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Gastric Acid Secretion Controlled by the Oxytocinergic Neuron in the Hypothalamic Paraventricular Nucleus

Takeo SAKAGUCHI

Department of Physiology (I), Niigata University School of Medicine, Asahimachi 1, Niigata 951, Japan

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Summary. **Morphological studies have revealed neural connections containing oxytocin (OXT) between the hypothalamic paraventricular nucleus (PVN) and medulla oblongata. Electrophysiologically, it has also been shown that there is a functionally specific correlation between the PVN and medullary neurons that are related to the gastric function. Moreover, it was observed that activation of oxytocinergic neurons in the PVN caused by electrical stimulation or OXT application strongly influences gastric acid secretion. The inhibitory response in acid secretion is substantially blocked by vagotomy or by an anticholinergic agent applied onto the medullary gastric neuron and the peripheral site.**

Since OXT has been shown to be synthesized in the PVN magnocellular nucleus and act locally within the nucleus to control its activity, these findings suggest that the activation of oxytocinergic neurons due to intrinsic OXT within the PVN participates in the control of gastric acid secretion with a change in vagal activity, and that a specific nucleus localized in the medulla oblongata is involved in this system as a relaying mechanism.

Introduction

Oxytocin (OXT) is a circulating peptide hormone produced by hypothalamic magnocellular neurosecretory neurons and released from the posterior pituitary. Recent studies utilizing immunohistochemical techniques have revealed a substantial network of fibers containing OXT throughout the central nervous system, and shown that the neurons in the paraventricular nucleus (PVN) containing OXT project not only to the neurohypophysis but also to the medulla oblongata.[1-3] The medulla oblongata appears to be a major target of these fibers, and independent neuroanatomical tracing studies have shown a direct projection to it from the PVN.[1,4] The medulla oblongata is the site where the autonomic function is controlled.

This paper introduces the role of the oxytocinergic neurons in the PVN in the secretory function of the stomach.

I. Gastric acid secretion associated with PVN activation

Electrical stimulation applied to the PVN produced a reduction in gastric acid secretion[5] (Figs. 1 and 2). The optimal electrical property for eliciting the maximum inhibitory response in the acid output was

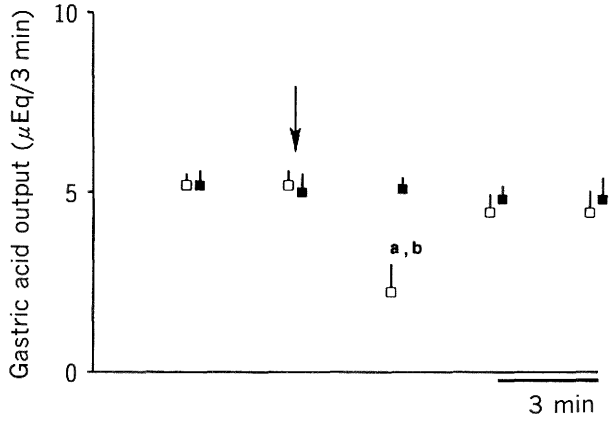

Fig. 1. Changes in gastric acid output produced by electrical stimulatin of the PVN. Sixty (□, n=12) or 0 (■, n=12) Hz stimulation was given. The arrow indicates the time at which electrical stimulation was applied. Stimulus intensity was 0.5 mA. Values are the mean ± SEM. a; $p<0.01$ vs. the time of the stimulation. b; $p<0.01$ vs. the value for 0 Hz 3 min after stimulation. Activation of the PVN reduces gastric acid output.

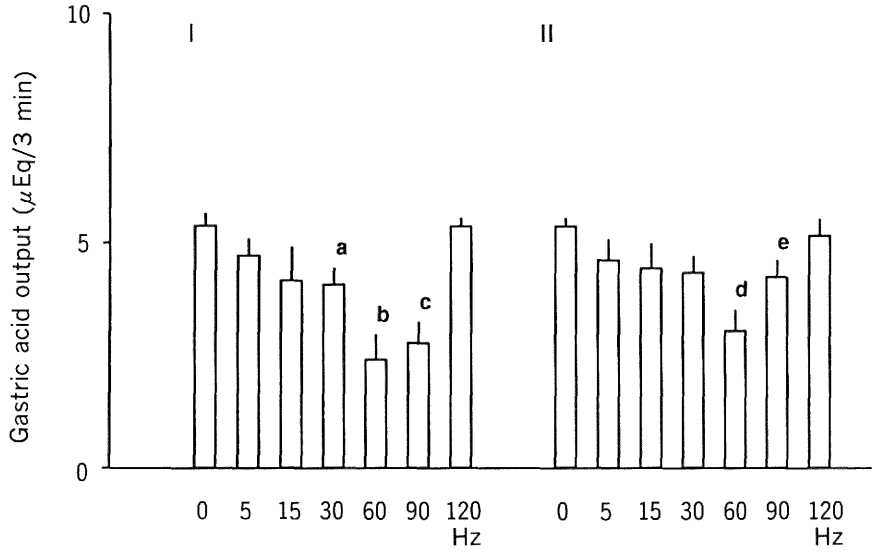

Fig. 2. Gastric acid outputs in response to paraventricular (I) and pituitary stalk (II) stimulations. The acid outputs 3 min after 0, 5, 15, 30, 60, 90 and 120 Hz stimulations are compared. Values are the mean ± SEM (n=12). a; $p<0.05$ vs. 0 Hz (I). b; $p<0.01$ vs. 30 Hz (I). c; $p<0.05$ vs. 30 Hz (I). d; $p<0.05$ vs. 90 Hz (II). e; $p<0.05$ vs. 0 Hz (II). The optimal frequency of 60 Hz for eliciting the maximum inhibitory response in the acid output is in a range that causes full activation of neurosecretory cells and OXT release.

in a range that caused full activation of neurosecretory PVN cells and OXT release.[6,7] The pituitary stalk stimulation also suppressed gastric acid output.[5] (Fig. 2). It is possible that the stalk stimulation affected the PVN directly through axonal branches, since magnocellular PVN cells have been shown to have axons divergent to the neurohypophysis both by double labelling methods[8] and antidromic activation techniques.[9] The elimination of the effect in the PVN-lesioned or the hypophysectomized animals indicated that there was no current spread to other areas of the hypothalamus. Activation of specific PVN neurons identified as oxytocinergic neurons provokes inhibitory secretion of gastric acid.

Although the gross methodological approach involved stimulating the PVN with rather large cannulas, nanomolar quantities of OXT injected into the PVN also evoked a reduction in gastric acid secretion[10] (Figs. 3 and 4). Activated neurons receptive to OXT located in the PVN resulted in the inhibitory acid response. OXT has been demonstrated to act locally within the PVN magnocellular nuclei to control their activity.[11] Chemically it has been considered that the normal concentration of OXT in the PVN and neural lobe of the pituitary stalk which would come from the PVN was at the nanomolar level;[12] it is not easy, however to estimate the physio-

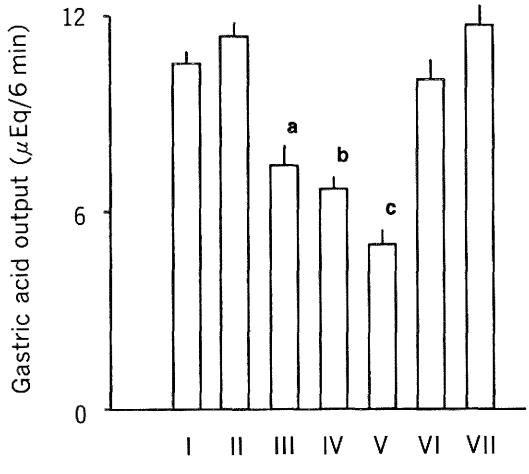

Fig. 3. Gastric acid outputs 6 min after OXT injection into the PVN. Different concentrations of OXT (5 nM, II; 10 nM, III; 20 nM, IV; 40 nM, V) were injected. Ten nM OXT with vagotomy at the subdiaphragmatic level (VI) and 10 nM OXT with atropin sulfate (VII) are shown. Saline was used as the control (I). Values are the mean ± SEM (n=7). a-b; $p<0.01$ vs. II. c; $p<0.01$ vs. III. The acid response specific to OXT is mediated by vagal and cholinergic fibers to the stomach.

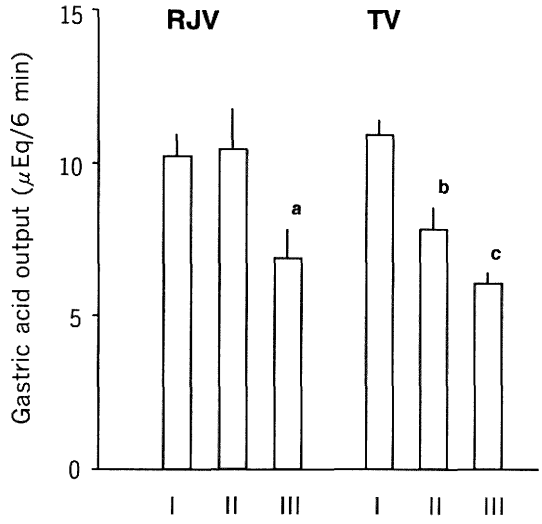

Fig. 4. Dosage of OXT evoking a reduction in gastric acid output after right jugular (RJV) or third ventricle (TV) injection. Different doses of OXT (200 nM, I; 400 nM, II; 800 nM, III) were injected. Values are the mean ± SEM (n=7). a; $p<0.05$ vs. II. b; $p<0.01$ vs. I. c; $p<0.01$ vs. II. Ten nM OXT inhibited acid output when injected into the PVN, whereas no change in the acid output was seen when 20 times larger doses of the peptide were injected into the RJV or into the TV. The peptide leaking from the brain tissue into the blood stream or cerebrospinal fluid is not active in the response.

logically acting concentration of the peptide. If OXT was released locally onto the PVN neurons and they acted as neurotransmitters or neuromodulators, the concentration of the peptide near the cell body might be much higher.[10] The effective concentration of OXT provoking inhibitory gastric acid secretion was similar to that applied in the study of rat hippocampal neurons and rat motoneurons.[13,14] These reports indicate a strong possibility that alterations in intrinsic OXT influence the secretory function in the stomach within the physiological range.

II. Signal pathway and relay nucleus

PVN activation resulted in a decrease in gastric acid secretion, and the acid response was completely blocked by lesion of the nucleus of the vagus nerve (DMX) in the medulla oblongata.[10] Electrophysiologically, it has been indicated that iontophoretic application of OXT inhibits medullary neurons which would relate to the gastric function.[15] Morphologically, oxytocinergic projections from PVN to the solitary nucleus (NST) which is adjacent to the DMX, have been established in many reports.[1,2,4,16] Because there are fibers connecting the DMX to the NST, it is possible that PVN signals affecting the gastric function make a neural circuit among these nuclei. Support for such a suggestion comes from a study indicating that PVN inhibitory effects on acid output were blocked by a lesion of the NST or DMX.[5] Magnocellular PVN cells have been shown to have divergent axons projecting to the neurohypophysis and to these medullary nuclei.[9] The secretory system in the stomach associated with oxytocinergic PVN neurons involves these specific nuclei as relay media.

Neurons in the relay nucleus are responsive to OXT. Micropressure injection of OXT altered the basal firing rates of neurons in the DMX that were specifically related to gastric function. Because the predominant response to OXT was an increase in spontaneous activity, OXT may activate neurons that project to inhibitory circuits in the enteric nervous system to reduce gastric function.[17] Half of the NST neurons that received gastric mechanoreceptor information were activated by this peptide. With reference to electrophysiological criteria, a large majority of the cells that were identified as gastric-related neurons in the NST and DMX were also found to be excited by OXT.[17] However, it should be remembered that OXT affects other, non-gastric, neurons in the DMX. Some of these neurons are linked to the regulation of the cardiovascular system.[17]

There exists a functional correlation between the PVN and relay nucleus. Gastric acid secretion was inhibited by OXT injection into the DMX in the medulla oblongata.[10] There was also an additive decrease in the acid secretion when OXT was applied onto the PVN and DMX simultaneously (Fig. 5). This type of gastric acid secretion is characteristic of the activation of the PVN and DMX, either separately or together.

III. Signal transmission to the relay nucleus

Both PVN stimulation and OXT injections to the PVN change the spontaneous activity of NST and DMX neurons and influence gastric secretory activity. Whereas OXT antagonists can block some of the gastric responses to PVN stimulation, it remains to be determined whether the excitatory or inhibitory effect of PVN stimulation on NST and DMX neurons is mediated by OXT.[17] With regard to the possible mechanism for this, PVN stimulation and medullary OXT injections may influence the gastric function by altering the activity of NST and therefore its targets, including the vagal efferent cell bodies in the DMX.

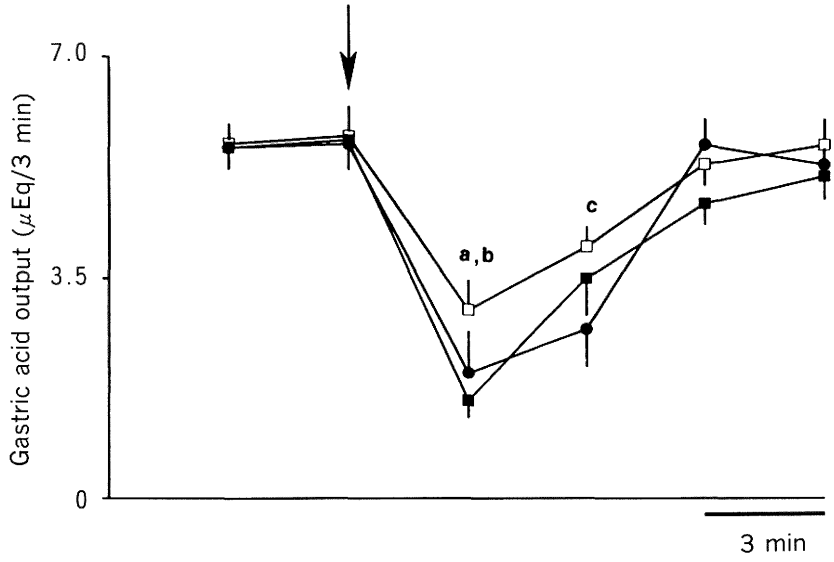

Fig. 5. Gastric acid output following OXT injection into two different regions of the brain. Twenty nM OXT was injected into the PVN (■), into the DMX (□) and into both these regions simultaneously (●). Values are the mean ± SEM (n=7). a; $p<0.01$ vs. the value just before injection. b; $p<0.01$ vs. ■. c; $p<0.01$ vs. ●. There is an additive interaction between the PVN and DMX.

The possibility that OXT acts on interneurons that project to NST and DMX neurons cannot be ruled out. However, with the *in vitro* slice preparation, it was demonstrated that the excitatory effect of OXT on DMX neurons persists under conditions of synaptic blockade.[18] OXT may be acting directly on vagal neurons that are related to the gastric function.

The origin of the OXT-containing neurons in the DMX is in the PVN. OXT can be released from these neurons by depolarizing medullary slices[19] or by electrically stimulating the PVN.[20] The released OXT is thought to alter the firing rate by binding to the high affinity OXT receptors that exist in the DMX.[18,21] OXT receptor antagonists were effective in blocking the enhanced firing of DMX neurons[22] and the gastric response evoked by medullary injections of OXT,[23] indicating that these responses were elicited by a specific action on OXT receptors. These findings indicate a role for OXT as a putative neurotransmitter in this system.

OXT was potent in modulating the firing rate of medullary neurons when a femtomolar amount of OXT was injected.[24] In the oxytocinergic cells that were tested with multiple doses, there was a dose-response relationship. The latency to respond to OXT tended to be long (range, 10s-2.5 min). This may be a result of diffusion of the peptide and/or the activation of a second messenger system.[24] The acid response to OXT was often long lasting[10] i.e. several minutes, which is consistent with the suggestion that OXT is activating a second messenger cascade.

IV. Relay nucleus and vagally mediated acid secretion

The inhibitory response in gastric acid secretion to electrical stimulation of the PVN or OXT injection into the DMX was eliminated by vagotomy at the subdiaphragmatic level and by atropin sulfate (Fig. 3), suggesting that the response was mainly mediated by vagal and cholinergic fibers to the stomach.[5,10] OXT activates vagal neurons that project to inhibitory circuits in the enteric nervous system to reduce the gastric secretory function.

V. Relationship between motor and secretory functions

Electrical stimulation applied to the PVN produced a reduction in intragastric pressure,[26] and the optimal electrical stimulation to elicit the maximum response in pressure was in the range to cause specific activation of OXT release.[6,7] PVN activation resulted in an inhibitory response in both motor and secretory functions of the stomach.[5,10,26] However, there were differences between the two functional responses in latent periods, and the threshold of stimulation was different in motility from that in acid secretion. This

implies that the action of OXT on motor and secretory functions was differentially determined at the PVN level.

There are two kinds of PVN neurons. It has been shown that certain experimental treatments administered to rats that evoke nausea, satiety, or cellular dehydration activate both magnocellular and parvocellular neurons and inhibit the gastric motor function.[28-30] Although the inhibition of feeding was correlated with the peak elevation in the plasma OXT concentration, the gastric motor dysfunction was not mediated by circulating OXT released from the posterior pituitary.[27] This could mean that the magnocellular oxytocinergic neurons projecting to the pituitary were co-activated with parvocellular oxytocinergic neurons projecting to the DMX which exclusively participates in the regulation of gastric motility. The increase in plasma OXT concentrations and the inhibition of the gastric motor function can be explained by the co-activation of magnocellular and parvocellular OXT-containing neurons.

VI. Factors affecting control of acid secretion by PVN

Glycemic condition: Electrical stimulation of the PVN evoking specific activation of OXT release or OXT applied to the PVN brought a reduction in gastric acid secretion associated with insulin-hypoglycemia.[5,10] The magnitude of these responses varied according to the glycemic condition of the animals, and it was noted that hyperglycemia masked the acid response accompanying the PVN activation (Fig. 6). Inhibition of gastric acid secretion by glycemia[31] has been shown to be determined at the hepatic portal[32,33] or medullary[34] level, and the medulla oblongata has been thought to be the site where the interaction between OXT and glucose takes place. However, there remains much scope to investigate concerning the interaction between OXT and glucose at the PVN level, especially since a mechanism receptive to glucose has been demonstrated in the PVN and the formed microcircuit.[35]

Estrogen: Gastric acid response to OXT injection into the PVN was reproducible at the same magnitude in male rats regardless of the experimental day. However, there was a cyclical response in female rats according to the estrus cycle; this response being greatest on the day showing the lowest concentration of estrogen (Fig. 7). The changes in the estrogen concentration in the blood influence the function of the alimentary canal has been well documented; estrogen causes the suppression of food and water

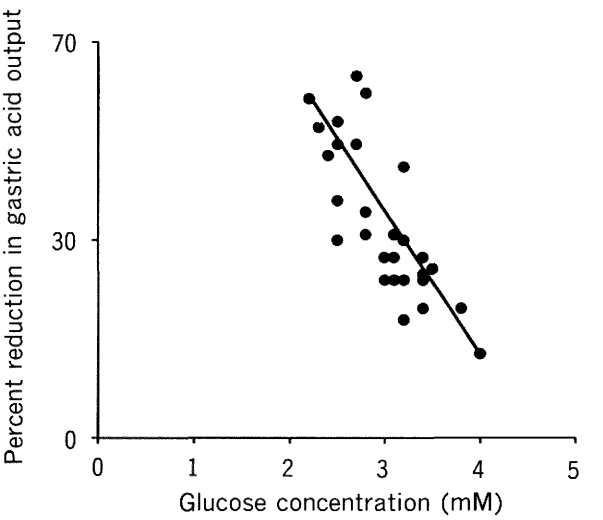

Fig. 6. Relationship between glucose concentration in the blood (X) and percent changes in gastric acid outputs (Y) caused by OXT injection into the PVN. Percent changes in acid outputs were calculated from values before and 3 min after OXT (20 nM) injection. The regression line is $Y=-22.764\ X+105.709$ and its coefficient ($r=-0.776$) is significant, $p<0.05$. Increasing the concentration of glucose consistently diminishes gastric acid response with OXT.

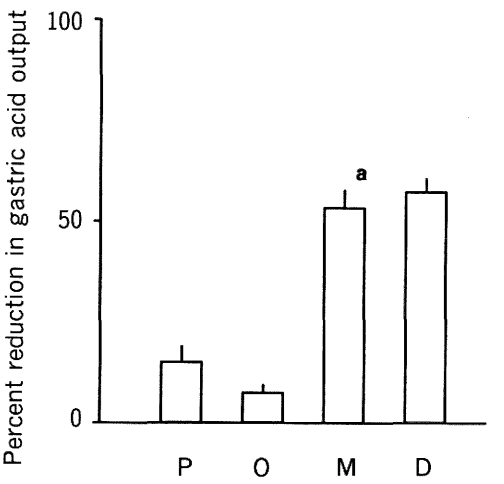

Fig. 7. Percent changes in gastric acid output evoked by OXT injection in different stages of the estrus cycle. Twenty nM OXT was injected into the PVN in rats at different estrus stages (P, proestrus; O, oestrus; M, metoestrus; D, diestrus). Values are the mean ± SEM ($n=6$). a; $p<0.01$ vs. P and O. The acid response is lowest in rats showing signs of oestrus.

intake by stimulating the estrogen-sensitive areas in the brain.[36,37] In humans, it has been shown that there is a great difference between males and females in the secretory function of the stomach.[38] Indeed, in women, the levels of acid secretion and the estradiol concentration vary with the menstrual cycle,[39] and the sites of estrogen-sensitive areas have been identified in specific nuclei in the hypothalamic regions.[40,41] The OXT effect on gastric acid secretion seemed to be modulated cyclically by sex hormone estrogen at the hypothalamic level.

VII. Action of peptides co-existing in the PVN

Gastrin: Neurohypophyseal gastrin is a prominent feature of the mammarian pituitary, because it occurred in all species examined in concentrations of the same magnitude.[42,43] Although the pituitary gastrin concentrations are low in comparison with concentrations in the antral mucosa, the consistent occurrence in constant amounts suggests that the hypothalamo-hypophyseal gastrin is significant. It is of particular interest that gastrin is synthesized in hypothalamo-hypophyseal neurons.[44] In contrast to gastrin, the pituitary occurrence of cholecystokinin (CCK) varied among species and pituitary lobes. The concentrations were higher than those in other regions of the central nervous system.[44] Gastrin-17 has been shown to stimulate gastric acid secretion when injected into the PVN.[45] The gut hormones gastrin and CCK have been shown to possess a common origin and a common COOH terminals, which constitute their active site,[44] however, CCK-8 had no effect on the acid secretion. Gastrin in the PVN may serve to control gastric acid secretion.

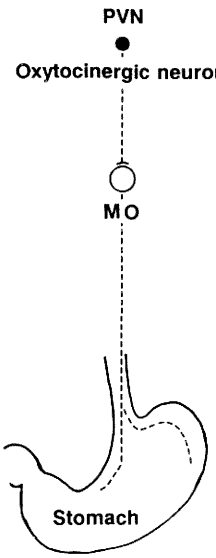

Fig. 8. Summary of the system for oxytocinergic control of gastric acid secretion. Oxytocinergic neurons respond to local OXT synthetized in the PVN. There are direct monosynaptic projections between the PVN neuron and preganglionic gastric neuron in the medulla oblongata (MO), and through which the cholinergic vagal fiber terminating the stomach is activated. Dotted lines show the efferent neural pathway.

TRH: Thyrotropin-releasing hormone (TRH) is contained in terminals in the NST and DMX,[46] and also influences the vagal control of the gastric function.[17] The response of brain stem vagal neurons to OXT is in contrast with that observed for TRH. Although DMX neural activity was increased by either TRH[17] or OXT,[17,22] TRH appeared to override incoming sensory signals by inhibiting spontaneous NST activity.[17] These two neuropeptides act in a fundamentally different manner to modulate the vagal function of the stomach.

Conclusion

Because OXT and vasopressin peptides seem to occur together with gastrin and CCK, it has been speculated that OXT and gastrin might be part of a large multihormonal precursor.[47] It now remains to be shown whether the pituitary cells translate the same precursor. Paraventricular magnocellular neurons contain not only OXT but also others such as vasopressin, all of which contain, in addition, any of a number of other peptides including met-enkephalin and dynorphin.[8,48] Small cells are also present in the PVN and contain a corticotropin releasing factor and a variety of other peptides.[49] Our findings suggest that the PVN neurons receptive to these peptides have a secretory function in the stomach. Thus, when several peptidergic neurons in the PVN are activated simultaneously with multiple-barrelled micro-iontophoretical application,[50] the results obtained may give us a qualitative picture of peptidergic PVN control of the gastric function (Fig. 8). Further study in this field is necessary.

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