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Role of metabotropic glutamate receptors in the regulation of pancreatic functions

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Abstract

The pancreas consists of two major divisions, the exocrine and the endocrine pancreas. Recent data from our laboratory have shown that the functions of the two divisions are under modulatory regulation by separate neurocircuits that originate in the dorsal motor nucleus of the vagus (DMV). Metabotropic glutamate receptors (mGluRs) are expressed throughout the central nervous system and have been implicated in the modulation of synaptic transmission. mGluRs consist of three groups of receptors, which can be distinguished based on their pharmacological properties and second messenger systems. Group I mGluRs predominantly increase, whereas group II and III mGluRs decrease synaptic transmission. Group II and group III mGluRs are present on excitatory and inhibitory synaptic terminals impinging on pancreas-projecting DMV neurons. We have shown that group II mGluRs regulate both exocrine pancreatic secretions and insulin release, whereas group III mGluRs only regulate insulin release. Several mGluR agonists and antagonists have been shown to have clinical uses for disorders accompanied by abnormal synaptic transmission, including anxiety and Parkinson's disease. Moreover, a negative allosteric modulator of Group I mGluRs is effective in alleviating symptoms of gastroesophageal reflux disease (GERD). Since the role of the three mGluR groups in mediating different gastrointestinal (GI) functions appears to be highly specific, the use of agonists or antagonists directed at a single receptor group could potentially provide highly selective targets for the treatment of GI disorders including GERD, functional dyspepsia and acute pancreatitis.

Keywords

Glutamate receptors; Pancreas; Vagus; Electrophysiology

1. Introduction

The pancreas plays a critical role in the maintenance of caloric and nutritional homeostasis. These functions are performed by two major parts of the pancreas, namely the exocrine pancreas, which is involved in the release of digestive enzymes; and the endocrine pancreas, involved in the release of hormones, such as insulin, glucagon, pancreatic polypeptide (PP) and somatostatin. Both pancreatic functions are under modulatory control of the vagus nerve, whose preganglionic neurons are located in the dorsal motor nucleus of the vagus

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(DMV). Recent data from our laboratory have shown that the activity of these neurons is modulated by metabotropic glutamate receptors (mGluRs) and that these receptors display a highly specific organization on vagal circuits that selectively regulate exocrine or endocrine pancreatic secretions [1].

Disorders of both the exocrine and the endocrine pancreas are highly prevalent world-wide. Acute pancreatitis, the most common disorder of the exocrine pancreas, is the most common reason for hospital admissions due to gastrointestinal (GI) disorders, accounting for approximately $5 billion in health care costs in the United States alone [2]. Diabetes mellitus is the most common disorder of the endocrine pancreas, affecting approximately 8% of the population in the United States, with an estimated annual cost of $245 billion [3]. Due to the high costs of pancreatic disorders, discovery of novel therapies for these disorders is an important step towards reducing their health and economic impact.

In this review, we provide an overview of the role of mGluRs in the regulation of pancreatic functions and potentially provide novel therapeutic targets for pancreatic disorders.

2. Neural regulation of pancreatic functions

The pancreas plays a crucial role in the control of caloric and nutritional homeostasis. The pancreas consists of two major divisions, the exocrine and the endocrine pancreas. The exocrine pancreas consists of acinar cells, which synthesize, store and secrete digestive enzymes; and ductal cells which secrete chloride and bicarbonate. Enzymes secreted by the exocrine pancreas into the duodenum aid in the break-down of macronutrients into smaller components and thereby play a role in the regulation of digestion and nutrient absorption. The endocrine pancreas comprises pancreatic islets, which secrete hormones involved in energy and glucose homeostasis. Within the endocrine pancreas, insulin-secreting β-cells are the most numerous. The remaining cell types include glucagon-secreting α-cells, δ-cells that secrete somatostatin and cells that secrete PP [4].

In order to ensure appropriate nutritional and energy homeostasis, the activity of the pancreas is regulated tightly by the central nervous system (CNS), particularly the brainstem area of the dorsal vagal complex (DVC), which consists of the nucleus tractus solitarius (NTS), dorsal DMV and area postrema. In this section, we provide a brief description of the parasympathetic (vagal) and sympathetic (spinal) regulation of the pancreas. These circuits have been described in detail in previous reviews [4–6,19].

2.1. Vagal pathways

Sensory information from the pancreas and other regions in the upper GI tract is relayed by the afferent vagus nerve, which has cell bodies in the nodose ganglion and terminates in the NTS. NTS neurons integrate this sensory information and relay it to the parasympathetic preganglionic neurons in the DMV via GABAergic, glutamatergic and catecholaminergic inputs [4,6].

Parasympathetic cholinergic preganglionic neurons innervating the pancreas are located in the DMV and project to the intrinsic pancreatic ganglia, which are scattered throughout the

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pancreas. Preganglionic neurons contain acetylcholine and activate post-ganglionic neurons primarily via nicotinic acetylcholine receptors. Post-ganglionic neurons excite acinar, ductal and islet cells via the release of acetylcholine and activation of muscarinic receptors, or via the release of non-adrenergic non-cholinergic neurotransmitters such as vasointestinal peptide, gastrin-releasing peptide, pituitary adenylate cyclase-activating polypeptide and nitric oxide [4].

Studies from our and other laboratories have demonstrated that under control conditions, a tonic GABAergic inhibition provides the predominant influence over the activity of DMV neurons. Microinjections of the $GABA_A$ receptor antagonist bicuculline into the DMV increase pancreatic exocrine secretions (PES), insulin release, gastric tone and motility [7,8]. In contrast, microinjections in the DVC of the ionotropic glutamate receptor antagonist kynurenic acid do not have an effect on gastric motility [8] or PES (Babic and Travagli, unpublished observations). Our laboratory has also demonstrated that both excitatory and inhibitory synaptic inputs to pancreas-projecting DMV neurons can be modulated by a variety of hormones, neurotransmitters and physiological conditions. Specifically, we have demonstrated that synaptic transmission to pancreas-projecting neurons can be modulated by hormones released from the GI tract following ingestion of meals, including PP, glucagon-like peptide-1 (GLP-1) and cholecystokinin (CCK) [9–12]. Following their release from the GI tract, these peptides can influence vagal activity via peripheral actions on vagal afferents as well as via direct actions on neurons in the DVC (reviewed in [6]). Since portions of the DVC have a leaky blood brain barrier, circulating peptides may access these neurons directly or via specialized transport proteins [13,14] without having to cross the blood brain barrier [15]. Studies using DVC microinjections of these peptides have demonstrated that PP decreases [16], whereas CCK [17] or thyrotrophin-releasing hormone (TRH) [18] increase PES. Conversely intra-DVC GLP-1 administration increases basal insulin release [1]. Taken together, these findings demonstrate that peptides released from the GI tract can modulate vagal outflow to the pancreas also via alterations of synaptic transmission impinging on pancreas-projecting neurons in the DMV. As described below, recent evidence suggests that different vagal neurocircuits may be involved in discrete regulation of pancreatic secretions. Furthermore, the ability of GI peptides to modulate pancreatic secretions and synaptic inputs to pancreas-projecting neurons indicates that these circuits display a great deal of synaptic plasticity and their activity can be finely tuned based on the hormonal and nutritional status of the animal.

2.2. Spinal pathways

Sympathetic innervation of the pancreas originates from the preganglionic neurons in the lower thoracic and upper lumbar segments of the spinal cord [19]. These neurons project to postganglionic neurons located in celiac and superior mesenteric ganglia, which, in turn, innervate the intrapancreatic ganglia, islets and blood vessels and to a lesser extent, the ducts and acini. Activation of sympathetic nerves innervating the pancreas decreases insulin secretion and elicits vasoconstriction, with little to no effect on ductal or acinar cells. Sympathetic postganglionic neurons use primarily noradrenaline, galanin and neuropeptide Y as neurotransmitters [4,19].

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2.3. Sensory pathways

Sensory information from the pancreas is conveyed to the CNS by both vagal and spinal pathways. Pancreatic afferent fibers are localized in both nodose and spinal ganglia [4,20]. A study using an *in-vivo* preparation has demonstrated that the majority of spinal pancreatic afferents are both mechano- and chemosensitive. Chemosensitive fibers have been shown to respond to nerve growth factor, CCK, bradykinin and 5-hydroxytryptamine (5-HT). Vagal pancreatic afferents, in contrast, are more scarce compared to spinal afferents and do not appear to be mechanosensitive [21].

2.4. Regulation of endocrine and exocrine pancreatic secretions

Several lines of evidence, including data from our laboratory, suggest that distinct vagal neuronal populations regulate pancreatic endocrine and exocrine functions. The influence of the vagus on exocrine or endocrine secretions depends on either the frequency of stimulation or the frequency of firing rate of DMV neurons [4,22]. Vagal innervation of the pancreas also shows an anatomical gradient, with the head of the pancreas receiving a greater density of vagal axons compared to the tail [23,24]. The influence of vagal innervation on pancreatic functions, especially endocrine secretion, depends on the particular subdiaphragmatic vagal branch involved. Despite anatomical evidence for the vagal celiac branches innervating the splenic end of the pancreas, electrical stimulation of the hepatic and gastric branches of the vagus are solely responsible for insulin and glucagon secretion [23], suggesting that the celiac branches innervate targets other than pancreatic α and β cells.

Recent data from our laboratory have provided further evidence that separate vagal pathways regulate PES and insulin release and that DMV neurons regulating these two functions can be distinguished based on their neurochemical and pharmacological properties [1,9,11]. We have demonstrated that CCK, PP and GLP-1 have both presynaptic and postsynaptic effects on pancreas-projecting DMV neurons [9–12]. Furthermore, pancreas-projecting DMV neurons that respond to GLP-1 do not respond to PP or CCK [9,11], whereas the majority of DMV neurons that respond to CCK also respond to PP [11]. These data suggest that pancreas-projecting DMV neurons comprise at least two distinct neuronal subpopulations that respond either to GLP-1 or to CCK and PP. Since CCK and PP have been shown to modulate PES, whereas GLP-1 modulates insulin release, these two subpopulations of DMV neurons likely serve different physiological functions: i.e. neurons that respond to CCK and PP likely regulate PES, whereas neurons that respond to GLP-1 are likely involved in the regulation of insulin release. This suggestion is supported by the observation that microinjections of CCK and PP into the DVC alter PES, whereas GLP-1 microinjections increased plasma insulin [16,1].

Finally, recent studies have also demonstrated in rats that copper deficiency, which causes a selective non inflammatory loss of pancreatic acinar tissue but leaves the islet of Langherans unaffected, diminishes the sensitivity of DMV neurons to CCK and PP, further supporting the notion that neurons responsive to these peptides specifically regulate PES [11]. These findings provide further evidence that pancreas-projecting DMV neurons comprise at least two subpopulations which modulate selectively exocrine or endocrine pancreatic functions.

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A recent study from our laboratory has demonstrated that DMV neuronal populations that regulate pancreatic exocrine secretions and insulin release can also be differentiated based on their responses to group III mGluR [1].

3. Metabotropic glutamate receptors

mGluRs are one of the major receptor types that regulate synaptic transmission in the CNS. Unlike ionotropic glutamate receptors, which are coupled to ion channels and mediate fast synaptic transmission, mGluRs are members of G-protein coupled receptor (GPCR) family of receptors and couple to different second messenger systems. The mGluR family of receptors consists of eight members, some of which can be alternatively spliced and couple to multiple signaling pathways.

3.1. mGluR classification and signaling pathways

There are eight known subtypes of mGluR family, which can be divided into three categories based on their pharmacological properties and second messenger systems. Each receptor group shares approximately 70% sequence homology, whereas 40% homology exists between different groups [25].

The topology of mGluRs includes a hydrophillic N-terminal extracellular domain, three extracellular and three intracellular loops and a cytoplasmic C-terminal tail, separated by 7 membrane-spanning regions. The N-terminal domain contains the glutamate-binding site and contains a highly conserved cystein-rich region. The intracellular domains are of variable lengths and interact with the G-proteins [26,27].

Although all mGluRs share some characteristics, the three groups of receptors display distinct pharmacological properties and second messenger systems. Group I mGluRs, which include mGluR1 and mGluR5, are predominantly located on the post-synaptic membrane and regulate neuronal excitability as well as positively modulate ionotropic glutamate and GABA neurotrans-mission [25,26,28]. Group I mGluRs are coupled to Gq/G11 to activate phospholipase C (PLC), resulting in the hydrolysis of phosphotinositides and generation of inositol 1,4,5-triphosphate (IP_3) and diacylglycerol. The classical pathway associated with PLC signaling leads to an increase in intracellular calcium and activation of protein kinase C (PKC). However, group I mGluRs can also activate alternate signaling pathways. These pathways include coupling to Gq, other pathways activated by coupling to Gi/ o, Gs as well as coupling to molecules other than G proteins [29].

Group II mGluRs (which include mGluR2 and mGluR3) and group III mGluRs (which include mGlu4, mGlu6, mGlu7 and mGlu8) are predominantly located on presynaptic terminals and are negatively coupled to adenylate cyclase via Gi/o [25,26]. Like group I mGluRs, group II and III mGluRs can also couple to different signaling pathways, including MAPK activation, and phosphoinositide-3 (PI3) kinase pathways. Group II and III mGluRs inhibit glutamate and GABA neurotransmission [25,29,30].

Several mGluRs undergo alternative splicing, which further contributes to the diversity of these receptors. In the mGluR family of receptors, alternatively spliced variants have been

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reported for mGlu1, mGlu3 and mGlu5-8. For mGluRs, alternative splicing most commonly occurs at the C-terminal domain, although short variants that lack the entire transmembrane domain have also been identified for several mGluRs [26,29].

3.2. Role of mGluR in mediating synaptic transmission

The most investigated role of mGluRs in the CNS is that of modulating synaptic transmission. In contrast to ionotropic glutamate receptors, which mediate fast synaptic transmission by opening ion channels, mGluRs exert modulatory effects on synaptic transmission via interactions with G proteins and activation of second messenger systems. mGluRs exert a negative feedback on glutamate release in conditions when excessive amounts of glutamate are released within the synapse. The diversity of mGluRs and their downstream second messengers contributes to a wide range of effects. Moreover, the three groups of mGluRs differ with respect to their localization within the synaptic terminal, further facilitating the diversity of their functions.

Group I mGluRs are predominantly located postsynaptically and their activation generally leads to depolarization and an increase in neuronal excitability via interactions with different ion channels, although inhibition of glutamate release by group I mGluRs has also been reported [29]. Activation of group I mGluRs in the hippocampus has been shown to promote the release of glutamate by an increase in Ca^{2+} currents, inhibition of slow after hyperpolarization K^+ currents, and potentiation of NMDA receptor currents and stimulation of PKC, which phosphorylates K^+ and Ca^{2+} channels, leading to an increased release of glutamate [27,29].

In contrast to postsynaptic group I mGluRs, group II and group III mGluRs are located on presynaptic membranes where they inhibit synaptic transmission, primarily via inhibition of PKC and cyclic AMP (cAMP) levels. Inhibition of transmitter release has been demonstrated at glutamatergic, GABAergic as well as neuromodulatory synapses [29].

Inhibition of cAMP is the main mechanism by which group II and group III mGluRs inhibit neurotransmitter release. Our laboratory has demonstrated that in the DMV, a tonic activation of group II mGluRs and the resulting low levels of cAMP within the synaptic terminals prevent the trafficking of opioid receptors in GABAergic terminals impinging upon gastric-projecting DMV neurons. Removal of this tonic activation of group II mGluR by pretreatment with the group II mGluR antagonist EGLU enables trafficking of opioid receptors to the membrane [31,32]. A decrease in cAMP has also been shown to be the mechanism by which mGluRs modulate the induction of long term depression in the hippocampal synapses [33].

In addition to inhibition of cAMP levels, activation of group II and group III mGluRs can inhibit the release of glutamate via actions on K^+ and Ca^{2+} channels. Group II and III mGluR agonists have been shown to inhibit N-type and PQ-type Ca^{2+} channels via direct interaction of these channels with G proteins Group III mGluRs can also decrease transmitter release by activating presynaptic inward rectifier K^+ channels without a direct effect on Ca^{2+} currents [34]. As observed with Ca^{2+} channels, modulation of K^+ channels may occur through the direct interaction with the $\beta\gamma$ subunit of the G protein [33,35]. Taken

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together, these data suggest that mGluRs can suppress neurotransmitter release via multiple mechanisms, which appear to be mediated by the interaction of G proteins with Ca^{2+} and K^{+} channels.

In addition to activating multiple downstream pathways, the three groups of mGluRs also display different subcellular distribution within the synapse, which further contributes to the diversity of their functions. Group III mGluRs are localized primarily in the presynaptic active zone, whereas group II mGluRs tend to be located in preterminal regions of axons, remote from the transmitter release site [26,36]. It has been demonstrated that group II mGluRs are only activated when the amount of glutamate in the synaptic cleft is high, such as that observed during high frequency stimulation. Group II mGluR antagonists had no effect on glutamate currents at low frequency of stimulation, but reduced the amplitude of excitatory postsynaptic currents when the frequency of stimulation was increased, suggesting that activation of group II mGluRs most likely requires a spread of glutamate from the site of release. Group III mGluRs, in contrast, are located at the synaptic terminal and likely act as autoreceptors to decrease the release of glutamate from the same synaptic terminal [37].

3.3. mGluR and vago-vagal reflexes

Anatomical studies have demonstrated that mGluRs are expressed on both peripheral and central components of GI-vagal circuits where they modulate their activity. mRNA for almost all members of the mGluR family is present in the nodose ganglia of rats, dogs, ferrets and humans [38]. Further studies have revealed that mGluR protein is expressed in gastric-projecting nodose ganglion neurons as well as in the NTS and the DMV [38,39]. Another study has demonstrated mGluR5, a member of group I mGluR, immunoreactivity in the nodose ganglion and myenteric plexus of the esophagus in humans [40]. These findings suggest that mGluRs are anatomically positioned to modulate both sensory and motor components of vago-vagal reflexes.

Anatomical evidence is supported by physiological studies. In vitro studies on isolated gastro-esophageal vagal afferent fibers have shown that group II and III mGluR agonists inhibited, whereas group III mGluR antagonist increased mechanosensitivity of these fibers [38], whereas, mGluR5 (i.e group I mGluR) antagonist inhibited mechanosensitivity of vagal afferent fibres [41]. These data suggest that group II and group III mGluRs inhibit, whereas group I mGluRs potentiate, mechanosensitivity of gastroesophageal afferent fibers. A study in conscious ferrets has demonstrated that systemic administration of mGluR agonists and antagonists affects transient lower esophageal sphincter relaxation (TLESR). Group I mGluR antagonist as well as group III selective agonist inhibited TLESR in response to gastric load. Inhibition of TLESR was also observed after administration of a selective mGluR8a agonist, whereas the administration of group II agonist had no effect. These findings demonstrate that group I mGluRs facilitate, group III mGluRs inhibit, and group II mGluRs have no effect on esophageal relaxation. Moreover, the effects of group III mGluRs are likely due to activation of mGluR8a, as application of the selective mGluR8a agonist 4-DCPG had a similar effect as the non-selective group III agonist [42]. In addition,

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these results suggest that although all three groups of mGluRs are present on vagal afferent fibers, they may serve different physiological functions.

At the level of the NTS, the site of termination of vagal afferent fibers, intracerebroventricular administration of mGluR8a agonist or mGluR5 antagonist reduced the gastric distension-induced activation of NTS neurons [39,43,44]. A study in goldfish demonstrated that activation of group III mGluRs decreased the field potential evoked by stimulation of primary gustatory afferent fibers. A similar effect was elicited by the application of selective mGluR4 and mGluR8 agonists, but not mGluR6 or mGluR7 agonists, suggesting that mGluR4 and mGluR8 participate in the modulation of gustatory inputs to NTS neurons [45].

Recent studies from our laboratory have demonstrated that mGluRs also modulate the efferent outflow to the GI tract by modulating the activity of preganglionic terminals synapsing onto DMV neurons [1,32]. Group II and group III mGluR display a discrete organization on synaptic terminals impinging on DMV neurons that regulate GI functions. DMV neurons that project to the stomach receive excitatory inputs that express both group II and group III mGluRs, inhibitory inputs to these neurons, however, express only group II mGluRs. Furthermore, group II mGluRs on inhibitory, but not excitatory synaptic terminals impinging on gastric-projecting DMV neurons are active tonically [32] and keep the levels of cAMP low, thereby preventing the modulation of synaptic activity in these terminals. Data from our laboratory have shown that, under resting conditions, various neurotransmitters negatively coupled to adenylate cyclase do not modulate GABAergic synaptic transmission impinging on gastric-projecting neurons. If, however, cAMP levels are elevated, for instance by antagonism of group II mGluRs, opioid peptides, pancreatic peptides neuropeptide Y and peptide YY, 5-HT or oxytocin are able to modulate GABAergic synapses [31,32,46]. Consistent with these findings, we have recently demonstrated that group II mGluR antagonist alters the ability of oxytocin microinjections into the DMV to induce a decrease in gastric tone [46].

Taken together, these findings suggest that mGluRs can modulate vago-vagal reflexes by acting at both peripheral and central levels. This complex organization of mGluRs on vago-vagal circuits suggests that neurotransmitter release can be modulated by mGluRs at different sites in vago-vagal circuits and be finely tuned to meet the demands of changing physiological and environmental conditions. Furthermore, different groups of mGluRs appear to play selective roles in the modulation of GI vago-vagal reflexes. In fact, esophageal relaxation appears to be modulated by group I and group III mGluRs, whereas gastric tone is under modulatory control of group II mGluRs. This hypothesis is supported by recent data from our laboratory on pancreatic functions [1].

4. Differential modulation of pancreatic endocrine and exocrine secretions by mGluRs in the dorsal motor nucleus of the vagus (DMV)

While the majority of studies have investigated the roles of mGluR on esophageal and gastric functions, less is known about the role of these receptors in the regulation of pancreatic secretions. In a recent study, we have demonstrated that the organization of

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mGluRs on vago-vagal circuits that regulate pancreatic function is distinct from the organization of circuits that regulate gastric functions. In addition, our data have demonstrated that mGluRs differentially regulate pancreatic endocrine and exocrine secretion [1].

4.1. Effects of group II and group III mGluR on excitatory and inhibitory synaptic transmission on pancreas-projecting DMV neurons

In a recent study, we reported that both group II and group III mGluRs are present on excitatory and inhibitory synapses impinging on identified pancreas-projecting neurons in the DMV [1]. Activation of group II mGluRs with the selective agonist APDC decreases synaptic transmission in the vast majority of excitatory (89%) and inhibitory (71%) synaptic terminals. Conversely, activation of group III mGluRs with the selective agonist L-AP4 affects fewer excitatory (65%) and inhibitory (58%) synaptic terminals. We also demonstrated that all neurons that responded to L-AP4 also responded to APDC, whereas another population of neurons responded only to APDC. These observations led to the hypothesis that pancreas-projecting neurons comprise two populations of neurons which can be distinguished by their responses to group III mGluR agonist [1].

Further characterization of pancreas-projecting DMV neurons demonstrated that majority of neurons that respond to L-AP4 also respond to the GLP-1 analogue exendin-4, but not to CCK or PP. Conversely, neurons that did not respond to L-AP4 responded to PP and CCK, but not exendin-4. These results demonstrated that group III mGluRs modulate the activity of a specific subpopulation of pancreas-projecting neurons in the DMV that has a unique neurochemical phenotype [1].

4.2. Group II and group III mGluRs differently regulate endocrine and exocrine pancreatic secretions

Observations that pancreas-projecting neurons comprised two sub-populations of neurons that can be distinguished based on their responses to group II and group III mGluR agonists raised the possibility that these two populations of neurons serve distinct physiological functions. In an attempt to determine the roles of these neurons in modulating pancreatic functions, we conducted a series of *in vivo* experiments using DVC microinjections of group II and group III mGluR agonists while monitoring PES and insulin secretions.

DVC microinjection of the group II mGluR agonist APDC dose-dependently increased pancreatic exocrine secretions and decreased plasma insulin levels. In contrast, microinjections of group III mGluR agonist decreased plasma insulin, but had no effect on pancreatic exocrine secretion [1]. Taken together with the observations that neurons that respond to activation of group III mGluR also respond to exendin-4, which is known to modulate insulin secretion, whereas neurons that do not respond to group III mGluR agonist respond to CCK and PP, both of which peptides modulate PES, these findings suggest that pancreatic exocrine secretion and insulin release are under modulatory regulation by separate populations of neurons and suggest that these functions are controlled by distinct neurocircuits [1]. The proposed distribution of mGluRs on neural circuits regulating PES and insulin release is shown in Fig. 1.

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These findings also indicate that there is a highly specific organization of mGluRs on vagal circuits serving distinct physiological functions. These data are consistent with the findings demonstrating that group II and group III mGluRs play different roles in the regulation of gastric tone and esophageal relaxation.

Mechanisms that underlie the different expression patterns and function of group II and group III mGluRs have not been investigated thoroughly. Previous studies have demonstrated that expression of mGluR7a and mGluR7b, both members of group III mGluR, is targeted to synaptic terminals making contacts with mGluR1-positive neurons in the hippocampus [36,47]. These observations raise the possibility that a similar distribution pattern may be present in the DMV and that expression of group III mGluRs may be limited to terminals impinging on DMV neurons of a specific phenotype. Furthermore, DMV neurons display mGluR1a immunoreactivity [48], however, the role of these receptors in modulation of pancreatic functions has not been investigated yet.

Electron microscopy studies have also shown that group III mGluRs are expressed in the synaptic terminal, whereas group II mGluRs are expressed in pre-terminal synaptic zone [36]. As described earlier, it has been suggested that these differences in expression along the axon reflect differences in the amount of glutamate required to activate two receptor types [37]. Activation of extrasynaptically located group II mGluRs requires glutamate spillover from the site of release, whereas group III mGluRs are activated by glutamate released into the synaptic cleft. The relevance of this finding to pancreatic functions is not known, however, the possibility exists that DMV neurons that regulate distinct pancreatic functions receive different afferent inputs, which differ in their activity and glutamate release. Given that group II mGluRs regulate both PES and insulin secretion, whereas group III mGluRs selectively regulate insulin secretion, our data suggest that a larger amount of glutamate may be required for the stimulation of PES than for stimulation of insulin release.

5. Potential therapeutic uses of mGluR agonists

The roles of mGluRs in the modulation of GI functions and neurotransmitter release imply that agents that modulate mGluR function can be used as potential therapeutic targets for treatments of pathological conditions. The discrete localization of different members of mGluR family on neural circuits regulating homeostatic functions entails that administration of mGluR agonists and antagonists would have highly specific effects on these circuits. In recent years, numerous selective agonists, antagonists and allosteric modulators of mGluRs have been developed [29,49], Some of these agents have been shown to cross the blood-brain barrier and their systemic administration is effective at altering synaptic transmission within the CNS, indicating a potential therapeutic use of these neuroactive agents.

The role of mGluRs has been investigated in a wide variety of conditions. In this section, we will describe the potential uses of mGluR agonists and antagonists in treatment of conditions characterized by disturbances of synaptic transmission, as well as disorders of the GI tract.

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5.1. Therapeutic uses of mGluR agents in treatment of disorders of synaptic transmission

Numerous neurological disorders are characterized by a dysfunction of glutamatergic neurotransmission. As mGluRs are expressed throughout the CNS, their effects and potential therapeutic uses have been investigated in several disorders, including anxiety, epilepsy and Parkinson's disease.

Animal studies have shown that group II mGluRs have anxiolytic effects. Anxiety and other stress-related disorders are characterized by excessive excitability in various regions of the CNS. Since glutamate is the main excitatory neurotransmitter in the CNS, recent approaches to treating these disorders have focused on glutamatergic signaling, and, specifically, on mGluRs. The compound LY354740 is a selective group II mGluR agonist and has been shown to dose-dependently block anxiety-like behaviors in several animal models [50]. Findings of these studies indicate that LY354740 modulates excitatory neurotransmission in the hippocampus and amygdala, CNS regions involved in producing anxiety-like behaviors. Similarly, the systemic administration of group I mGluR antagonist MPEP reduces anxiety in several animal models and these actions are mediated via group I mGluRs in the hippocampus and amygdala [50]. Although these findings suggest that group II mGluR agonists may have anxiolytic effects, a recent randomized, double-blind clinical trial has failed to demonstrate a significant reduction in the severity of a panic disorder [51], suggesting that findings of animal studies may have limited clinical relevance. mGluRs have also been implicated as potential targets in the treatment of epilepsy, a condition characterized by excessive glutamatergic transmission [52]. Current antiepileptic drugs act by prolonging the inactivation of Na^+ channels, blocking Ca^{2+} currents or by enhancing GABAergic transmission [52]. The efficacy of mGluR agonists as therapeutic agents for clinical epilepsy has not been investigated, although numerous studies in animals have demonstrated that group I mGluR agonists are pro-convulsant, whereas group II and group III mGluR agonists are anticonvulsant [52]. In humans, mGlu2/3 immunoreactivity is considerably reduced in the molecular layer of the CA1 region of the hippocampus following medial temporal lobe epilepsy [53], whereas mGlu1 immunoreactivity is increased [54]. These findings are consistent with the suggestion that group I mGluRs potentiate epileptic seizures, whereas group II mGluRs diminish them. In a mouse model of generalized seizures, intracerebroventricular administration of the group I mGluR antagonist MPEP exhibits a similar therapeutic index as current antiepileptic drugs [52]. These findings support the use of mGluR agents as potential targets in treatments of epilepsy.

Clinical evidence has shown that mGluRs may also be efficacious in treating the motor symptoms of Parkinson's disease. Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta that project to the striatum. The loss of dopaminergic neurons results in movement disorders, such as resting tremor, bradykinesia, rigidity and gait disorders. Furthermore, loss of nigrostriatal neurons is accompanied by overactive glutamatergic transmission in the striatum [55,56]. mGluR5 is highly expressed in the striatum, where it potentiates NMDA-induced membrane depolarization and stimulates cholinergic interneurons [57]. Furthermore, systemic administration of mGluR5 antagonist decreases muscle tone in an animal model of Parkinson's disease [57]. Findings of animal studies have been corroborated by studies in

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human patients with Parkinson's disease. In a double-blind placebo-controlled study on Parkinson's disease patients, administration of the mGluR5 antagonist AFQ056 decreased the severity of involuntary movements [58]. Group II and III mGluRs are also expressed in the striatum and have been shown to inhibit glutamate release; however, systemic administration of group II and group III mGluR agonists does not appear to have a beneficial effect on parkinsonian symptoms in animal models of the disease [57].

5.2. Therapeutic uses of mGluR agents in treatment of GI disorders

Studies from different groups, including our, have demonstrated that modulation of synaptic transmission in the neurocircuits comprising vago-vagal reflexes plays a critical role in the function of the GI tract. Derangements of vago-vagal circuits and consequently of synaptic transmission, have been implicated in several functional GI disorders, including functional dyspepsia, GERD and acute pancreatitis. Given the role of mGluRs on modulation of vago-vagal circuits, they may prove to be effective in treatment of some of these disorders, in fact, mGluRs have already been targeted as potential therapeutic agents for GERD.

As described previously, group I and group III mGluRs play a role in the regulation of lower esophageal sphincter relaxation [49], where reducing the frequency of TLESR is one of the main strategies in the treatment of GERD. Recent clinical trials demonstrated that the mGluR5 negative allosteric regulator ADX10059 and mGluR5 antagonist AZD2066 improved clinical symptoms of reflux disease [59,60]. As mGluR5 is expressed at several levels along vago-vagal reflex neurocircuits, ADX10059 may act via both peripheral and central mGluR5 to alleviate GERD symptoms. Although the efficacy of group III mGluR agonists on GERD symptoms has not been clinically evaluated, data from animal studies would suggest a potential therapeutic effect in the treatment of GERD [42].

The efficacy of mGluR agents on other functional GI disorders has not been evaluated as of yet. Data from our laboratory, however, have demonstrated that group II and group III mGluRs play discrete roles in the regulation of gastric and pancreatic functions, indicating a potential target in the treatment of other GI disorders. For example, functional dyspepsia is correlated with psychological stress, anxiety and depression [61,62] and includes symptoms such as impaired gastric accommodation reflex and antral hypomotility, which may be due to derangement of vago-vagal reflexes [63,64]. Recent data from our laboratory have demonstrated that DVC administration of the group II mGluR antagonist EGLU decreases gastric tone and either decreases or reverses the gastroinhibition induced by DVC microinjection of the prototypical antistress hypothalamic hormone oxytocin [46]. Oxytocin release from the paraventricular nucleus of the hypothalamus is increased following chronic homotypic stress [65]. Oxytocin attenuates the stress-induced activation of the hypothalamo-pituitary-adrenal axis [66] and improves stress-induced delay in gastric emptying in rodents [67]. Taken together with these observations, data from our laboratory suggest that group II mGluR agonists may provide the link between anxiety and gastrointestinal disorders. Strategies directed at modulation of group II mGluR function may prove efficatious in the treatment of stress-induced GI disorders such as functional dyspepsia.mGluRs may also be useful targets for treatment of pancreatic disorders. As group III mGluRs modulate insulin secretion, and group II mGluRs modulate both insulin secretion and PES, the possibility

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exists that administration of group III mGluR agonists would have a beneficial effect on insulin secretions in type I diabetes. Type I diabetes results in the loss of pancreatic islet cells and diminished insulin release and most current therapies include replacement of insulin. In cases where β cell function is not completely lost, GLP-1 receptor agonists, such as Exenatide, are efficacious in restoring some insulin release [68]. As administration of group III mGluR agonist into the DVC decreases insulin secretion [1], and same population of neurons that respond to group III mGluR agonist and GLP-1, group III mGluR antagonist may be efficacious in improving insulin release in type I diabetes.

Conversely, administration of group II mGluR agonists would be a candidate in the treatment of disorders of the exocrine pancreas, such as acute pancreatitis. Acute pancreatitis is a severe and sometimes fatal disorder of the exocrine pancreas. It has an annual incidence of 40 cases per 100,000 adults [69] and is the most common reason for hospital admissions due to GI problems [70]. Acute pancreatitis is characterized by premature activation of zymogens, leading to acinar cell injury, release of chemokines and cytokines and an inflammatory response. Pain is the major symptom of acute pancreatitis and usually resolves within one week, however, severe cases of acute pancreatitis can lead to tissue autodigestion, multiorgan failure and even death [71].

Although early events involved in the development of acute pancreatitis are initiated in the pancreas itself and the majority of studies investigating the role of CNS have focused on spinal pain pathways, it has also been demonstrated that the vagus nerve plays a role in acute pancreatitis. In fact, acute pancreatitis increases the excitability of primary vagal afferents, denervation of the pancreas by neonatal capsaicin treatment or celiac ganglionectomy attenuates [72], whereas cervical vagotomy has been shown to increase the severity of acute pancreatitis [73]. These findings raise the possibility that acute pancreatitis may be accompanied by changes in synaptic transmission to DMV neurons. Given that PES is regulated by vagal neurocircuitry that is affected by group II, but not group III mGluRs, acute pancreatitis is likely to selectively affect the function of group II mGluRs on brainstem vagal neurons.

Our unpublished data demonstrate that acute pancreatitis decreases the sensitivity of glutamatergic synaptic inputs to pancreas-projecting DMV neurons to the group II mGluR agonist APDC, while the sensitivity of synaptic terminals to group III mGluR agonist is unaffected by acute pancreatitis. These findings suggest that acute pancreatitis selectively affects group II mGluRs on excitatory synaptic terminals impinging on pancreas-projecting DMV neurons (Babic and Travagli, unpublished observations). A decreased sensitivity to group II mGluR agonist would lead to an increase in excitatory input to DMV neurons that regulate PES, and may, therefore, account for the increased PES observed in acute pancreatitis. Administration of group II mGluR agonist would, therefore, be expected to alleviate the symptoms associated with increased stimulation of the exocrine pancreas in acute pancreatitis.

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6. Conclusions

While the importance of synaptic transmission in vago-vagal reflexes is well established in the regulation of GI functions under normal conditions, changes in synaptic activity in pathological conditions affecting the GI tract are still relatively unexplored. If it is accepted that GI disorders including GERD, functional dyspepsia and acute pancreatitis, stem from changes in the activity of vagal circuits, agents that alter synaptic transmission in these circuits would provide potential therapeutic targets in the treatment of GI conditions. Furthermore, the role of the three mGluR groups in mediating GI functions appears to be highly specific, suggesting that the use of agonists or antagonists directed at a single receptor group would provide a highly selective target for the treatment of GI disorders.

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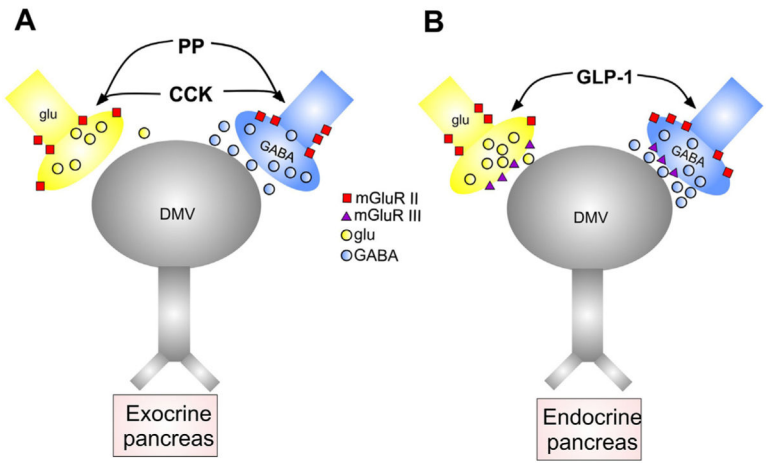

Fig. 1.

A schematic summary showing the organization of group II and group III mGluRs on synaptic terminals impinging on preganlionic pancreas-projecting DMV neurons. A Distribution of mGluRs on synaptic terminals impinging on DMV neurons that regulate PES. Note that these synaptic terminals express only group II mGluRs. B Distribution of mGluRs on synaptic terminals impinging on DMV neurons that regulate endocrine functions. Group II mGluRs are present on the majority of excitatory and inhibitory synaptic terminals impinging on pancreas-projecting neurons and activation of these receptors increases PES and decreases insulin release. The distribution of group III mGluRs is more limited and their activation decreases insulin release, but has no effect on PES. CCK, cholecystokinin; DMV, dorsal motor nucleus of the vagus; GLP-1 glucagon-like peptide-1; Glu, glutamate; mGluR, metabotropic glutamate receptors; PP pancreatic polypeptide.