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Tsukasa Nozu ^a, Shima Kumei ^b, Kaoru Takakusaki ^c, Koji Ataka ^d, Mineko Fujimiya ^d, Toshikatsu Okumura ^b

^aDepartment of Regional Medicine and Education, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa , 078-8510, Japan

^bDepartment of General Medicine, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa , 078-8510, Japan

^cResearch Center for Brain Function and Medical Engineering, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa , 078-8510, Japan

^dDepartment of Anatomy, Sapporo Medical University School of Medicine, Minami 1, Nishi 17, Chuo-Ku, Sapporo 060-8556, Japan

Address for corresponding:

Tsukasa Nozu, MD, PhD, FACP, FJSM

Department of Regional Medicine and Education, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, 078-8510, JAPAN

Ph; +81-166-68-2844

Fax; +81-166-68-2846

e-mail; tnozu@sea.plala.or.jp

Abstract

Increasing evidence has indicated that brain orexin plays a vital role in the regulation of gastrointestinal physiology such as gastric secretion, gastric motility and pancreatic secretion. However, little is known whether orexin in the brain is involved in the physiology of the lower gastrointestinal tract. The aim of this study was therefore to elucidate whether orexin-A in the brain is involved in the regulation of colonic motility. In this study, we measured fecal pellet output and recorded intraluminal colonic pressure waves in freely moving conscious rats to evaluate the effects of central orexin-A on colonic motor functions. Intracisternal but not intraperitoneal injection of orexin-A dose-dependently (1- 10 μ g) increased fecal pellet output. Findings obtained from manometric recordings revealed that intracisternal administration of orexin-A at a dose of 10 μ g significantly enhanced colonic motor contractions. These results suggest for the first time that orexin-A acts centrally in the brain to enhance fecal pellet output and stimulate colonic motility in conscious rats. The present study would furthermore support our hypothesis that orexin-A in the brain may be an important candidate as a mediator of the cephalic phase gut stimulation including stimulated colonic motility in addition to well known physiological response such as stimulation of gastric acid and pancreatic acid secretion, and gastric motility.

Key words

orexin, colon, motility, pressure wave, conscious rat

Introduction

Orexins/hypocretins are novel neuropeptides that are localized in neurons in the lateral hypothalamus [7, 27]. On the other hand, orexin-immunoreactive fibers and terminals, and specific orexin receptors are distributed in a wide variety of nuclei in the central nervous system [10]. Based upon these neuroanatomical evidence, orexinergic projection should be involved in a number of biological functions. In fact, orexins may be implicated in a wide variety of physiological functions. These include feeding [27, 32], behavioral activity [11], sleep/awake [6], anxiety [29], energy balance [15], neuroendocrinological response [14] and cardiovascular functions [28]. In addition to these functions, we have demonstrated for the first time that orexin-A is involved in central regulation of gastric acid secretion [24, 31, 33]. In the brainstem, orexin receptors are expressed in the dorsal motor nucleus of the vagus (DMN) in the medulla oblongata [23], and the parasympathetic preganglionic neurons project their axon terminals through the vagus nerve to the digestive system [21]. Intracisternal but not peripheral injection of orexin-A dose-dependently stimulated gastric acid secretion through the vagus nerve in conscious rats [31]. Considering the potent orexigenic action of orexin-A, it may be an important candidate as a mediator of the cephalic phase secretion as proposed by Pavlov [25].

With regard to the roles of brain orexin in gastrointestinal functions

other than gastric secretion, a couple of studies demonstrated that orexin-A acts centrally in the brain to stimulate gastric motility. Kobashi et al. [12] have examined the effects of the intracisternal administration of orexin-A on gastric motility in anesthetized rats. Phasic contractions in the distal stomach were facilitated in response to centrally injected orexin-A. Facilitation in the distal stomach was blocked by vagotomy, suggesting that central orexin facilitates distal stomach motility via the vagus nerve. It has been shown that microinjection of orexin-A into the DMN increased intragastric pressure and antral motility in anesthetized rats [13], indicating that orexin-A in the DMN stimulates gastric motor function. In addition to the evidence in anesthetized rats, Bülbül et al. [4] have very recently demonstrated that intracerebroventricular injection of orexin-A at a dose of 10 µg enhanced postprandial gastric motility in conscious rat. Thus, these provided the evidence in conscious rats that orexin-A acts centrally in the brain to increase gastric motility. However, little is known about a role of central orexin-A in colonic motility.

Gastric and colonic motility are regulated by different mechanisms. For instance, centrally administered corticotropin-releasing factor inhibits gastric emptying while simultaneously increasing colonic motility, transit and defecation in rats [16, 17, 19]. The aim of this study was therefore to elucidate whether orexin-A in the brain is involved in the regulation of colonic motility. In this study, we measured fecal pellet output and recorded

intraluminal colonic pressure waves in freely moving conscious rats to evaluate the effects of central orexin-A on colonic motor functions.

Materials and methods

Animals

Male Sprague-Dawley rats weighing about 250 g were housed under controlled light /dark conditions (lights on: 07:00 - 19:00) with the room temperature regulated to 23-25°C. Rats were allowed free access to standard rat chow (Solid rat chow, Oriental Yeast Co., Tokyo, Japan) and tap water.

Chemicals

Synthetic orexin-A (human/bovine/rat/mouse) was purchased from Peptide Institute Inc., Osaka, Japan and were dissolved in normal saline just before experiments.

Measurement of fecal pellet output

Fecal pellet output was measured according to the previous studies [17]. Rats received intracisternal injection (ic) with either orexin-A (1, 3 or 10 µg in 10 µl) or vehicle (saline 10 µl). Ic was performed under brief ether anesthesia within a couple of minutes with a 10-µl-Hamilton microsyringe after rats were mounted in a stereotaxic apparatus (David Kopf Instruments,

Tijunga, CA, USA) as reported previously [20]. Immediately after ic, rats were put individually in the cage and fecal pellet output was counted for 1 h. To assess the peripheral action of orexin-A on fecal pellet output, orexin-A (10 μ g in 0.3 ml) or vehicle (saline 0.3 ml) was administered intraperitoneally under brief ether anesthesia and fecal pellet output was counted for 1 h.

Implantation of catheter for manometric recordings

The rats were anesthetized with ether, and open-tipped catheter (3-Fr, 1 mm ID; Atom, Tokyo, Japan) for manometric measurement was inserted into the colon at 3 cm from the ileocecal junction (proximal colon). The catheter was held in place by purse-string sutures at the point of exit from colonic wall (2 cm proximal to the recording point), brought out through the abdominal wall musculature, and tunneled subcutaneously to exit at the back of the neck and secured to the skin. The rats were allowed to recover in individual cages for 2-5 days before the experiments.

Manometric recordings

Colonic motility was measured by manometric methods described in previous studies [1, 2]. Conscious animals without fasting were put in wire-bottom and non-restraint polycarbonate cages. Manometric catheter from each animal was threaded through a flexible metal sheath to protect

from biting and connected to the infusion swivel (Instech Laboratories, Plymouth Meeting, PA) to allow free movement. It was connected to a pressure transducer (TP-400T; Nihon Koden Kogyo, Tokyo, Japan) and was continuously infused with degassed distilled water at a rate of 1.5 ml/h by a heavy-duty pump (CVF-3100; Nihon Koden). Pressure signals from the transducer were digitized and stored using a PowerLab system (AD Instruments, Colorado Springs, CO). Manometric measurement of pressure wave was started after 1-h of stabilization of animals. First, the basal state of the colonic pressure wave was measured for 1 h. Then, the manometric catheter was disconnected and the rats were removed from polycarbonate cages. Under brief ether anesthesia, rats received orexin-A at a dose of 10 μ g/10 μ l or saline (10 μ l) intracisternally as described above. After that, the rats were put in the cages again and the catheter was re-connected to a pressure transducer. The pressure recording was continued for 2 h after ic.

Evaluation of the motor index

The motor index (MI) was assessed by area under the manometric trace (AUT). AUT was calculated using a data-acquisition software (LabChart v7, AD instruments, Colorado Springs, CO). The baseline drifting and recording noise due to movement of the animals was very minor. To avoid any baseline drifting, we selected the analysis points with stable baseline. Basal MI was determined by calculating AUT for 1-h

period before ic. The %MI was determined by calculating following the formula; (AUT for each 1-h period after orexin-A or vehicle ic)/(basal MI) \times 100. Changes in the %MI were compared between orexin-A and vehicle treated group. In this experiment, pressure signals were continuously recorded up to 4 h (1 h for stabilization, 1 h for basal MI and 2 h for determining the changes induced by orexin-A or vehicle ic), but the measurement was temporally stopped in order to perform ic at the middle of the recordings. In relation to ic, we also need the time for recovery from the anesthesia and re-stabilization of baseline of manometric pressure in order to obtain the adequate recordings for the analysis. Therefore, the manometric data during the recovery period from approximately 5 min was excluded from later analysis.

Statistical analysis

Data were expressed as means \pm S.E. Comparison of fecal pellet output was performed by Kruskal-Wallis one-way analysis of variance (ANOVA) followed by Non-Parametric Bonferroni-type multiple comparison. Comparison of %MI was performed using ANOVA followed by the least significant difference test. Statistica (StatSoft Inc. Tulsa, Okla., USA) was used throughout the study.

Ethical considerations

The approval of the Research and Development and Animal Care committees at the Asahikawa Medical University was obtained for all studies.

Results

First, we have examined the effect of intracisternal orexin-A on fecal pellet output in freely moving conscious rats. As demonstrated in Figure 1, ic of orexin-A stimulated pellet output dose-dependently ($H = 12.8$, $P < 0.05$, saline: 1.14 ± 0.42 , orexin-A 1 μg : 1.05 ± 0.18 , 3 μg : 1.74 ± 0.32 , 10 μg : 3.42 ± 0.47 , $n = 6-10$). At a dose of 10 μg , it potently increased pellet output ($P < 0.05$ vs saline). In contrast, intraperitoneally administration of orexin-A at the dose of 10 μg failed to increase pellet output (saline: 1.12 ± 0.56 , vs orexin-A: 0.73 ± 0.28 , $P > 0.05$, $n = 5-6$), suggesting that orexin-A acts centrally in the brain to enhance fecal transit.

Next, to clarify whether colonic contractions would be changed by centrally injected orexin-A, we measured intraluminal colonic pressure in freely moving conscious rats. Figure 2 illustrated the representative recordings of colonic contractions. As demonstrated in Figure 2A, ic of orexin-A at a dose of 10 μg enhanced the amplitude of colonic pressure waves. The stimulatory effect of colonic contractions was observed immediately after ic of orexin-A, while centrally injected saline did not change (Figure 2B). As clearly demonstrated in Figure 3, ic of orexin-A

significantly increased MI change of the colon during 0 to 60 min after the injection ($F = 5.96$, $P < 0.05$, saline: 90.5 ± 5.0 , vs orexin-A: 160.8 ± 20.9 , $P < 0.05$, $n = 5-7$). The mean value of MI change during 60 to 120 min in rats treated with central orexin-A was higher but did not reach to the statistical significance ($P > 0.05$, saline: 96.6 ± 6.9 , vs orexin-A: 135.1 ± 32.2 , $P > 0.05$).

Discussion

Although increasing evidence has indicated that brain orexin plays a vital role in the regulation of gastrointestinal physiology such as gastric secretion, gastric motility and pancreatic secretion, little is known whether orexin in the brain is involved in the physiology of the lower gastrointestinal tract. The current study was performed to clarify whether orexin-A is implicated in the regulation of colonic motor functions. For the aim, we used two methods such as counting pellet output and manometric measurement to assess colonic motility. The major finding in this study is that orexin-A acted centrally to increase fecal pellet output and stimulated colonic contractions in conscious unrestrained rats. The present study therefore suggested for the first time that orexin-A acts centrally in the brain to play a role in the regulation of lower gastrointestinal tract functions.

As demonstrated in the present study, MI was significantly

increased to approximately 160 % in the first 1-h period after administration of orexin-A at a dose of 10 μ g into the cerebrospinal fluid. Bülül et al. [4] demonstrated that the same dose (10 μ g) of central orexin-A increased MI to 160% in stomach, and this stimulatory effect was observed immediately after administration and persisted for about 50 min. Thus it is of interest that centrally injected orexin-A at the same dose stimulated both gastric and colonic motor activity at the same degree, suggesting that orexin-A acts in the brain to stimulate not only gastric but colonic motility under the same condition. As shown by Bülül et al. [5] central orexin-A-induced change of gastric motility was blocked by atropine and surgical vagotomy in rats, suggesting that vagal cholinergic pathways play a role in the central orexin-A-evoked changes of gastric motility. It is well known that the motor activity of the colon is regulated by the pelvic and vagal cholinergic pathways in rats [3]. All these findings led us to speculate that vagal cholinergic pathways might mediate the stimulated colonic motility by central orexin-A. Further study should be needed to explore the above speculation.

The cephalic phase of GI response produces coordinated GI alterations that prime the gut to assist digestion of the impending meal. Since the alterations in response to cephalic stimulation in stomach and pancreas were mimicked by orexin-A [12, 18, 31], this peptide is thought to be a candidate molecule which triggers the process of cephalic phase

stimulation [23]. Moreover, it has been reported that cephalic stimulation also increases colonic motility [26]. The present evidence that orexin-A acts centrally to increase colonic motility may furthermore support our hypothesis that orexin-A in the brain plays a role as a trigger molecule that undergoes cephalic phase gut stimulation.

Functional gastrointestinal disorders (FGIDs) are characterized as chronic or recurrent GI symptoms, which are not explained by structural or biochemical abnormalities. Brain-gut interaction plays an important role in the pathophysiology of FGIDs [8]. The patients with functional dyspepsia (FD), which is one of the FGIDs frequently complain of GI symptoms after meals, and postprandial antral hypomotility or reduced fundic accommodation was reported to be one of the physiological mechanisms of FD [9, 30]. Since fundic accommodation and hypermotility in the distal stomach were observed in rats treated with intracerebroventricular orexin-A in rats [12], we suggest in turn decreased orexin signaling may contribute to the pathophysiology of FD as we have shown in recent publications [22, 23]. In addition to the role of brain orexin in the physiology of upper GI tract, the present finding that orexin-A acts centrally in the brain to increase colonic motility might support a speculation that orexin signaling would contribute to the pathophysiology of FGIDs which are associated with disturbance of lower GI tract motility.

Conclusions

We have shown for the first time that central orexin-A stimulated colonic motility. This result may further support the hypothesis that orexin-A is a possible molecule mediating the cephalic phase response of digestive system.

Acknowledgments

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Figure legends

Figure 1.

The effect of intracisternal (ic) or intraperitoneal (ip) orexin-A on fecal pellet output. Fecal pellet output for 1 h was measured in rats injected with either orexin-A or vehicle. Each column represents the mean \pm S.E. Number of rats was shown in the parenthesis. *P < 0.05 vs vehicle-treated group.

Figure 2.

Representative recordings of the colonic contractions in rat injected intracisternally with either orexin-A (A) or saline (B). * indicated the period which was needed for intracisternal injection and re-stabilization of baseline. The manometric data during the period were omitted from the analysis.

Figure 3.

The effect of intracisternal administration of orexin-A on contractions of proximal colon. Orexin-A significantly increased the motor index as compared to saline treatment at the first 1-h period after administration. However, this effect was no longer observed at next 1-h period. Each column represents the mean \pm S.E. Number of rats was shown in the parenthesis. *P < 0.05 vs saline-treated group.





