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Orexins are neuropeptides that are localized in neurons within the lateral hypothalamus and regulate feeding behavior. The lateral hypothalamus plays an important role in not only feeding but the central regulation of gut function. Along this line, accumulating evidence have shown that orexins acts in the central nervous system to regulate gastrointestinal functions. The purpose of this review is to summarize recent relevant findings on brain orexins and a digestive system, and discuss the pathophysiological roles of the peptides. Centrally administered orexin or endogenously released orexin in the brain potently stimulates gastric acid secretion in rats. The vagal cholinergic pathway is involved in the orexin-induced stimulation of acid secretion. Considering its stimulatory action on feeding, it should be hypothesized that orexin in the brain is a candidate mediator of cephalic phase gastric secretion. In addition, brain orexin may be involved in the development of depression and functional gastrointestinal disorders which are frequently accompanied with the inhibition of gut function, because lack of orexin action might induce the inhibition of gastric physiology and evoke depressive state. These evidence suggest that orexin in the brain would be a possible molecular target for the treatment of functional gastrointestinal disorders.

## Introduction

Approximately 10 years ago, the orexins, also called hypocretins were first described as a pair of neuropeptides expressed by a specific population of neurons in the lateral hypothalamic area (LH), a region of the brain implicated in feeding, arousal and motivated behaviour. [1,2] More than 1,500 papers on the peptides have already been published. Orexin neurons project widely to numerous brain regions, and the orexinergic system is involved in not only feeding behavior but also sleep/wakefulness and energy homeostasis. [3-7] In addition, accumulating evidence have indicated that orexin in the brain plays a role in central regulation of gut function through an autonomic nervous system. The purpose of the present review is to give a view that orexin in the brain plays a role as a trigger molecule to drive the process of cephalic phase gut stimulation. We would also propose our hypothesis that lack of orexin action in the brain might contribute to the development of functional gastrointestinal disorders which is frequently associated with the inhibition of gut function.

## Distribution of orexin neurons and receptors in the brain

Orexins A and B/hypocretins 1 and 2 were discovered simultaneously by two independent research groups and thus separately named. [1, 2] The orexins were discovered by Sakurai et al. during a

search for endogenous ligands that activate orphan G protein-coupled receptors.[1] Independently, de Lecea et al.[2] using directional tag PCR subtraction, identified a hypothalamic-specific mRNA encoding a precursor protein that they called prepro-hypocretin and predicted that processing of this prepro-peptide would yield two peptides, hypocretins 1 and 2. Orexins A and B are coded from the same prepro-mRNA, and prepro-orexin neurons are located in the LH and its adjacent area.[1] Sakurai et al.[1] also identified the amino acid sequences of the receptors for the two peptides. $OX_1R$, was shown to bind orexin-A with high affinity and bind orexin-B with 100- to 1,000-fold lower affinity. An another receptor, $OX_2R$, identified by searching database entries with the $OX_1R$ sequence, was shown to have equally high affinities for both peptides. Thus, $OX_2R$ was concluded to be a nonselective receptor for both orexin-A and orexin-B, while $OX_1R$ was concluded to be selective for orexin-A (Table 1). Immunohistochemical and *in situ* hybridization studies have shown that orexin-producing neurons in the brain are restricted to a few nuclei in the hypothalamus, the perifornical nucleus, the LH, and the dorsomedial hypothalamic nucleus.[1,2] Despite their highly restricted origin, orexin nerve fibers are identified widely throughout the central nervous system.[3-6] In parallel to the diffuse orexin-containing projections from the LH, orexin receptors are expressed in a pattern consistent with orexin nerve fibers.[8-11] Based upon these

evidence, Table 2 summarizes the distribution of specific orexin receptors in the brain. As demonstrated, orexin receptors are site-specifically localized in the brain, suggesting a physiological role of each orexin receptor in relation to site-specific functions. It has been furthermore speculated that the widespread projections of the orexin neurons throughout the neuroaxis suggest that activation of orexin circuits probably modulates a variety of biological systems.

**Orexins and feeding**

Because of the strong localization of orexins in the LH, orexins might play a role in physiological functions associated with this brain site. Since the LH regulates feeding behavior,[12, 13] Sakurai et al. [1] have examined the effect of orexins on food intake and showed that intracerebroventricular administration of orexins potently stimulated food consumption in rats. They have also shown that fasting up-regulated prepro-orexin mRNA levels, indicating that orexins may be involved in the regulation of feeding behavior. In addition, Yamada et al. have demonstrated that intracisternal but not intraperitoneal injection of the orexin antibody dose-dependently suppressed feeding in rats, suggesting that immunoneutralization of endogenous orexins in the brain reduced food intake.[14] In other words, endogenous brain orexin may have a physiologically relevant action on feeding behavior. When orexin was injected into several specific brain areas such as the hypothalamic arcuate,

perifornical, lateral, dorsomedial and paraventricular nuclei, the ventral tegmental area and the nucleus accumbens, [15-21] food intake was increased, suggesting that these areas in the brain may be sites of action of orexin to stimulate food intake. Behavioral observation studies also indicate that central orexin-A administration induces feeding-related activities such as grooming, burrowing and rearing,[15] furthermore supporting the hypothesis that orexins is implicated in central regulation of feeding behavior.

**Stimulation of acid secretion by intracisternal injection of orexin-A**

In addition to feeding behavior, earlier investigators have demonstrated that the LH contributes to the central regulation of gastric secretion. [22] These findings led to speculate that orexins in the brain may play a role in not only feeding but gastric secretion. Intracisternal injection of orexin-A increased volume of gastric juice and stimulated gastric acid output in a dose-dependent manner in pylorus-ligated conscious rats. In contrast, intraperitoneal administration of orexin-A did not stimulate gastric secretion, suggesting that orexin-A acts in the central nervous system to stimulate gastric secretion. [23] A number of peptides and chemicals tested before failed to stimulate acid secretion. [22, 24-27] In fact, among these, only thyrotropin releasing hormone (TRH) has been convincingly established by several groups of investigators to be

a central stimulant of gastric acid secretion. [22] Based upon the evidence, orexin-A in the brain should be considered to be a specific molecule that is capable of stimulating gastric acid secretion. The doses to stimulate acid secretion were as the same or smaller as the doses injected by Sakurai et al. [1] to stimulate food consumption in rats. The evidence that orexin-A stimulates both gastric secretion and food intake in the same dose range should be mentioned because the both response to orexin-A might be triggered by a common mechanism. Electrical stimulation of the LH increases gastric acid secretion. [28,29] Earlier studies had shown that lesions or anesthetization of the LH attenuated the increase in gastric acid secretion caused by the peripheral administration of hypoglycemic agents. [30-32] Thus, LH plays a vital role in acid secretion especially under hunger sensation which is probably induced by lowering blood glucose levels. However little is known about the mechanisms by which stimulation of LH neurons increases gastric acid production in a molecular/neurotransmitter basis. Because of the striking localization of orexin-containing neurons in the LH and some of its adjacent areas, [1] and the stimulation of gastric acid by central orexin-A, we would raise a speculation that release of orexin-A in the terminal nerve endings of LH neurons may activate a neuronal system to stimulate acid secretion. Thus orexin-A may function as an efferent signal from the LH neurons to increase gastric acid secretion.

**Involvement of $OX_1$ receptor in the acid stimulation by orexin-A**

The stimulation of gastric acid secretion was seen after intracisternal injection of orexin-A but not orexin-B, suggesting that orexin-A stimulates acid production in a specific manner. Considering the characterization of orexin receptors that OX1R is selective for orexin-A while OX2R is non-selelctive for both orexin-A and -B, the results that centrally administered orexin-A but not orexin-B stimulated acid secretion[23] may indicate that $OX_1R$ mediates the orexin-A-induced acid stimulation. Orexin-A is a peptide consisting 33 amino acids with two intrachain disulfide bonds, namely Cys6-Cys12 and Cys7-Cys14 whereas orexin-B is a peptide containing 28 amino acids without disulfide bond (Table 1). To furthermore characterize the structure-activity relationship of orexin-A to stimulate gastric acid secretion, orexin-A-related peptides with modification of disulfide bonds were made and their activity on receptor activation *in vitro* or stimulatory action of acid secretion *in vivo* was evaluated.[33] Intracisternal injection of orexin-A but not orexin-B or orexin-A (15-33) that does not contain both disulfide bonds stimulated gastric acid secretion in pylorus-ligated conscious rats. The ability of the stimulation of gastric acid output was less in three alanine-substituted orexin-A, [Ala $^{6, 12}$]orexin-A, [Ala $^{7, 14}$]orexin-A and [Ala $^{6, 7, 12, 14}$]orexin-A, than orexin-A. Orexins-induced calcium

increase was measured in CHO-K1 cells expressing $OX_1R$ or $OX_2R$. From *in vitro* studies, orexin-A induced a transient increase in $[Ca^{2+}]i$ in CHO-K1/$OX_1R$ cells in a dose-dependent manner. $EC_{50}$ values for $OX_1R$ of orexin-A, orexin-B or orexin-A (15-33) was 0.068, 0.69 or 4.1 nM, respectively, suggesting that peptides containing no disulfide bonds have lower potency for $OX_1R$. Agonistic activity for $OX_1R$ of the three orexin-A analogues with modification of one or both disulfide bonds was significantly reduced as compared with that of orexin-A. $EC_{50}$ values for $OX_2R$ of orexin-A and orexin-B was almost equal but potency for the receptor of orexin-A (15-33) and three alanine substituted orexin-A was less than that of orexin-A. A significant inverse relationship between gastric acid output and $EC_{50}$ values for $OX_1R$ but not $OX_2R$ was observed. These results suggest that orexin-A-induced acid stimulation requires $OX_1R$ activation and that disulfide bonds in orexin-A may have a key role in the receptor activation.

**Vagal-dependent mechanism of acid stimulation by central orexin-A**

With regard to the mechanism of action of brain orexin-A in stimulating gastric acid secretion, the vagal system is involved in the stimulation of acid secretion because atropine or surgical vagotomy completely blocked the acid stimulation by intracisternal orexin-A. [23] The vagal-dependent mechanism of the stimulation of acid secretion by

central orexin-A is also supported by the evidence as described below that the dorsal vagal nucleus of the vagus (DMN) in the medulla oblongata is considered to be the site of action of orexin-A to stimulate gastric acid.

**DMN as a site of action in the brain to stimulate acid secretion**

Cells of origin innervating the stomach through the vagus nerve are located in the DMN in the medulla oblongata. [34, 35] Since intracisternally injected orexin-A-induced acid production is mediated by the vagus nerve, [23] the DMN neurons projecting their axon terminals to the stomach should be activated by the injection of orexin-A into the cisterna magna. Although orexin-immunoreactive neurons are located only in the hypothalamus, [1] orexin-immunoreactive fibers are widely distributed in the central nervous system including the DMN. [4, 6, 14, 36] The fact that orexin-immunoreactive fibers are identified in the DMN and that the DMN neurons receive axon terminals from the LH neurons[37, 38] may support the idea that the site of action of intracisternally injected orexin-A to induce acid production is on the DMN neurons. Results from immunohistochemical studies indicate that the majority of DMN neurons in the rat express orexin receptors, with the $OX_1R$ found in greater abundance than $OX_2R$. [39] In addition, Krowicki et al., showed by combining immunostaining for $OX_1R$ with retrograde labeling of neurons

following injections of fluorescently tagged cholera toxin into the gastric wall that $OX_1R$ is expressed in a majority of preganglionic vagal motor neurons that innervate the stomach.[39] These neuroanatomical studies indicate that orexin-A is capable to binding to $OX_1R$ on DMN neurons innervating the stomach. Moreover, recordings obtained in rat medullary slices revealed that orexin directly depolarize a fraction of DMN neurons, including some that were identified as preganglionic parasympathetic neurons based on their retrograde labeling following intraperitoneal administration of Fluorogold.[40] Grabauskas and Moises have demonstrated using whole-cell recordings obtained from DMN neurons in rat brainstem slices that orexins act preferentially within the DMN to directly excite DMN neurons that project to the stomach.[41] These electrophysiological studies together with the neuroanatomical evidence described above and the pharmacological results suggest that endogenous orexin-A from descending hypothalamic projections into the DMN activates $OX_1R$ on the DMN, followed by stimulating the vagal flow that should cause the increase in acid output from the stomach. The finding by Krowicki et al. that microinjection of orexins into the DMN increased intragastric pressure and antral motility in rats indicates that orexins indeed acts in the DMN to stimulates gastric function.[39]

**Endogenous orexin-A in the brain plays a role in the stimulation of acid secretion**

The blockade of receptors by selective antagonists is a commonly used approach to assess the physiological role of endogenous peptides. While intraperitoneal administration of SB334867, a specific $OX_1R$ anatagonist, [42-45] by itself did not change gastric acid secretion in pylorus-ligated conscious rats, pretreatment with SB334867 completely blocked the stimulated acid output by intracisternal orexin-A but not TRH, suggesting that SB334867 specifically blocked the action of orexin-A in the brain. [46] 2-deoxy-D-glucose (2-DG) has been used as a tool for central activation of the vagal pathway. It has been reported that 2-DG administered peripherally acts in the brain especially in the hypothalamus to increase vagal tone, thereby stimulating gastric acid secretion. [47,48] 2-DG -induced stimulation of gastric acid output was significantly blocked by pretreatment with intraperitoneal administration of SB334867. It would be therefore suggested that endogenously released orexin-A in the brain indeed plays a vital role in central regulation of gastric secretion and that $OX_1R$ is involved in the acid stimulation by endogenously released orexin-A. A couple of reports showed hypoglycemia activates orexin-A neurons. Cai et al. have demonstrated that insulin-induced hypoglycemia stimulated c-fos expression in orexin-A neurons in the LH in rats. [49] 2-DG is also known as a compound that inhibits glucose

utilization (glucoprivation) and causes intracellular glucopenia.[50] Briski and Sylvester have examined the effect of 2-DG on c-fos expression in neurons containing orexin-A in the hypothalamus and demonstrated that a large majority of orexin-A neurons in the LH were immunostained for c-fos, while orexin-A neurons expressed negligible c-fos immunoreactivity following vehicle administration,[51] suggesting that central glucopenia induced by 2-DG activates orexin-A neurons in the LH. These studies shown by c-fos expression may support that 2-DG activates hypothalamic orexin-A system, followed by stimulation of gastric secretion through the vagal system.

**Cephalic phase acid stimulation by central orexin-A**

The cephalic phase of gastrointestinal secretion, which occurs in response to the sight, smell, taste, and anticipation of feeding, produces a coordinated secretory response that primes the gut to assist digestion of the impending meal. The most important component of the cephalic phase responses is gastric acid secretion as first characterized by Pavlov.[52] The cephalic phase of gastric secretion is important because it primes the secretory capability of the gut, increasing the efficiency of the subsequent gastric and intestinal phases of secretion that occur in response to a meal. Despite this, little is known about the precise molecular mechanism of cephalic phase stimulation. Although TRH is

only one established neuropeptide that acts in the brain to stimulate gastric secretion,[22] TRH does not initiate feeding.[53,54] In addition to its powerful effect on feeding behavior of orexins,[1] the evidence that orexin-A has a potent stimulatory effect on the major secretory component of the cephalic phase makes orexin-A an important candidate as a mediator of the cephalic phase secretory response to feeding (Fig. 1). As decribed, endogenous orexin-A in the brain may play a vital role in 2-DG-induced acid secretion because an $OX_1R$ antagonist, SB334867, blocks the stimulation of gastric acid by 2-DG.[45] Since 2-DG induces central glucoprivation as a hunger state, the evidence furthermore support the speculation that orexin-A may be an important molecule that triggers the cephalic phase gastric acid secretion. The importance of vagus in conveying the neural impulses that mediate cephalic phase gastric secretion has been recognized.[55] The vagal dependent stimulation of gastric secretion of orexin-A furthermore support our speculation that orexin-A plays a key role in cephalic phase gastric secretion. The concept that the same peptide responsible for activating feeding also triggers an appropriate preparatory secretory response is attractive because it suggests the sort of simple economy that characterizes so many biological system.

The LH, so called subthalamic locomotor region (SLR), is one of major driving sources for initiating locomotion.[56] Efferent signals from

the SLR are considered to evoke locomotion by activating neurons in the mesencephalic locomotor region (MLR) and the medullary reticular formation. The location of the SLR largely corresponds to the prefornical lateral hypothalamic area, an origin of orexinergic neurons. Because there are dense orexinergic projections to the midbrain, Takakusaki et al.[57] injected orexin-A into the midbrain areas including the MLR and the pedunculopontine tegmental nucleus (PPN) in decerebrate cats. They demonstrated that microinjections of orexin-A into the PPN/MLR enhanced the level of postural muscle tone and facilitated locomotor movements. Locomotion is one of expressions of emotional motor behaviors, including attack, defense, feeding and searching.[58] Starting locomotion, which are accompanied by the sequence of seeking and taking foods, is an initial step of feeding behavior.[59] The above evidence might facilitate our hypothesis that orexin-A is a vital molecule in the brain which trigger the process of cephalic phase stimulation such as food intake and an appropriate preparatory secretory responses.

**Gastric motility and pancreatic secretion by brain orexin**

A couple of reports have demonstrated that centrally injected orexin changes gastric motility. Kobashi et al.[60] examined the effects of the intracisternal administration of orexin-A on gastric motility in rats. Orexin induced relaxation of the proximal stomach lasting for more than

30 min. Phasic contractions in the distal stomach were facilitated in response to orexin. Facilitation in the distal stomach was not seen in the vagotomized animals. Relaxation of the proximal stomach was identified in vagotomized animals but the magnitude of relaxation was significantly smaller than that in intact animals, suggesting that central orexin facilitates distal stomach motility and relaxation of the proximal stomach via the vagus nerve. Since relaxation in the proximal stomach and enhanced motility in the distal stomach are observed during feeding,[61] the gastric motility change evoked by central orexin-A suggest that orexin-A may function to coordinate gastrointestinal motility during feeding. From this point of view, orexin-A should be mentioned furthermore as a trigger molecule that plays a vital role in cephalic phase stimulation as decribed above. In addition, Krowicki et al.[39] have shown that microinjection of orexins into the DMN increased intragastric pressure and antral motility in rats, indicating that orexins in the DMN stimulates gastric motor function. Thus, orexin acts in the DMN to stimulate not only gastric acid secretion but gastric motility.

Miyasaka et al. have demonstrated that intracerebroventricular injection of orexin-A significantly stimulated pancreatic exocrine secretion through the vagus nerve in rats.[62] The stimulation of pancreatic secretion by central orexin-A was seen after pretreatment with omeprazole, indicating that the pancreatic stimulatory action by orexin-A

is independent of gastric acid secretion. Thus orexin-A acts in the brain to stimulate not only gastric but pancreatic secretion through the vagal system. Wu et al. [63] have recorded vagal pancreatic efferent nerve activities in anesthetized rats. Insulin-induced hypoglycemia stimulated an increase in pancreatic efferent nerve firing. Microinjection of the $OX_1R$ antagonist SB334867 into the DMN inhibited pancreatic nerve firing evoked by insulin-induced hypoglycemia by 56%. In contrast, injection of orexin-A into the DMN elicited a 30-fold increase in pancreatic nerve firing. From these results, they suggested that hypoglycemia activates release of orexin from the LH, which acts on DMN neurons to stimulate pancreatic efferent nerve activities, thereby stimulating pancreatic functions. Because pancreatic secretion is one of the important components of cephalic phase gut secretion, the evidence that the stimulation of pancreatic secretion by central orexin-A may further support our hypothesis that orexin-A may be a trigger molecule that is involved in the cephalic phase stimulation.

**Gastroprotection by orexin-A**

The effect of central orexin-A on the development of gastric mucosal damage evoked by ethanol was examined in rats. Intracisternal but not intraperitoneal injection of orexin-A significantly inhibited the severity of gastric mucosal damage by 70 % ethanol in a dose-dependent

manner, suggesting that orexin-A acts in the brain to prevent ethanol-induced gastric mucosal damage.[64] The anti-ulcer action was observed in rats received with central administration of orexin-A but not orexin-B, indicating that the action is mediated through $OX_1R$. The gastroprotective action of central orexin-A was blocked by pretreatment with atropine, $N^w$-nitro-L-arginine methylester or indomethacin, respectively, suggesting that orexin-A acts in $OX_1R$ in the brain to exert a gastroprotective action against ethanol through a vagal muscarinic system, nitric oxide and prostaglandins pathways. It has been reported the involvement of nitric oxide (NO) in orexin pathway. According to Farr et al., subcutaneous injection of $N^w$-nitro-L-arginine methylester (L-NAME), an inhibitor of NO synthase, blocked orexin-A-induced increase in food intake in rats and orexin-A failed to increase food intake in the NO synthase knockout mice.[65] They further demonstrated that L-NAME drastically inhibited NO synthase activity in the hypothalamus, suggesting that NO in the brain plays a vital role in the orexin-A-induced food consumption. In addition, Zheng et al. have demonstrated that as many as 20 % of hypothalamic orexin neurons project to the dorsal vagal complex including the DMN neurons in the medulla and some of which are in close anatomical apposition with NO synthase-immunoreactive neurons,[66] indicating that NO in the brain might regulate the tone of the vagal system. Thus NO in the brain may be involved in the orexin-A-

induced central regulation of gastrointestinal functions through the vagal system. In any events, the evidence that orexin-A in the brain possesses gastroprotective action against ethanol may suggest that orexin-A might protect gastric mucosa from alcohol to be possibly injured during taking food with alcohol.

**Depression, functional gastrointestinal disorders and orexin**

Immunohistochemical and electrophysiological studies showed that orexin neurons in the lateral hypothalamus regulate monoaminergic and serotonergic neurons in the brainstem.[67-70] Since depression is associated with a lack of monoaninergic or serotonergic activity in the brain,[71] orexins may be involved in the pathology of depression. With regard to the relationship between orexin in the brain and depression, a couple of papers have been recently reported as following. Wistar-Kyoto (WKY) rats exhibit depressive characteristics and patterns of sleep disruption similar to that observed in depressed human patients.[72] Allard et al.[73] have shown by immunocytochemistry that 18% fewer orexin-A positive neurons as well as a 15% decrease in average neuronal soma size of orexin-A producing cells in the hypothalamus of WKY rats compared to control rats, suggesting that reduced number or size of hypothalamic orexinergic neurons may be involved in the depressive characteristics in WKY rats. Lutter et al.[74] have demonstrate that 10

days of calorie restriction, corresponding to a 20-25% weight loss, causes a marked antidepressant-like response in two rodent models of depression and that this response is dependent on the hypothalamic orexin, suggesting that orexin plays a role in mediating reduced depression-like symptoms induced by calorie restriction. These findings obtained by rodent models suggest that inhibition of hypothalamic orexinergic projection might contribute to the development of depression. In addition, Brundin et al.[75] measured orexin-A in the cerebrospinal fluid (CSF) of 66 patients with major depressive disorder, dysthymia and adjustment disorder after a suicide attempt. CSF levels of orexin-A were significantly lower in patients with major depressive disorder than in patients with adjustment disorder and dysthymia. All these evidence suggest that hypothalamic orexin may be implicated in depressive state.

The functional gastrointestinal disorders (FGID) comprise a major portion of gastrointestinal practice and primary care, and are associated with significant absenteenism from work, impaired health-related quality of life, and increased medical costs.[76] Brain-gut interaction plays an important role in the pathophysiology of FGID. Possibly through the brain-gut axis, psychosocial factors including depression influence gut physiology, the symptom experience, health behavior, and outcome.[76] In other words, depression is closely associated with the pathophysiology of FGID, which is characterized by

disturbance of gastrointestinal functions. Because lack of orexin action might induce the inhibition of gastric physiology shown by us and other investigators as described above [23, 33, 39, 46, 60] and evoke depressive state,[73-75] decreased activity of orexin in the brain might play a vital role in the mechanism of FGID which is frequently associated with both the inhibition of gut function and depression. These evidence might allow us to speculate that orexin in the brain would be a possible molecular target for the treatment of FGID.

**Interaction with ghrelin**

Accumulating evidence have suggested that ghrelin, a peptide produced in the stomach, plays a key role in feeding behavior and several gastrointestinal functions.[77-79] It has been shown that orexin neurons are regulated by ghrelin,[80] suggesting that there is a close relation between orexn and ghrelin in the brain to regulate physiological functions. Further studies on the relationship between orexin and ghrelin in the central regulation of gut functions should be needed.

**Perspective**

As shown in this review, we would stress our hypothesis here again that orexin-A might be a trigger molecule that is involved in the cephalic phase gut stimulation. In addition, we would also propose our

hypothesis that lack of orexin action in the brain might contribute to the development of functional gastrointestinal disorders. Considering above, we would hope that artificial control of orexinergic projection would make a progress to establish a novel therapeutic approach for the treatment of functional gastrointestinal disorders.

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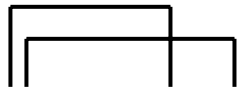
**Figure legend**

**Figure 1**

Schematic illustration of our hypothesis that orexin might be a trigger molecule that in involved in the cephalic phase gut secretion. The cephalic phase of gastrointestinal secretion, which occurs in response to the sight, smell, taste, and anticipation of feeding, produces a coordinated secretory response through a vagal pathway. Orexin neurons in the lateral hypothalamus (LH) project their terminals to the dorsal motor nucleus (DMN). Stimulated DMN neurons by orexin increases gastric acid secretion, gastric motility and pancreatic secretion through the vagus nerve. Since orexin plays a vital role in the stimulation of feeding behavior, orexin in the brain may be a trigger molecule to complete the process of feeding and gut secretion in response to the cephalic phase stimulation.

**Table 1. Amino acid sequence of orexin-A and –B and their receptor affinity**

| | Amino acid sequence | Receptor affinity |
|---|---|---|
| Orexin-A |  <EPLPDCCRQKTCSCRLYELLHGAGNHAAGILTL-NH2 | OX1R = OX2R |
| Orexin-B | RSGPPGLQGRLQRLLQASGNHAAGILTM-NH2 | OX2R >> OX1R |

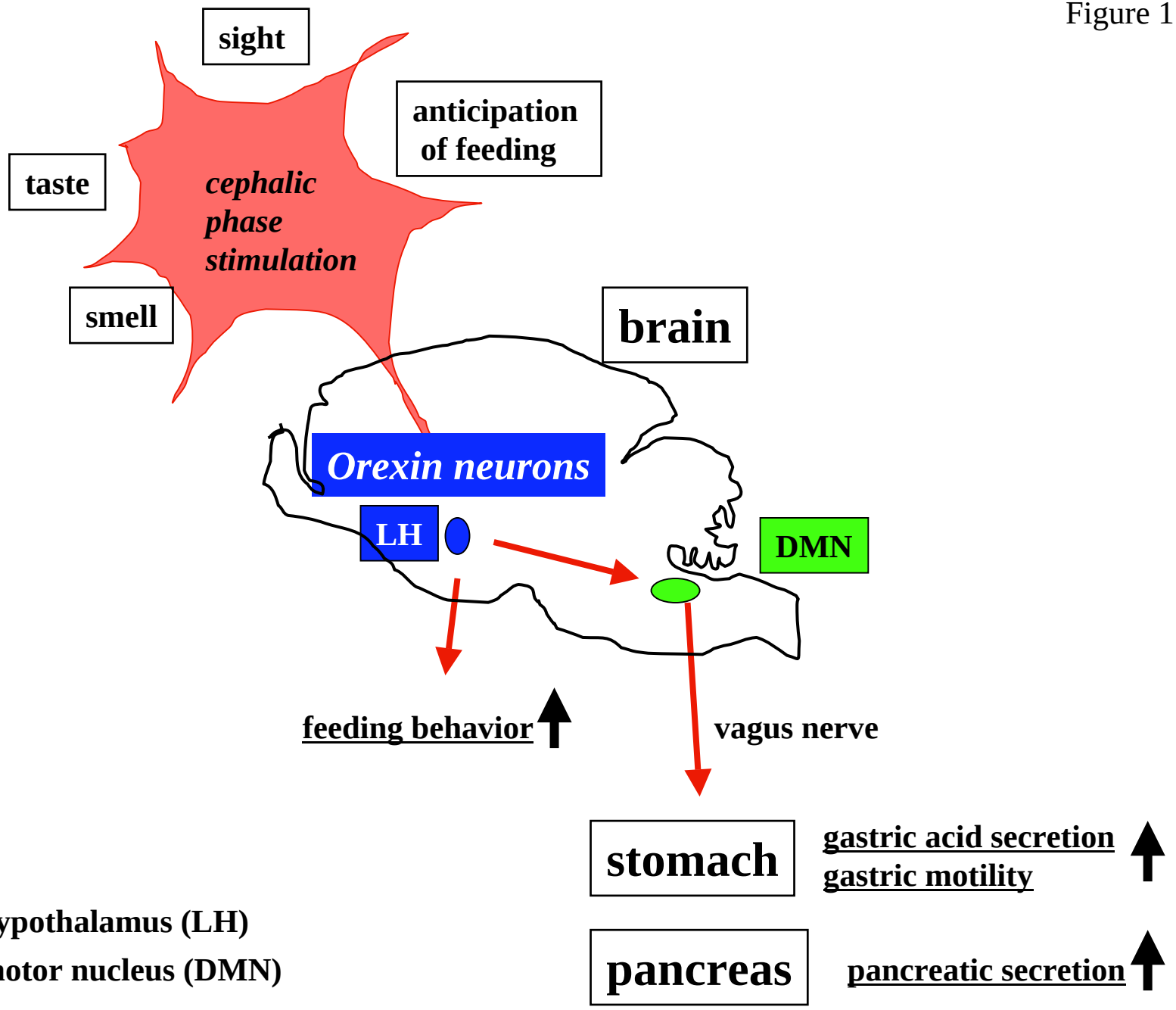
Characterization of orexins and their specific receptors was shown according to the previous report[1].

**Table 2. Distribution of orexin receptors in the brain**

| Brain region | | Receptor type |
|---|---|---|
| cortex | | OX1R and OX2R |
| hippocampus | | OX1R and OX2R |
| paraventricular thalamic nucleus | | OX1R |
| ventromedial hypothalamic nucleus | | OX1R |
| paraventricular nucleus of the hypothalamus | | OX1R and OX2R |
| arcurate nucleus | | OX1R and OX2R |
| substantia nigra (SNr) | GABAergic | OX2R |
| locus coeluleus (LC) | noradrenergic | OX1R |
| tuberomamillary nucleus (TMN) | histerminergic | OX2R |
| raphe nuclei | serotonergic | OX1R and OX2R |
| laterodorsal tegmental nucleus (LDT) | cholinergic | OX1R and OX2R |
| ventral tegmental area (VTA) | dopaminergic | OX1R |
| pedunculopontine tegmental nucleus (PPN) | cholinergic | OX1R and OX2R |
| dorsal motor nucleus | | OX1R |

Distribution of orexin receptors in the brain is shown according to previous reports[8-11].

Figure 1




lateral hypothalamus (LH)

Dorsal motor nucleus (DMN)