measured and AUC/min (drug or vehicle) was calculated. Finally, MI was shown as AUC/min (drug or vehicle) / AUC/min (internal control). All values were shown as average ± S.E.M. All 3 animals were used in the experiments and statistical analysis. Statistical analyses were performed with GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA) by using Student's t-test. Differences with P<0.05 were considered to be statistically significant.

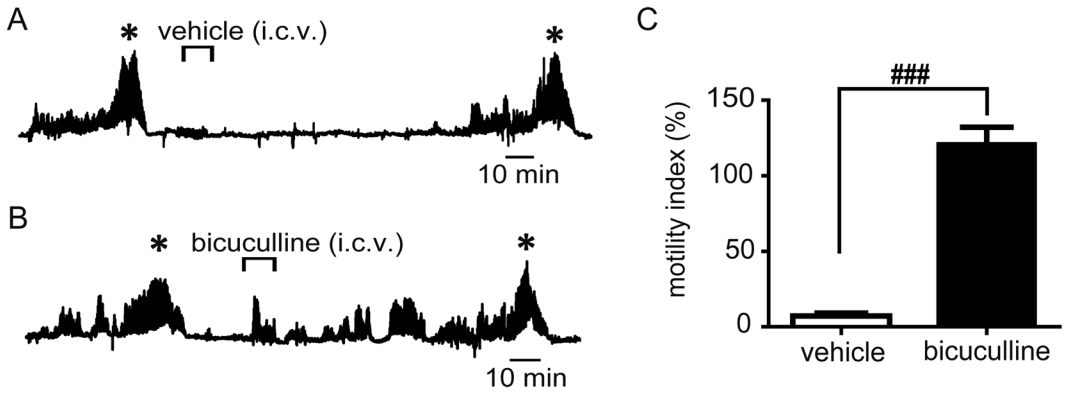

Fig. 2. The effect of i.c.v. administration of $GABA_A$ receptor antagonist on the phase I of MMC. The i.c.v. administration of vehicle at phase I did not change gastric contractions (A). On the other hand, i.c.v. administration of bicuculline (0.5 μg/kg/min) at phase I immediately stimulated gastric contractions with irregular and low amplitudes (B). The motility index by bicuculline administration at phase I was significantly more than that of vehicle (C). ###P<0.001 vs. vehicle, n=3. *: phase III.

Results

Effect of i.c.v. administration of motilin on phase I of MMC

Motilin (50 ng/kg/min) was injected i.v. or i.c.v. for 10 min at 10 min after the termination of spontaneous phase III contractions. While i.v. administration of motilin induced strong phase III-like contractions (Fig. 1A), i.c.v. injection of same concentration of motilin had no effect on phase I of MMC (Fig. 1B). The MI of i.c.v. motilin administration on gastric contractions (5 ± 1%) was significantly lower than that of i.v. injected animals (100 ± 8%) (Fig. 1C).

Effect of i.c.v. ghrelin on phase II of MMC

The i.c.v. administration of ghrelin (0.1 μg/kg/min) or vehicle was performed for 10 min at 10 min after the initiation of spontaneous phase II contractions. As a result, the i.c.v. injection of vehicle had no effect on MMC phase II contractions (Fig. 1D). Similarly, i.c.v. ghrelin injection did not change the pattern and amplitude of phase II contractions (Fig. 1E). There was no significant difference between the MI of vehicle group (100 ± 43%) and that of the ghrelin injected group (150 ± 4%) (Fig. 1F).

Effect of a $GABA_A$ receptor antagonist (bicuculline) on phase I of MMC

At 10 min after the completion of spontaneous phase III contractions, i.c.v. administration of bicuculline (0.5 μg/kg/min) or vehicle was performed for 10 min. Vehicle injection did not change the pattern of phase I contractions of MMC and phase I contractions continued until the occurrence of phase II and subsequent phase III contractions (Fig. 2A). On the other hand, bicuculline administration immediately changed the contractile pattern to phase II-like contractions from phase I contractions (Fig. 2B). The MI in bicuculline administered suncus (122 ± 11%) was significantly higher than that of vehicle injected animals (7 ± 2%) (Fig. 2C).

Central effect of GABA on phase II of MMC

To examine the effect of central GABA on phase II, i.c.v. injection of GABA (1 μg/kg/min) or vehicle was performed for 10 min at 10 min after the initiation of spontaneous phase II contractions. Vehicle injection had no effect on phase II contractions and following phase III contraction was induced at the normal intervals (Fig.

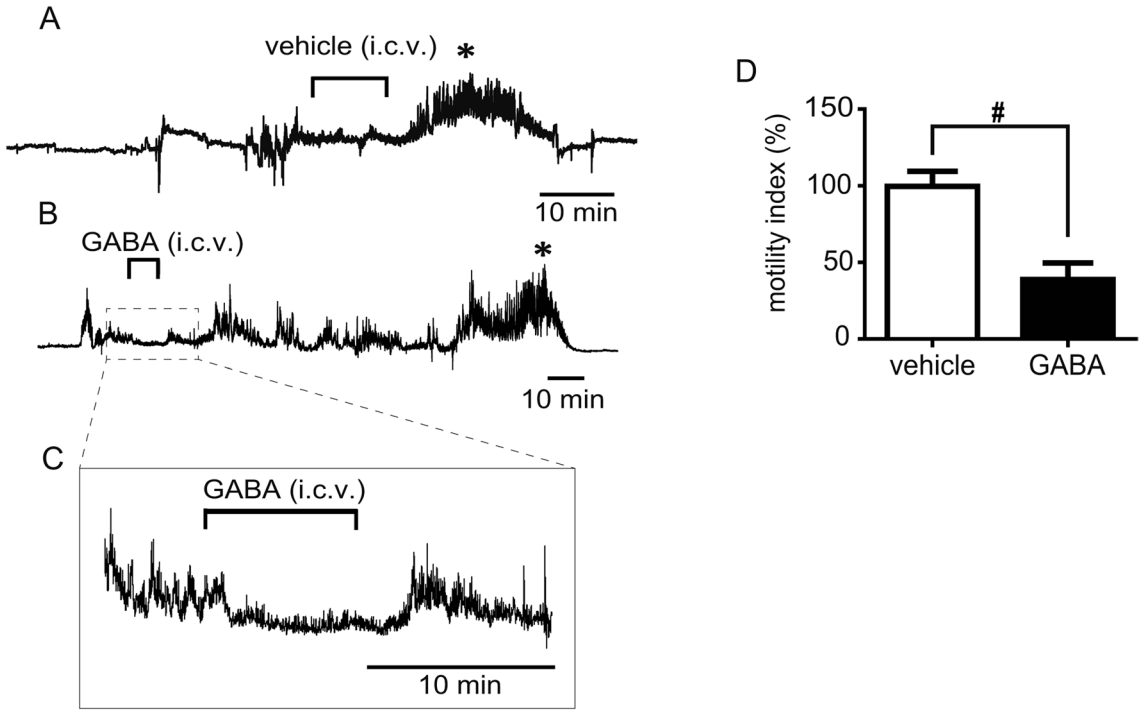

Fig. 3. The effect of i.c.v. administration of GABA on phase II of MMC. Although i.c.v. administration of vehicle at phase II did not induce gastric contractions (A), i.c.v. administration of GABA (1.0 μg/kg/min) at phase II transiently decreased its spontaneous gastric contractions (B, C). The motility index by GABA administration at phase II was significantly reduced compared with that of vehicle (D). #P<0.05 vs. vehicle, n=3. *: phase III.

3A). On the other hand, i.c.v. injection of GABA immediately and transiently inhibited phase II contractions during infusion of GABA and phase II contractions were resumed after i.c.v. administration (Fig. 3B, C). The MI during drug infusion of GABA injected suncus (38 ± 11%) was significantly lower than that of vehicle group (96 ± 10%) (Fig. 3D).

Central effect of L-glutamate on phase I of MMC

At 10 min after the completion of spontaneous phase III contractions, L-glutamate (0.1 μg/kg/min) or vehicle was administered i.c.v. for 10 min. The i.c.v. administration of vehicle had no effect on MMC phase I contractions (Fig. 4A), whereas administration of L-glutamate immediately induced irregular and low amplitude contractions similar to normally observed spontaneous gastric phase II contractions (Fig. 4B). The duration of phase III contractions after administration did not differ between the vehicle and L-glutamate administrations. The MI in L-glutamate induced contractions (99 ± 2%) was significantly higher than that of the vehicle (16 ± 2%) (Fig. 4C).

Discussion

GI motility is important in biological functions for the processes of feeding, digestion and absorption of nutrients to maintain life activities. In addition, it has been considered that MMC observed in the fasted state are also critically significant for the maintenance of the internal environment of the GI tract and preparation for processing the next meal. Abnormalities in MMC are thought to be the cause of several GI disorders such

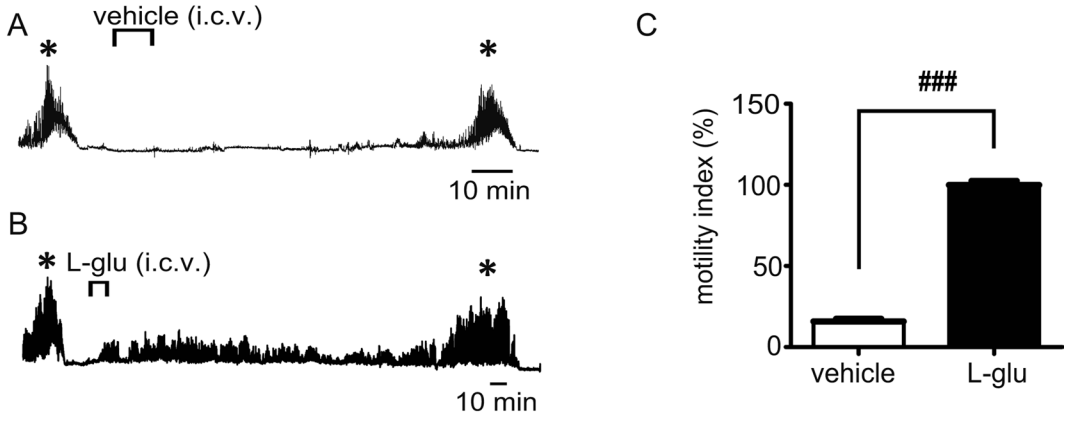

Fig. 4. The effect of i.c.v. administration of L-glutamate on phase I of MMC. The i.c.v. administration of vehicle at phase I did not change the spontaneous gastric contractions (A), but i.c.v. administration of L-glutamate (0.1 μg/kg/min) at phase I immediately changed and increased gastric contractions with irregular and low amplitude (B). The motility index by L-glutamate administration at phase I was significantly increased than that of vehicle (C). ###P<0.001 vs. vehicle, n=3. *: phase III.

as functional dyspepsia (FD) and small intestinal bacterial over growth (SIBO). Therefore, the unveiling of the mechanisms of the MMC is necessary not only for understanding the basic aspects of GI physiology, but also for the translational studies of GI disorders and therapies.

Phase II of MMC showing irregular and low amplitude contractions is known to have biological meaning as the preliminary phase before the strong phase III contractions. In previous studies using *Suncus murinus* as an animal model, we have shown that ghrelin administration in phase II enhanced gastric contractions and treatment with ghrelin receptor antagonist diminished phase II gastric contractions (13). On the other hand, administration of motilin or motilin receptor antagonist did not change gastric contraction of phase II, suggesting that ghrelin regulates phase II of MMC (13). Moreover, we found that vagotomy completely inhibited the phase II contractions and ghrelin-induced enhancement of phase II contractions, and that GHS-R are known to be expressed in the nodose ganglion of the vagal afferent (7). These results suggest that ghrelin secreted from the ghrelin-producing cells binds to its receptor expressed in the nerve terminal of the vagal afferent located near the ghrelin-producing cells, then stimulates phase II contractions via the vago-vagal reflex. The signals from afferent terminals are transmitted by ghrelin to the brain stem, however, the neural circuits involved and the mechanisms of how these signals induce gastric phase II contractions following the input on brain by afferents has not been fully understood.

GPR38 and GHS-R are expressed within the areas of hypothalamus and medulla oblongata in CNS (7), but the central effect of these hormones have not been clarified. Therefore, we first examined the central effect of motilin and ghrelin on GI motility in fasted state suncus. Intracerebroventricular injections of motilin and ghrelin neither induced gastric motility nor the change of gastric phase II contractions. These results suggest that GPR38 and GHS-R expressed in hypothalamus and medulla oblongata are not directly involved in regulation of GI motility, and those receptors may have other physiological functions apart from GI motility.

To reveal the neural circuits involved after the signal input of brain stem by ghrelin in phase II, we focused on the effect of neurotransmitters, GABA and L-glutamate on the gastric motility. GABA is known as the amino acid which contributes to inhibitory synaptic transmission in CNS, and it works as the main inhibitory neurotransmitter in NTS to DMV connection in rats and mice (11, 12). It has been shown that microinjection of $GABA_A$ antagonist in DMV increased gastric motility in rats (11, 14, 15). In this study, we then investigated

GABAergic neuron in phase II contractions and found that i.c.v. administration of GABA in phase II decreased spontaneous phase II contractions. In addition, i.c.v. administration of $GABA_A$ antagonist in phase I induced phase II-like contractions. These results indicate that GABAergic neurons play an important inhibitory role in the regulation of phase II contractions in suncus. Moreover, it has been reported that L-glutamate works as a neurotransmitter in NTS to DMV connection (16) and it is well known to be the main excitatory neurotransmitter in mammalian CNS. Therefore, we next examined the central effect of L-glutamate and showed that its i.c.v. administration induced phase II-like contractions. This result suggests that glutamatergic neurons stimulate the vagus efferent nerve in DMV and play a key excitatory role in the regulation of phase II contractions. The phase II-like contraction observed with $GABA_A$ antagonist and L-glutamate in this study was regarded as a similar characteristic to that in phase II with amplitude and frequency, and was followed by a phase III contraction in suncus. Moreover, we found that i.c.v. administration of neither $GABA_A$ antagonist nor L-glu immediately stimulated phase III-like contractions. Taken together, the results suggest that GABAergic and glutamatergic neurons coordinately regulate phase II contraction but not phase III contraction.

It has been shown that glutamic acid decarboxylase (GAD), and glutamine synthetase (GS) of GABA,-immunoreactive cells, were observed in the NTS and DMV (17), and $GABA_A$ receptors were also expressed in NTS and DMV in rats (18). Similarly, expression of NMDAR1, glutamate receptor, was observed in DMV in rats (19). Taken together, these observations suggest that although additional studies are needed to further understand the projection of GABAergic and glutamatergic neurons in suncus. It is possible that GABA and L-glutamate bind the receptors expressed in NTS and DMV in suncus and regulate vagus efferent nervous activation. In addition, L-glutamate is further considered to induce gastric phase II contraction when the inhibitory effects of GABA on the vagus nerve decreases.

In summary, we have demonstrated that central ghrelin and motilin are not involved in gastric motility, and that GABAergic and glutamatergic neurons in the brain play an important role in regulating gastric phase II contractions. In addition, these results suggest that GABAergic and glutamatergic neurons in the brain stimulate vagal efferent nerves which project to the stomach for controlling phase II gastric contractions.

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