REVIEW

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Role of peripheral glutamate receptors in regulation of gastric secretion and motor function of stomach

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Abstract: Anatomical, physiological and pharmacological evidence suggests that glutamate is neurotransmitter in the peripheral nervous system. The aim of this review is to show the distribution of the glutamatergic system within the mammalian gastric wall and how this system regulates gastric functions. There have been reports that different types of glutamate receptors are involved in regulation of gastric acid secretion, gastric motility and food intake.

Key words: glutamate receptors, glutamatergic neurons, stomach, gastric acid secretion, gastric motility, food intake

INTRODUCTION

The enteric nervous system (ENS) is the only region of the peripheral nervous system that is intrinsically capable of mediating reflex activity [1, 2]. This activity is made possible by the presence within the gastrointestinal tract of microcircuits that contain the necessary primary afferent neurons and interneurons, as well as the excitatory and inhibitory motor neurons that innervate gastrointestinal smooth muscle and glands. The complexity of the functions controlled by the ENS is reflected in an equally complex organization that resembles that of the central nervous system (CNS) more than the remainder of the peripheral nervous system. Many different classes of neurotransmitters have been found in the ENS, including most of those known also to be present in the CNS. Glutamate, the major excitatory neurotransmitter of the brain [3, 4], seems to be a conspicuous exception in that it has not previously been found to be a neurotransmitter in the ENS. As is the case in other parts of the brain, glutamatergic circuits in the stomach are generally confined to networks of interneurons in the ENS. Through various feedback and feed-forward loops, glutamatergic interneurons react to certain aspects of the gastric function. Enteric glutamatergic fibres are profuse, ramifying throughout the ganglionated and non-ganglionated enteric nerve networks of the gastrointestinal wall [2]. The glutamatergic neurons have been shown to be present in the submucous and myenteric plexuses [5-8]. There is evidence indicating a role of glutamatergic neurons in the regulation of gastric motility, secretion and gastric reflexes [9]. However, the receptor subtypes and mechanism that mediate the effects of L-Glutamate (L-Glu) in the stomach are still poorly understood. The aim of this review is to show the distribution of the glutamatergic system within the mammalian gastric wall and describe the regulation of gastric functions by this system.

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GLUTAMATERGIC NEURONS IN THE STOMACH

Anatomical, physiological and pharmacological evidence suggests that L-Glu is an excitatory neurotransmitter in the peripheral nervous system [2, 9]. The glutamate receptors in rat gastrointestinal tract are located on cholinergic nerves prejunctionally to enhance nerve-mediated responses. 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 [2].

Immunohistochemical studies support the notion that glutamatergic neurons are present in the stomach [9]. The distribution of glutamatergic neurons and their processes in both myenteric ganglia and circular muscle are heterogeneous within the stomach [10]. 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 [11, 12]. 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 [13-18]. Glutamatergic varicosities, which often contain choline acetyltransferase (ChAT) and the vesicular acetylcholine transporter, are apposed to a subset of neuronal cell bodies in the submucous and myenteric plexus in the stomach [18]. 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 gastrointestinal tract [19]. 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 [20]. 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 vasoactive intestinal polypeptide (VIP) are found in the myenteric and submucosal ganglia.

TYPES OF GLUTAMATE RECEPTORS IN STOMACH

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) [20, 21]. Ionotropic glutamate receptors – which can be further divided into N-methyl-D-aspartate (NMDA) and non-NMDA receptors – are responsible for synaptic transmission and plasticity [22-24]. Both ionotropic and metabotropic glutamate receptors have been shown to localize in enteric ganglia using immunocytochemistry and *in situ* hybridization [25-27].

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

NMDA receptors are heteromeric pentamers. The subunits are the products of two gene families, one NR1 gene and four NR2 (NR2A–D) genes. Although NR1 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 NR1 and NMDA [13, 14, 28] 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 [29]. These findings are also consistent with the idea that the enteric glutamate receptors are involved in neurogenic motility [18, 30] or secretion of the stomach [10, 29]. Recently, the NR1 subunits have been localized immunohistochemically in peripheral terminals of primary afferent nerves of dorsal root ganglia [29, 31]. 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 [29].

AMPA receptors are mainly involved in mediating fast glutamatergic neurotransmission. There are four subunits, known as GluR1 to GluR4 (also called GluRA to GluRD) [32]. 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 [33]. The latter can be viewed as coincidence detectors of pre- and postsynaptic activity, since the gating of the integral ion channel requires two close and simultaneous events, namely, presynaptic release of glutamate and depolarization of the postsynaptic membrane. Depolarization is induced by the activation of AMPA receptors.

Other non-NMDA ionotropic receptor subunits are known as GluR5, GluR6, KA1 and KA2. They normally form receptor assemblies which have high affinity for kainate, and hence are designated as KA glutamate receptors, although some researchers classify GluR5 as an AMPA receptor subunit. KA receptors were previously thought to be mostly presynaptic [34-36]. In contrast to AMPA, which facilitates glutamate release via presynaptic action, kainate acting on presynaptic autoreceptors decreases glutamate release and also depresses glutamatergic synaptic transmission [37].

Metabotropic glutamate receptors. The ENS in the stomach contains metabotropic glutamate receptors (mGluR), as does CNS [38], which are members of the G-protein-coupled receptor family. At present, eight different mGluRs have been cloned, termed from mGluR1 to mGluR8 [39]. 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 Ca2+ 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 gastrointestinal tract [9].

ROLE OF GLUTAMATE RECEPTORS IN STOMACH

1. Gastric smooth muscle contraction. Peripheral contractile effects of glutamate were demonstrated for the first time 21 years ago on isolated guinea pig ileum [40]. From that time, the majority of literature was devoted to investigating the effect of different types of glutamate receptors on intestine. However, several later attempts [41, 42] only partially shed the light on the mechanism of that action. Later, it was established that 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 [43]. 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 [43] However, the physiological significance of glutamate contractile effect is completely unknown.

2. Food intake. Several researchers have reported the increase of food intake after treatment with NMDA or non-NMDA receptor agonists or antagonists [44-47]. 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 [48]. 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 [48]. 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 [49]. Systemically administered MK-801 could enhance gastric emptying through actions via a central and/or peripheral mechanism. Such NMDA receptor-mediated modulation of gastric motor function could play an important role in controlling meal size and, hence, controlling daily food intake.

3. Gastric acid secretion. The literature is mostly devoted to the role of central glutamate receptors in the regulation of gastric acid secretion [50-52]. Our knowledge of the role of peripheral glutamate receptors is very limited. This is connected with the fact that peripheral glutamate receptors were discovered only recently. We intend to generalize the data to date about the role of glutamate and different types of peripheral glutamate receptors in the regulation of gastric acid secretion.

It has been shown that nonselective agonist of glutamate receptors L-Glu [50] and selective agonist of NMDA type glutamate receptors N-methyl-D-aspartate [53, 54] had no effect on basal gastric acid secretion. Thus, peripheral glutamate receptors of NMDA-type, which are stimulated by endogenous glutamate, are not involved in the regulation of basal gastric acid secretion. It is quite another matter with AMPA/KA glutamate receptors. In our experiments we established that the central and peripheral AMPA/KA glutamate receptor blocker IEM 1751 diminished the basal gastric acid secretion in rats with an intact nervous system, but enhanced it in rats after bilateral vagotomy. As in rats with an intact nervous system, IEM 1751 blocked both central and peripheral receptors, while in rats after bilateral vagotomy we observed only the peripheral effect of IEM 1751. We therefore concluded that central and peripheral AMPA/KA glutamate receptors play different roles in the regulation of basal gastric acid secretion [55]. Excitement of central AMPA/KA glutamate receptors increased basal gastric acid secretion, which supports the data of other authors [50-52]. On the other hand, excitement of peripheral AMPA/KA glutamate receptors diminished basal gastric acid secretion [55].

The question arises: why L-Glu – which stimulates all types of glutamate receptors, including AMPA/KA glutamate receptors – has no influence on basal gastric acid secretion? [50]. Evidently, as a result of summation of the stimulatory effect of the central and oppressive effect of peripheral AMPA/KA glutamate receptors, the influence of L-Glu on basal gastric acid secretion was absent.

We established that the antagonist of nicotinic acetylcholine receptors Pentamini removed the excitatory action of IEM 1751 on basal gastric acid secretion in rats after bilateral vagotomy. It was observed that peripheral AMPA/KA glutamate receptors realize their effect through vagal cholinergic neurotransmission in the ENS, and that peripheral AMPA/KA glutamate receptors are located on preganglionic cholinergic nerves prejunctionally or on interneurones of ENS [55].

In natural conditions. gastric acid secretion is the result of excitement of parietal cells by acetylcholine, histamine and gastrin. That is why it is important to analyze the role of peripheral glutamate receptors in the regulation of gastric acid secretion evoked by these stimulators.

Systemic injection of synthetic L-Glu [50] and NMDA [54] to the rats had no effect on acid secretion induced by pentagastrin. As in the case of basal gastric acid secretion in our experiments, the excitement of peripheral AMPA/KA glutamate receptors led to the diminishing of pentagastrin gastric acid secretion (in press).

It was showed that infusion with NMDA had no effect on acid secretion induced by histamine [54]. L-Glu reduced histamine stimulated gastric acid secretion. This inhibitory effect was blocked by 6,7-dinitroquinoxaline-2,3-dione (DNQX), a non-NMDA receptor antagonist [50]. Thus L-Glu suppress histamine gastric acid secretion via excitement of AMPA/KA glutamate receptors. Our data about the increasing effect of IEM 1751 on histamine gastric acid secretion in rats after bilateral vagotomy support this conclusion (in press).

L-Glu, quisqualic acid (QA), kainic acid (KA) and NMDA reduced oxotremorine- stimulated gastric acid secretion [10, 29, 50]. 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-carboxypiperazine-4-gl) propyl-phosphonic acid (CPP). The mechanism underlying the effect of NMDA inhibiting oxotremorine-induced acid secretion may be mediated by the NO-dependent cyclic GMP system. But the inhibitory effect of L-Glu on oxotremorine-stimulated gastric acid secretion was blocked by 6,7-dinitroquinoxaline-2,3-dione (DNQX), a non-NMDA receptor antagonist [50]. Also, in our experiments it was established that the excitement of peripheral AMPA/KA glutamate receptors led to a marked reduction of carbachol gastric acid secretion (in press).

Therefore, we can conclude that peripheral ionotropic NMDA receptors are involved in the regulation of stimulated gastric acid secretion, just as oxotremorine and carbachol and peripheral ionotropic AMPA/KA glutamate receptors are involved in the regulation of stimulated gastric acid secretion by pentagastrin, histamine, oxotremorine and carbachol. These results suggest that different types of glutamate receptors are involved in the regulation of gastric acid secretion.

As for the role of metabotropic glutamate receptors in the regulation of gastric acid secretion, we could only demonstrate that the competitive metabotropic glutamate receptor antagonist (+)-alpha-methyl-4-carboxyphenylglycine (MCPG) did not antagonize the suppressed effect of endotoxin on pentagastrin gastric acid secretion. The role of metabotropic glutamate receptors in regulation of gastric acid secretion remains poorly understood.

CONCLUSIONS

The investigation of the role of different types of peripheral glutamate receptors in the regulation of gastric acid secretion is a very real problem. First of all, because the disturbance of glutamate neurotransmission causes different diseases (Parkinson's, epilepsy, encephalopathy, schizophrenia, Alzheimer's), and these diseases are often accompanied by a disturbance of gastric acid secretion. Secondly, the agonists and antagonists of different types of glutamate receptors are widely used in the treatment of neuro-degenerative diseases. Further development of more potent and selective glutamate receptors antagonists and agonists is needed in order to fully understand the role of glutamate in the enteric system, and to create new medications that will not induce collateral action on gastrointestinal secretion and motility.

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