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Commentary

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 gastro-esophageal 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.

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 (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

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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 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].

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.