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Function of GABAergic and glutamatergic neurons in the stomach

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Summary

γ-Aminobutyric acid (GABA) and L-glutamic acid (L-Glu) are transmitters of GABAergic and glutamatergic neurons in the enteric interneurons, targeting excitatory or inhibitory GABA receptors or glutamate receptors that modulate gastric motility and mucosal function. GABAergic and glutamatergic neuron immunoreactivity have been found in cholinergic enteric neurons in the stomach. GABA and L-Glu may also subserve hormonal and paracrine signaling. Disruption in gastrointestinal function following perturbation of enteric GABA receptors and glutamate receptors presents potential new target sites for drug development.

Introduction

As is the case in other parts of the brain, GABAergic and glutamatergic circuits in the stomach are generally confined to networks of interneurons in the enteric neuron system. Through various feedback and feedforward loops, GABAergic and glutamatergic interneurons react to certain aspects of the gastric function. This body of work has not only established γ-aminobutyric acid (GABA) and L-glutamic acid (L-Glu) as one of the major neurotransmitters in the stomach, but it has provided insight into the overwhelming complexity of the stomach. Enteric GABAergic and glutamatergic fibers are profuse, ramifying throughout the ganglionated and non-ganglionated enteric nerve networks of the gut wall. The GABAergic and glutamatergic neurons have been shown to be present in the submucous and myenteric plexuses [1–5]. Several lines of evidence indicate a role of GABAergic and glutamatergic neurons in the regulation of gastric motility, secretion and gastric reflexes. However, the receptor subtypes and mechanism that mediate the effects of GABA and L-Glu in the stomach are still poorly understood.

The aim of this review is to show the distribution of the GABAergic and glutamatergic system within the mammalian gastric wall and how this system fits into a model for GABAergic and glutamatergic transmission with multiple signaling pathways. In addition, the interneuron of GABAergic and glutamatergic systems involved in enteric neural circuits controlling spontaneous and reflex motor and secretomotor activity are demonstrated. When viewed in the context of the extensive pharmacological data on GABA and L-Glu action in the stomach, the major neuronal and minor endocrine distribution of GABA and L-Glu, the presence of GABA and glutamate receptor subunits in the mammalian gastric wall, GABAergic and glutamatergic neurotransmission must be major components in the control of gastric function. It will become evident in the following discussion that GABAergic and glutamatergic interneurons represent the ideal candidate for the integration of changes in the 'balance' between excitation and inhibition to controlling gastric motility and secretion. These findings open up an entirely new area to study the roles of GABAergic and glutamatergic neurons in gastric function and present potential new target sites for drug development.

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GABAergic and glutamatergic neurons in the stomach

GABAergic neurons

Like the CNS, the primary synthesis reaction for enteric GABA is catalyzed by L-glutamate decarboxylase (GAD) using the substrate glutamate. Enteric GABA can also be derived from putrescine via the actions of diamine oxidase/aldehyde dehydrogenase. The high GAD activity in the gastric wall is found in the myenteric plexus (Figure 1). GABA contents have been measured using guinea pig stomachs [4]. GABAergic neurons have also been visualized in cultures of the myenteric plexus by studies showing the high-affinity uptake, localization, and release of GABA [6]. GABAergic neurons are localized immunocytochemically using antibodies against its synthesizing enzyme, GAD. Numerous ganglion cells and nerve bundles in the myenteric plexus were found to be GAD-positive, while the longitudinal muscle, submucosa and mucosa were largely devoid of GABAergic innervation. The distribution of GABAergic neurons and their processes in both myenteric ganglia and circular muscle is rather uneven throughout the stomach (Figure 1).

Glutamatergic neurons

Immunohistochemical studies support the notion that glutamatergic neurons are present in the stomach (Figure 2). The distribution of glutamatergic neurons and their processes in both myenteric ganglia and circular muscle is heterogeneous within the stomach [7].

Different experimental models clearly suggest that most of the glutamate-containing axons in the intestinal and stomach walls originate from cell bodies within the myenteric and submucous plexus

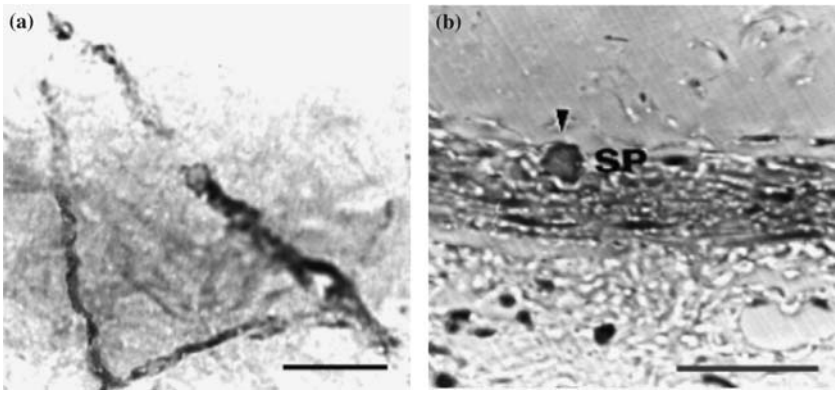

Figure 1. Immunohistochemical localization of GABAergic neurons in the rat stomach. GAD positive processes in the muscle layers (a) and submucosal layers (b). Bar = 50 μm. The illustration of (b) is modified from Ref. [5].

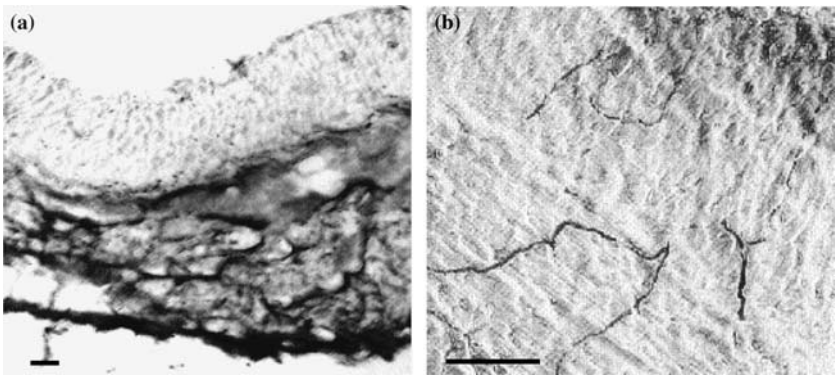

Figure 2. Immunohistochemical localization of glutamatergic neurons in the rat stomach. Glutamate positive processes in the muscle layers. Bar = 50 μm. The illustration of (a) is modified from Ref. [7].

[8, 9]. Furthermore, there is evidence suggesting that the gastrointestinal tract is also innervated by extrinsic glutamate-immunoreactive axons. Axon terminals contain large numbers of small and clear synaptic vesicles [10–15]. Glutamatergic varicosities, which often contain choline acetyltransferase and the vesicular acetylcholine transporter, are apposed to a subset of neuronal cell bodies in the submucous and myenteric plexus in the stomach [15]. The submucosal neurons that contain ChAT are thought to be the primary afferent neurons that project to the mucosa and respond to the sensory stimuli from the gut [16]. Thus, some of the enteric glutamatergic neurons are likely to be sensory neurons and glutamate may be involved in the transfer of sensory information from the mucosa to the enteric plexuses.

The synapse in the ENS appears to possess a high-affinity glutamate uptake system. This is compatible with the observation that proteins expressed by epithelia isolated from the rumen showed high-affinity glutamate transporter activity. Excitatory amino acid carrier 1 (proteins EAAC1) is widely distributed in the stomach, as shown by immunohistochemical studies [17]. However, the function of EAAC1 in the stomach still remains poorly understood.

Types of GABA and glutamate receptors in stomach

GABA receptors

GABA is the main inhibitory neurotransmitter in the central nervous system. The inhibitory action of GABA is mediated by the receptors present on the cell membrane, and results in a reduction of neuronal excitability. At least three types of GABA receptors have been characterized. Table 1 summarizes some of the general properties of these three types of GABA receptors. There are two main classes: $GABA_A$ and $GABA_C$ receptors are ligand-gated chloride channels, $GABA_B$ receptor is metabotropic. Class one $GABA_A$ receptor is a ligand-gated chloride channel specifically blocked by bicuculline and picrotoxin, heterooligomers composed of the α, β, γ, δ, and ε subunit families. The distribution of $GABA_A$ receptor subunit mRNAs in adult rat ENS is heterogenous [5, 18, 19], reflecting a varied physiological/pharmacological profile of GABA-mediated transmission in both regions. The expression of the presence of $GABA_A$ receptor subunit (α, β, γ) mRNAs by *in situ* hybridization in myenteric and submucosal neurons [20], generally two pairs of α and β subunits and a γ subunit in the gut. The subunits are thought to form a tight group with the chloride channel in the center. There is considerable protein sequence similarity between the $GABA_A$ receptor and the nicotinic acetylcholine receptor. Properties of the receptor can be modified by phosphorylation. Insect GABA receptors which resemble vertebrate $GABA_A$ but do not bind bicuculline and have significantly different pharmacological profiles are known as $GABA_C$ receptors.

A second class of GABA-gated chloride channel, the $GABA_C$ receptor, has recently been cloned from the white perch retina and human heart [21, 22]. It has its highest expression in this tissue, although it is also found in lesser amounts in other parts of the brain [23]. $GABA_C$ receptors are not blocked by bicuculline and do not recognize the benzodiazepines, barbiturates or the neuroactive steroids. $GABA_C$ receptor consists of homooligomers of $\rho1$, $\rho2$, or $\rho3$ subunits. In contrast to the $GABA_A$ receptor, the $GABA_C$ receptor is

Table 1. Characteristics of GABA receptors.

	Receptor types		
	$GABA_A$ receptor	$GABA_B$ receptor	$GABA_C$ receptor
Category	Ligand-gated channel	G-protein-coupled receptor	Ligand-gated channel
Subunits	α, β, γ, δ, ε, π	GBR1, GBR2	ρ
Agonists	Muscimol, THIP	Baclofen	
Antagonists	Bicuculline, picrotoxin	Phaclofen	TPMPA, picrotoxin
Desensitization	Yes	No	No
Modulator	Benzodiazepines, barbiturates		Zinc

non-desensitizing and therefore produces tonic, sustained inhibition rather than a phasic response. Nothing is known about $GABA_C$ receptors in the gut. It is likely that enteric $GABA_C$ receptors will eventually be found, given that two of the components of the CNS GABA system mediate signaling in the gut wall.

The $GABA_B$ receptor is a G-protein-coupled receptor found in the brain and differs from the $GABA_A$ receptor both in agonist specificity (baclofen is a specific agonist) and its effects on cells. GABA also activates metabotropic $GABA_B$ receptors, which are widely distributed within the central nervous system and also in peripheral autonomic terminals. Their activation causes an inhibition of both basal and forskolin stimulated adenylate cyclase activity together with a decrease in Ca^{++} and an increase in K^+ conductance in neuronal membranes.

Recent studies also demonstrated that two GABAergic motor neurons in *C. elegans* are excitatory at target muscles because GABA activates a ligand-gated cation conductance, which is structurally similar to several other ligand-gated channels. The protein encoded by *exp-1* is found at the neuromuscular junctions on the anal depressor and intestinal muscles. A series of electrophysiological experiments also show that *exp-1* codes for a novel GABA-activated cation conductance [24, 25]. Functional GABA receptors in vertebrates are thought to require residues found on both α and β subunits to form the GABA binding site. The *exp-1* gene encodes an excitatory cation-selective GABA receptor that mediates enteric muscle contraction in *C. elegans* [25]. But in vertebrate species, these channel genes become completely clear.

Glutamate receptors

There are two main classes of receptors for glutamate, namely, ionotropic glutamate receptors (ligand-gated ion channels) and metabotropic glutamate receptors (coupled to G proteins) [17, 26]. Ionotropic glutamate receptors, which can be further divided into NMDA (N-methyl-D-aspartate) and non-NMDA receptors, are responsible for synaptic transmission and plasticity [27–29]. Both ionotropic and metabotropic glutamate receptors have been shown to localize in enteric ganglia using immunocytochemistry and *in situ* hybridization [30–32].

1. Ionotropic glutamate receptors

Ionotropic glutamate (iGlu) receptors are ligand-gated ion channels comprising three subtypes, NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainate (KA) receptors.

NMDA receptors

NMDA receptors are heteromeric pentamers. The subunits are the products of two gene families, one NRl gene and four NR2 (NR2A–D) genes. Although NRl provides a functional receptor, it is thought that NR2 increases the activity of the channel. Results from *in situ* hybridization studies have demonstrated the presence of mRNA for NRl and NMDA [10, 11, 33] in both myenteric and submucosal ganglia. The distribution pattern of NR1, NR2A and NR2B-containing NMDA receptors in rat stomach is determined immunohistochemically using specific antibodies against NR1, NR2A and NR2B (Figure 3) [34]. These findings are also consistent with the idea that the enteric glutamate receptors are involved in neurogenic motility [15, 35] or secretion of the stomach [7, 34]. Recently, the NRl subunits have been localized immunohistochemically in peripheral terminals of primary afferent nerves of dorsal root ganglia [34, 36]. In addition, the peripheral NMDA receptors are also found in both vagal and spinal primary afferent in the stomach, where the function of NMDA receptors is believed to be involved in gastric motility and gastric secretion [34].

Non-NMDA receptors

AMPA receptors are mainly involved in mediating fast glutamatergic neurotransmission. There are four subunits, known as GluRl to GluR4 (also called GluRA to GluRD) [37]. These AMPA receptor subunits are widely, but differentially, distributed throughout the CNS [38–41]. The functional AMPA receptors could be tetrameric or pentameric subunit assemblies.

AMPA receptors mediate the fast component of excitatory postsynaptic currents, whereas the slow component is contributed by NMDA receptors [42]. The latter can be viewed as coincidence detectors of pre- and postsynaptic activity, since the gating of the integral ion channel requires two

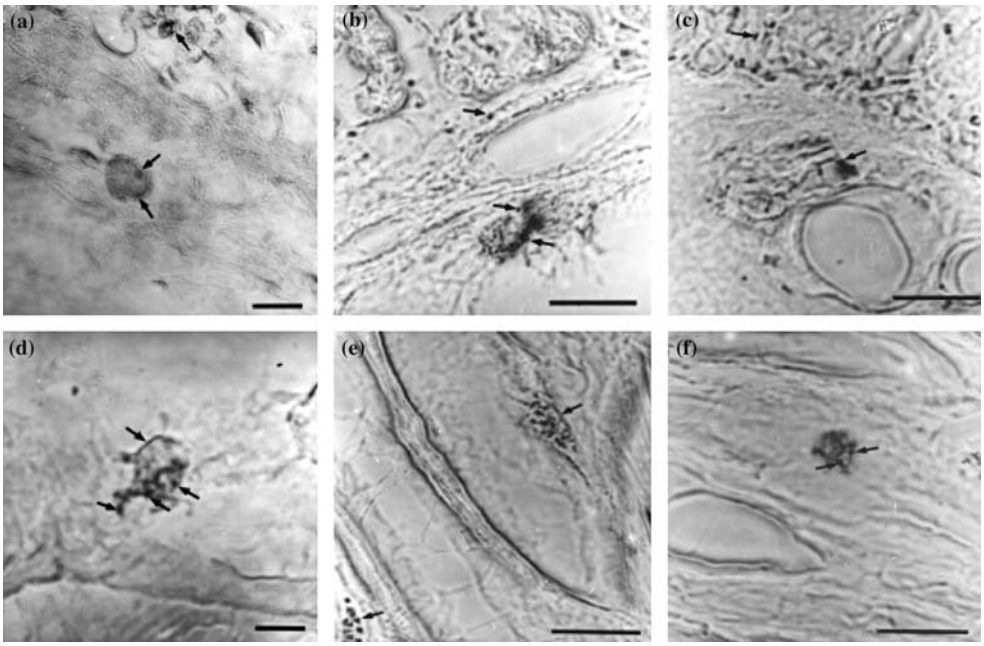

Figure 3. Immunohistochemical localization of NMDA receptors subunits NR1, NR2A and NR2B in the rat stomach. Light microscopy of a cross-section showing NR1 (column 1)-, NR2A (column 2)- and NR2B (column 3)-positive cell processes in the body. (a, c, f) Submucosal plexus layer; bar = 20 μm. (b, d, e) Myenteric plexus expresses NR2A and NR2B. Arrowheads indicate NR2A and NR2B-positive processes. Scale bar, 50 μm.

close and simultaneous events, namely, presynaptic release of glutamate and depolarization of the postsynaptic membrane. Depolarization is induced by the activation of AMPA receptors. Coincidence detection by the NMDA receptors rests on their voltage-dependent channels, which are blocked by extracellular Mg^{2+}. NMDA receptors are designed for high Ca^{2+} permeability, and Ca^{2+} influx through the NMDA receptor channel is thought to be essential for activity-dependent synaptic modulation [43, 44].

Other non-NMDA ionotropic receptor subunits are known as GluR5, GluR6, KAl and KA2. They normally form receptor assemblies, which have high affinity for kainate and hence are designated as kainate receptors, although some researchers classify GluR5 as an AMPA receptor subunit. Kainate receptors were previously thought to be mostly presynaptic. In addition, they are expressed in the dorsal root ganglia [45–47]. In contrast to AMPA, which facilitates glutamate release via presynaptic action, kainate acting on presynaptic autoreceptors decreases glutamate release from rat hippocampal synaptosomes and also depresses glutamatergic synaptic transmission [48]. Recent evidence indicates that non-NMDA receptors are also involved in mediating neurotransmission in the spiny lobster stomatogastric ganglion (STG) [49, 50]. It is conceivable that different glutamate receptor subtypes in the dorsal vagal complex may activate gastric secretion and motility in a different way. This provides a framework for glutamate receptor diversity in regulating gastric function.

2. Metabotropic glutamate receptors

The enteric nervous system in the stomach contains metabotropic glutamate receptors (mGluR) like CNS does [50], which are members of the G-protein-coupled receptor family. At present, eight different mGluRs have been cloned, termed from mGluR1 to mGluR8 [51]. Based on their sequence similarities, pharmacology and signal transduction mechanism, mGluRs are classified into three groups. Group I receptors (mGluR1 and mGluR5), which are coupled to phospholipase C, exert their effects by activating protein kinase C and releasing Ca^{2+} from intracellular stores. Group II (mGluR2 and mGluR3) and group III (mGluR4 and mGluR6–mGluR8) receptors are negatively coupled to adenylyl cyclase. Group I

receptors generally increase cell excitability by inhibiting K^+ channels and are mostly postsynaptic, although presynaptic effects have also been reported. Group II and III receptors are mostly present in glutamatergic presynaptic terminals and are believed to exert their action by inhibiting neurotransmitter release. However, the function of metabotropic glutamate receptors in the stomach is still poorly understood. The subcellular localization of mGluR receptors in enteric neurons might have functional implications in physiology and pathology of the gut.

GABA and glutamate receptors in the stomach

Role of GABA receptors responses

Motility

Since myenteric neurons are mainly involved in the regulation of smooth muscle activity, the role of GABA is as a regulator of gastric motility. We know that GABAergic neurons in the myenteric plexus system may have widespread consequences for motility. GABA-induced contraction is mediated by the $GABA_A$ receptor and not the $GABA_B$ receptor. The GABA action in eliciting smooth muscle contraction acts through a direct or indirect interaction between GABAergic and cholinergic neurons upon the smooth muscle [5, 52]. In *in vivo* study, $GABA_A$ receptors mediate the pathway(s) controlling NO-related spontaneous relaxations of the antrum [53]. The $GABA_B$ agonist baclofen enhances rhythmic gastric activity by increasing the vagal drive to the intramural cholinergic neurons in the regulation of gastric pressure [54]. GABA may play an important role in controlling gastric motility.

In addition to the contribution of baclofen, $GABA_B$ metabotropic receptors decrease the rate of transient lower esophageal sphincter relaxation (tLESR) and increase the lower esophageal sphincter pressure in healthy humans [55] and in patients with gastroesophageal reflux disease (GERD) [56–59]; a modest increase in lower esophageal sphincter pressure has been observed in some studies [55, 59]. The $GABA_B$ receptor effect may be a result of a central site of action in the dorsal vagal complex, where upper gastrointestinal vagal reflexes are integrated [60]. Symonds et al. reported that baclofen accelerated gastric emptying of solids but delayed emptying of liquid. It may have differential effects on proximal and distal stomach emptying [61]. Baclofen is used for the treatment of spastic disorders and chronic hiccups. Recent reports indicate that baclofen reduced the number of tLESRs in humans, dogs, and ferrets [55, 62, 63]. This effect is mediated by both central and peripheral $GABA_B$ receptors.

Thus, baclofen or another $GABA_B$ receptor agonist may be clinically useful in treatment of gastroesophageal reflux disease [63].

Modulation of gastric acid secretion

Immunohistochemical studies support the notion that GABAergic neurons are present in the stomach [5]. GABA induces acid secretion via the A type of GABA receptor, probably located mainly on the cholinergic neurons and partially on the non-neuronal cells in the guinea pig stomach [4, 64]. GABA and its $GABA_A$ receptor analogs affect the release of acetylcholine, gastrin, and somatostatin from rat gastric mucosa [65].

Peptic ulcer

Systemically applied GABA aggravates duodenal ulcers by stimulation of the $GABA_A$ receptor, whereas treatment with the $GABA_B$ receptor agonist baclofen causes a reduction in the incidence of ulcers [66]. Baclofen has been found to be more effective than the histamine H_2 blocker cimetidine, and, when given together, the antiulcer actions of these agents are found to be additive. Thus $GABA_B$ receptors present an alternative pharmacological site for targeting of antiulcer drug therapies. Benzodiazepines produce their effects by acting on the $GABA_A$-benzodiazepine receptor complex [67]. Ethanol is also reported to act on the $GABA_A$-benzodiazepine receptor complex to increase the receptor mediated Cl^- transport mechanism [68]. The antiulcer activity of benzodiazepines may protect against ethanol-induced gastric damage [69]. The $GABA_A$ in the stomach may protect against ethanol-induced gastric damage or even peptic ulceration.

In addition, GABA may also influence epithelial cell mitosis and migration. Interestingly, decreased mucosal cell turnover has been shown to be involved in stress-induced gastric ulceration,

and this may be a mechanism by which GABA exerts its protective effects in the disease models.

Role of glutamate receptors responses

Gastric smooth muscle contraction

Anatomical, physiological and pharmacological evidence suggests that L-Glu is an excitatory neurotransmitter in the peripheral nervous system [1]. The glutamate receptors in rat bronchi and gut are located on cholinergic nerves prejunctionally to enhance nerve-mediated responses [70–72]. Glutamate immunoreactivities have been detected in cholinergic enteric neurons. The immunoreactivities of both NMDA and non-NMDA receptors are also detected in neurons in submucosal and myenteric plexuses [1]. In *in situ* hybridization studies, mRNA coding for the glutamate NMDA receptor has been expressed in rat enteric neurons in the stomach. Enteric neurons expressing mRNA for both NMDA receptors and VIP are found in the myenteric and submucosal ganglia.

There is a difference in functional roles of different types of glutamate receptors between the isolated rat fundus and intestine. L-Glu shows a powerful stimulating effect on most smooth muscle layers in the stomach. NMDA and kainic acid stimulate contraction of isolated rat gastric fundus with almost identical strength of action, whereas the metabotropic receptor agonist ACPD has no effect [73]. The gastric excitatory motor response is elicited through NMDA and non-NMDA receptors that activate intrinsic excitatory neurons within the wall of rat gastric fundus, while in the intestine, it is due to the release of acetylcholine [73].

Modulation of gastric acid secretion

The effect of L-Glu on gastric acid secretion has been investigated on an everted preparation of isolated rat stomach. L-Glu alone had no effect on acid secretion. The oxotremorine-, histamine-, or gastrin-stimulated acid secretion is markedly reduced by L-Glu. Among glutamate receptor agonists, quisqualic acid (QA) is the most potent, followed by kainic acid (KA) and NMDA in inhibiting oxotremorine-stimulated acid secretion. Aspartate and NMDA inhibit the oxotremorine-stimulated acid secretion, which is antagonized by two specific antagonists of NMDA receptors, namely, 2-amino-5-phosphonovaleric acid (AP-5) and (±) 3-(2-carboxypiperazin-4-gl) propyl-l-phosphonic acid (CPP). In *in vivo* study, aspartate and NMDA reduce histamine-induced increase in the gastric mucosal blood flow. AP-5 reverses the inhibitory effect of aspartate and NMDA. These findings suggest that glutamate receptors are involved in the modulation of gastric acid secretion via ionotropic QA/KA receptors, and aspartate regulates acid secretion in the stomach by inhibiting histamine release through the NMDA receptors [7, 34, 74]. There is also evidence showing a role for enteric ionotropic and metabotropic glutamate receptors in the regulation of acid secretion [7, 34, 74]. Our recent studies demonstrated that L-Asp and NMDA, two glutamate receptors agonists, inhibit histamine-induced gastric mucosal blood flow (GMBF) via a mechanism involving the NR1 subunit of NMDA receptors and α_1-adrenoceptors activation. The subunits NR1, NR2A and NR2B of NMDA receptors are found to be localized in the rat stomach.

Their analogues such as glutamate, NMDA, QA and KA are able to protect against cold-restraint stress (CRS)-induced gastric ulcer formation through their interaction with NMDA and non-NMDA receptors [75]. These results suggest that glutamate receptor agonists can modulate gastric secretion and protect against CRS-induced gastric ulcer.

Food intake

Several groups have reported the increase of food intake after treatment with NMDA or non-NMDA receptor agonists or antagonists [76–79]. NMDA receptor-mediated modulation of gastric motor function may be of great importance for the regulation of acceleration in gastric emptying and daily food intake [80].

MK-801 (dizocilpine), an antagonist of NMDA receptors, increased meal size and duration in rats. MK-801 did not increase sham feeding or attenuate reduction of sham feeding by intra-intestinal nutrient infusions. These results suggested that the MK-801-induced increase in meal size was not due to the antagonism of postgastric satiety signals. Consequently, NMDA antagonists might increase food intake by directly antagonizing gastric mechanosensory signals or by accelerating gastric emptying, thereby reducing gastric mechanoreceptive feedback [80].

Although these results are consistent with NMDA receptor-mediated glutamatergic transmission of vagal satiety signals in general, MK-801 lends limited support for such a role in the transmission of specific gastric distension signals [81]. NMDA receptors are expressed in intrinsic gastric neurons, as well as in CNS [82].

Systemically administered MK-801 could enhance gastric emptying through actions via a central and/or peripheral mechanism. Nonetheless, several observations of our own, as well as those from other laboratories, strongly support the hypothesis that acceleration of gastric emptying and increased meal size are mediated by NMDA actions in the dorsal vagal complex.

The source(s) of excitatory amino acid afferents to the dorsal vagal complex and the precise sites where such afferents might increase gastric emptying and meal size are unknown. However, the presence of glutamate in primary vagal sensory neurons [83] and the existence of NMDA receptors in both axon terminals of vagal sensory neurons and the postsynaptic site of these terminals [82] suggest that modulation of vagal motor output could be mediated by adjusting the responsiveness of primary and higher order viscerosensory neurons within the dorsal vagal complex. Such NMDA receptor-mediated modulation of gastric motor function could play an important role in controlling meal size and, hence, controlling daily food intake and ingestive behavior.

Conclusions

Half a century of researches on GABAergic and glutamatergic neurons, substantially accelerated during the last 10 years, have brought forward a detailed knowledge of the distribution and properties of GABA and glutamate receptors. With advances in molecular and cellular biology and improvement in immunocytochemical and *in situ* immunohistochemical techniques, a detailed biochemical and morphological characterization of the neuronal systems containing GABA and glutamate receptors has been achieved. In spite of the considerable amount of data on the distribution and actions of GABA and glutamate receptors in many parts of the nervous system, the function of GABA and glutamate receptors in ENS of the stomach is still poorly understood.

It is suggested that the GABA receptors are involved in the modulation of stomach motility. This conclusion is based on the following observations: firstly, GABAergic and glutamatergic nerve cells and fibers are present in the gastric enteric nervous system; secondly, release of GABA and L-Glu has been demonstrated from these neurons and thirdly, the effect of GABA and L-Glu on gastric smooth muscle. Enteric GABAergic neurons appear to be exclusively interneurons that release GABA as an excitatory neurotransmitter, in contrast to its inhibitory role in the CNS. GABA can either stimulate (via $GABA_A$ receptors) or inhibit (via $GABA_B$ receptors) intrinsic cholinergic motor neurons. GABA is a transmitter of interneurons within separate excitatory and inhibitory pathways regulating gastric motor and secretomotor function. Nothing is known about $GABA_C$ receptors in the gut. It is likely that enteric $GABA_C$ receptors will eventually be found, given that two of the components of the CNS GABA system mediate signaling in the gut wall. The recent finding about $GABA_B$ receptor-mediated modulation of gastric motor function can be considerably important for the control of gastric emptying, gastroesophageal reflux and daily food intake. Pharmacological manipulation of these receptors would allow for modulation of enteric and vago-vagal reflexes. In conclusion, $GABA_B$ receptors have selective influences on both peripheral and central vagal sensory transduction. These receptors are likely to be those mediating therapeutic effects, which may underlie future treatment of gastroesophageal reflux disease. The extent of the enteric GABAergic system, together with the disruption in gut behaviors following the perturbation of either the $GABA_A$ or the $GABA_B$ receptor, suggests that the GABAergic system presents potential new target sites for the development of gastrointestinal drugs. According to the recent report, GABA mediates enteric muscle contraction in *C. elegans* by activating the EXP-1 receptor, an excitatory GABA-gated cation channel. EXP-1 is expressed in the enteric muscles. What about vertebrates? This is the subject of ongoing investigation. There is also plenty of evidence suggesting a role for enteric ionotropic and metabotropic glutamate receptors in controlling acid secretion and protecting against gastric ulcer formation. Ionotropic glutamate receptors are involved in the modulation of stomach motility supplied by studies on the distribution of

glutamatergic nerve cells and fibers in the enteric nervous system, by indirect demonstration of a release of L-Glu from these neurons, and by the depolarizing and muscle stimulating effects of L-Glu in the smooth muscle of the stomach. There is also plenty of evidence that supports a role for enteric ionotropic and metabotropic receptors in the control of acid secretion and protecting against cold-restraint stress (CRS)-induced gastric ulcer formation. The recent finding of NMDA receptor-mediated modulation of gastric motor function can be very important for control of accelerating gastric emptying and daily food intake. NMDA receptors are present in ENS of the stomach. Pharmacological manipulation of these receptors would allow for modulation of enteric and vago-vagal reflexes. The role of glutamate receptors in transmission of nociceptive information has been extensively studied, but the mechanism remains elusive. A recent observation indicates that highly specific glutamate receptor antagonists are potent antinociceptive agents, however, this strongly suggests that glutamate is involved in this mechanism. The discoveries of specific glutamate receptor antagonists and agonists have proven to be invaluable in the study of the physiological significance of glutamate in nociceptive system and also provide a molecular basis for developing new types of antinociceptive drugs.

Metabotropic glutamate receptors also play a role in enteric reflexes. It is believed that internalization of receptor molecules might be a major mechanism for regulation of mGluR activity. Enteric mGlu receptors may present potential new target sites for the development of gastrointestinal drugs. Further development of more potent and selective mGlu receptor antagonists and agonists is needed in order to fully understand the role of glutamate in the enteric system.

Furthermore, the biochemical and pharmacological similarities between the CNS and ENS make the gut a model system in which to study GABAergic and glutamatergic neurons in the stomach.

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