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Neural Control of the Pancreas

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1. Introduction

The pancreas plays a critical role in the control of nutritional homeostasis. It consists of two major parts, the exocrine pancreas, which releases digestive enzymes; and the endocrine pancreas, which releases hormones such as insulin, glucagon, pancreatic polypeptide and somatostatin and maintains glucose homeostasis. Cells in the endocrine pancreas are organized in pancreatic clusters of cells, the islets of Langerhans. Within the islets, the β-cells, which secrete insulin, are the predominant cell type and comprise approximately 70% of the cells within the islets. The remaining cells consist of α-cells that secrete glucagon, δ-cells that secrete somatostatin, and cells that secrete pancreatic polypeptide. The main function of the exocrine pancreas is to aid in digestion by secreting digestive enzymes and bicarbonate into the duodenum. The exocrine pancreas consists of only two major cell types, namely acinar cells that synthesize, store and secrete digestive enzymes; and ductal cells that secrete chloride and bicarbonate.

Both parts of the pancreas are innervated by the sympathetic and parasympathetic nervous system, with separate pathways regulating the exocrine and the exocrine pancreas. In this chapter, we provide an overview of the central neural pathways that control the pancreas and the main neurotransmitters expressed in these pathways.

2. Sensory innervation of the pancreas

Sensory information from the pancreas is transmitted to the central nervous system (CNS) *via* both vagal and spinal pathways. Cell bodies of the spinal afferent pancreatic neurons are located in the T6-L2 dorsal root ganglia (DRG) and their axons traverse the splanchnic nerves and celiac plexus, before they enter the pancreas. These fibers comprise small myelinated (Aδ) and unmyelinated (C) fibers that transmit both mechanoreceptive and nociceptive information to the preganglionic sympathetic neurons in the intermediolateral cell column (IML) *via* interneurons in the spinal cord laminae I and IV (51). Most DRG neurons are capsaicin-sensitive and contain substance P (SP), calcitonin gene-related peptide (CGRP) or both (27, 63, 67, 68, 70, 83). Mechanosensitive fibers are primarily associated with blood vessels and although their

axons are located within the pancreatic parenchyma, they do not appear to innervate the ductal system (65). SP and CGRP may be involved in pain associated with chronic pancreatitis, as intrathecal administration of their antagonists attenuated behavioral pain responses in a rat model of chronic pancreatitis (48).

Pancreatic vagal afferent neurons originate in the nodose ganglia and are relatively sparse compared to spinal afferents. Most of these neurons are capsaicin-sensitive and contain substance P and calcitonin gene-related peptide or both (27, 67, 68). Anterograde tracing studies have shown that axons originating in the nodose ganglion supply large blood vessels, pancreatic ducts, acini and islets, and are only sparsely distributed in the pancreatic ganglia (51). Interestingly, injections of an anterograde tracer into the right nodose ganglion resulted in labelling primarily in the duodenal pancreatic lobe, whereas injections into the left ganglion predominantly labelled the splenic lobe, indicating that sensory innervation of the pancreas is distributed in a regionally specific manner (57).

The role of sensory nerves on pancreatic functions in control conditions is not completely understood, however. Chemical ablation of pancreatic sensory nerves has been shown to increase (37) or have no effect (38) on glucose-stimulated insulin secretion, suggesting that sensory nerves may exert tonic inhibition of insulin secretion. Similarly, substance P has been shown to either stimulate (29, 66) or inhibit (14) insulin secretion. Effects on glucagon secretion are equally contradictory. Calcitonin gene-related peptide has been reported to either stimulate or inhibit glucagon release (1, 35). Furthermore, ablation of the sensory nerves with capsaicin has been reported to either reduce (38) or have no effect (35) on stimulated glucagon secretion. Although the role of sensory afferents in the regulation of exocrine secretion has not been fully established, it has been shown that calcitonin gene-related peptide and substance P inhibit pancreatic exocrine secretion indirectly *via* actions on ganglionic transmission (40).

3. Sympathetic nervous system control of the pancreas

Anatomy of the sympathetic pathways regulating pancreatic functions

Sympathetic innervation of the pancreas originates from the sympathetic preganglionic neurons in the lower thoracic and upper lumbar segments of the spinal cord. Axons from these neurons exit the spinal cord through the ventral roots and supply either the paravertebral ganglia of the sympathetic chain via communicating rami of the thoracic and lumbar nerves, or the celiac and mesenteric ganglia via the splanchnic nerves. The catecholaminergic neurons of these ganglia innervate the intrapancreatic ganglia, islets and blood vessels and, to a lesser extent, the ducts and acini. These differences in the innervation of various portions of the pancreas are evident following sympathetic nerve activation, as sympatho-activation decreases insulin secretion and results in vasoconstriction, while it has little or no effect on ductal and acinar cell secretions. The principal neurotransmitters released by the postganglionic sympathetic neurons that innervate the pancreas are noradrenaline, galanin and neuropeptide Y (NPY).

Retrograde tracing studies using trans-synaptic tracers such as the Bartha strain of pseudorabies virus have revealed the distribution of neurons that supply the sympathetic innervation to the pancreas. Unlike traditional retrograde tracers, trans-synaptic tracers can cross synapses and therefore enable identification of higher order neurons in the neurocircuits that innervate the locus of injection (19). Injections of the virus into the pancreas of vagotomized rats has demonstrated that second order neurons in the sympathetic circuits to the pancreas are located in the brainstem, specifically in the A5 cell group, locus coeruleus, ventrolateral medulla and the caudal raphe, as well as in the paraventricular, lateral and retrochiasmatic nuclei of the

hypothalamus and the prefrontal cortex. Third-order neurons are located in the bed nucleus of the stria terminalis, medial preoptic area, and subfornical organ, in the dorsomedial, ventromedial and arcuate nuclei of the hypothalamus and the central nucleus of the amygdala (18). A schematic representation of the sympathetic innervation of the pancreas is shown in **Figure 1**.

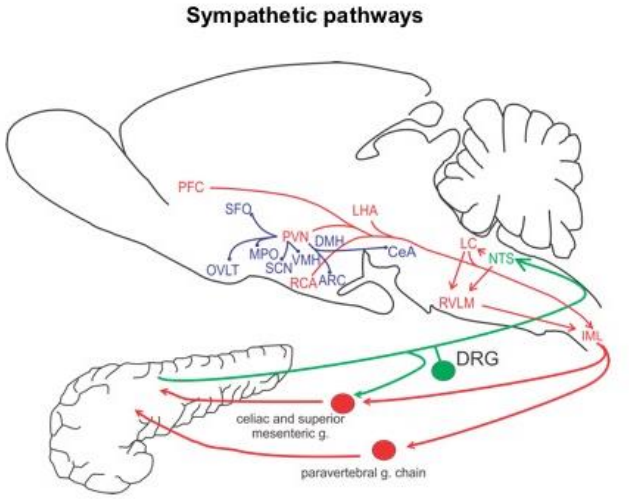

Figure 1: Sympathetic innervation of the pancreas. Abbreviations: Arcuate Nucleus (ARC), Dorsal root ganglion (DRG), Dorsomedial nucleus of the hypothalamus (DMH), Lateral hypothalamic area (LHA), Medial preoptic area (MPO), Nucleus of the tractus solitaries (NTS), Organum vasculosum of the lamina terminalis (OVLT), Prefrontal cortex (PFC), Retrociasmatic area (RCA), Suprachiasmatic nucleus (SCN), Subfornical organ (SFO), Ventromedial hypothalamus (VMH)

Effects of Sympathetic Nervous System Activation on Pancreatic Functions

The role of the sympathetic nervous system in the regulation of pancreatic functions still remains somewhat controversial. Stimulation of the sympathetic nerves elicits diverse effects, including effects on blood pressure, blood flow and hormone release and therefore direct effects of sympathetic nervous system stimulation are difficult to discern from effects secondary to changes in blood flow or hormone release. Nonetheless, the sympathetic nervous system has been shown to affect the function of the endocrine, and to a lesser extent, exocrine pancreas.

Stimulation of the splanchnic nerve, which supplies the sympathetic innervation to the pancreas, has been shown to decrease plasma insulin levels, possibly *via* direct actions of noradrenaline on pancreatic β-cells (2, 3, 6, 26, 33). Splanchnic nerve stimulation also increases catecholamine levels, which have been shown to decrease insulin secretion via α2 adrenoreceptors on pancreatic β cells (26, 31). Furthermore, both splanchnic nerve stimulation and adrenaline administration/release increase glucagon secretion (3, 4, 33). In contrast, disruption of the splanchnic nerve increases insulin levels, suggesting that the sympathetic nervous system exerts a tonic inhibition of the endocrine pancreas. Taken together, these findings indicate that the overall effect of sympathetic nervous system stimulation is to maintain glycemic levels during stressful conditions by decreasing insulin and increasing glucagon secretion.

The effects of sympathetic nerve stimulation on pancreatic exocrine secretions are not as clear. Although the sparse innervation of acinar and ductal by the sympathetic nervous system would suggest that the sympathetic nervous system does not play a major role in the regulation of the exocrine pancreas, some studies have reported that the sympathetic nervous system may exert profound effects on exocrine secretions (51). Electrical stimulation of the splanchnic nerves inhibits, whereas cutting the splanchnic nerves in pigs increases PES, suggesting a tonic inhibition of pancreatic exocrine secretion by the sympathetic nervous system (32). However, studies using more selective stimulation of the sympathetic nervous system have reported conflicting results. Noradrenaline, as well as selective α- and β-adrenoreceptor agonists or antagonists have been shown to decrease, increase or have no effect on pancreatic exocrine secretion (51). These conflicting findings may be due to the fact that these agents influence blood flow, which exerts secondary effects on PES. For

example, vasoconstriction induced by activation of α-adrenoreceptors would result in reduced blood flow to the exocrine pancreas, thus causing a decrease in the amount of fluid secreted by the exocrine pancreas. In support of this suggestion, noradrenergic vasoconstriction has been shown to decrease pancreatic exocrine secretion (11). In addition, denervation of the celiac ganglion in the dog reduced pancreatic secretions by approximately 70%, but increased blood flow by approximately 350%, suggesting that the sympathetic nervous system exerts a tonic effect on both pancreatic exocrine secretion and vasoconstriction (41). Considering these constraints of studying pancreatic exocrine secretion independently of vasoconstriction, it is not clear how much influence the sympathetic nervous system has in the regulation of PES.

4. Parasympathetic innervation of the pancreas

Anatomy of parasympathetic pathways innervating the pancreas

The parasympathetic nervous system provides the major excitatory input to the pancreas. Preganglionic parasympathetic neurons that innervate the pancreas originate in the dorsal motor nucleus of the vagus (DMV) and activate parasympathetic post-ganglionic neurons in the pancreatic ganglia, primarily via activation of nicotinic acetylcholine receptors. Vagal motor output from DMV neurons is conveyed to the GI tract via two pathways, which can be distinguished based on their post-ganglionic neurotransmitters. The excitatory cholinergic pathway releases acetylcholine, which acts on muscarinic M3 and M1 receptors and provides a tonic input to the gastrointestinal viscera. The inhibitory non-adrenergic, non-cholinergic pathway uses nitric oxide, vasointestinal peptide, gastrin-releasing peptide or pituitary adenylate cyclase-activating polypeptide (51, 73). Nicotinic transmission between pre- and post-ganglionic neurons can be modulated by various neurotransmitters and neuromodulators (17, 51). It should also be kept in mind that species differences in the parasympathetic innervation of the pancreas have been reported. In the mouse, parasympathetic axons provide input to both alpha and beta cells, while parasympathetic axons are rare in the human islets (64).

The DMV, which contains preganglionic parasympathetic neurons that supply various regions of the GI tract, shows viscerotopic organization, with neurons that project to different parts of the GI tract distributed in anatomically distinct mediolateral columns. Neurons in the medial part of the DMV project to the proximal GI tract, whereas neurons in the lateral DMV project to the more distal parts of the GI tract (73). Vagal preganglionic DMV neurons that innervate the pancreas are usually located in the left DMV in the area which comprises the hepatic and anterior gastric branches of the vagus, although a few scattered neurons innervating the splenic end of the pancreas are located in the areas corresponding to the celiac branches. Pancreas-projecting DMV neurons can be distinguished from gastric- and intestinal-projecting DMV neurons based on their morphological and electrophysiological properties, further reinforcing the observation that DMV neurons display a highly specialized organization with respect to regulation of various GI functions (16). Some pancreas-projecting DMV neurons display a slowly-developing apamin-insensitive afterhyperpolarization, which is not present in other DMV neurons (15). Compared to gastric-projecting neurons, pancreas-projecting neurons have a longer action potential duration and longer afterhyperpolarizaton decay time. Pancreas-projecting neurons also have higher input resistance, smaller afterhyperpolarization amplitude and a higher firing rate in response to current injections compared to intestinal-projecting neurons. Furthermore, pancreas-projecting neurons have a smaller soma area and a larger diameter than gastric-projecting neurons and fewer segments than gastric- or intestine-projecting DMV neurons (15).

The major input to DMV neurons originates in the adjacent nucleus tractus solitarius (NTS) (**Figure 2**). Although NTS neurons express a wide variety of neurotransmitters and neuromodulators, NTS projects to the DMV primarily via glutamatergic, GABAergic and catecholaminergic inputs (73). Despite this relatively simple neurochemistry, NTS-DMV synapses display a great deal of plasticity and can be modulated by numerous neurotransmitters, neuromodulators, hormones and physiological conditions (10).

Studies using injections of transsynaptic retrograde tracers into the pancreas of sympathectomised rats have demonstrated the distribution of higher order neurons that innervate the pancreas (18, 49, 69). These studies have revealed that neurons that comprise the parasympathetic circuitry to the pancreas show a wider distribution compared to the neurons involved in the sympathetic innervation to the pancreas, with some regions overlapping those that comprise sympathetic inputs to the pancreas (51). In addition to the NTS, second order neurons that innervate the pancreas are located in the area postrema, accessory nucleus of the spinal trigeminal nerve, raphe pallidus, raphe obscurus, substantia reticulata, ventrolateral medulla and the A5 area (**Figure 2**). Parasympathetic second order neurons are also located in the hypothalamic areas, namely the paraventricular, lateral, dorsomedial and arcuate nuclei; medial preoptic area, retrochiasmatic area, subfornical organ, bed nucleus of stria terminalis. Furthermore, higher order neurons have been detected in the prefrontal, piriform and gustatory cortices, and these neurons provide anatomical basis for the cephalic phase of exocrine secretion (18, 50).

Effects of parasympathetic stimulation on pancreatic functions

Parasympathetic innervation plays a major role in the regulation of pancreatic functions. Activation of the vagus nerve directly affects pancreatic exocrine and endocrine secretion (12, 42, 43, 60, 62). Electrical stimulation of the DMV or the NTS

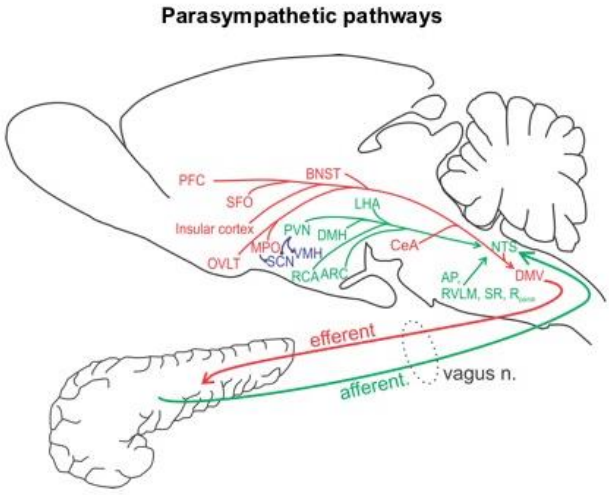

Figure 2: Parasympathetic pathways innervating the pancreas.
Abbreviations: Area postrema (AP), Arcuate Nucleus (ARC),Bed nucleus of the stria terminalis (BNST), Dorsomedial nucleus of the hypothalamus (DMH), Dorsal motor nucleus of the vagus (DMV), Lateral hypothalamic area (LHA), Medial preoptic area (MPO), Nucleus of the tractus solitarius (NTS), Organum vasculosum of the lamina terminalis (OVLT), Prefrontal cortex (PFC), Paraventricular nucleus (PVN), Retrochiasmatic area (RCA), Suprachiasmatic nucleus (SCN), Subfornical organ (SFO), Ventromedial hypothalamus (VMH),

increases insulin secretion (34), as do microinjections of the $GABA_A$ receptor antagonist bicuculline (8, 56). In addition, the vagus nerve modulates the intrinsic pacemaker activity of the pancreas, which is responsible for pulsatile insulin secretion, indeed patients with complete resection of the subdiaphragmatic vagus display a longer periodicity of plasma insulin oscillations (74).

The vagus nerve also plays a crucial role in the regulation of PES. Effects of peptides that modulate pancreatic secretions, such as cholecystokinin (CCK), somatostatin, calcitonin gene-related peptide (CGRP), and pancreatic polypeptide (PP), are vagally mediated (20). Furthermore, vagotomy has been shown to almost completely abolish pancreatic exocrine secretion induced by feeding or by pharmacological or electrical stimulation (22, 45, 46), whereas disinhibition of the DMV by

microinjections of the $GABA_A$ receptor antagonist bicuculline increase pancreatic exocrine secretion (9).

The cephalic phase response, which refers to the release of gut hormones and digestive enzymes before the ingested nutrients have induced a systemic hormonal response, is also dependent on the vagus nerve and its inputs from the gustatory, piriform, and prefrontal cortices (17). In fact, vagally-mediated exocrine secretion in the cephalic phase accounts for a significant portion of total postprandial enzyme secretion (5), suggesting that inputs from higher CNS centers to pancreas-projecting DMV neurons play an important role in regulation of PES.

5. Neurotransmitters in central pathways regulating the pancreas

The brainstem plays an important role in the regulation of autonomic outflow to the pancreas. The NTS and the DMV have reciprocal connections with higher CNS regions, and these connections contain many neurotransmitters and neuromodulators that influence efferent outflow to the pancreas. In addition to receiving inputs from other CNS regions, the dorsal vagal complex is a circumventricular organ with fenestrated capillaries, which expose it to the influence of circulating hormones (73). While autonomic output to the pancreas can be regulated by numerous substances, we will focus on the neurotranmsitters that have been most extensively studied.

GABA and Glutamate

GABA and glutamate provide major inhibitory and excitatory synaptic inputs to pancreas projecting DMV neurons, respectively. GABA is the main inhibitory neurotransmitter in the CNS and is the principal neurotransmitter regulating vagal outflow to the pancreas. Microinjections of the $GABA_A$ receptor antagonist bicuculline into the dorsal vagal complex increase pancreatic exocrine secretion (7, 56) and glucose-stimulated insulin secretion (54), suggesting that GABA exerts a tonic inhibition on both pancreatic exocrine secretion and insulin release (54). In addition to modulating pancreatic functions directly, GABAergic synapses in the DMV are subject to modulation by various other neurotransmitters and hormones. Studies from our laboratory have shown that GABAergic synapses impinging on pancreas-projecting DMV neurons can be modulated by PP, GLP-1, CCK, as well as metabotropic glutamate receptor agonists (10).

Although glutamate is one of the principal neurotransmitters in synapses impinging onto pancreas-projecting DMV neurons, it does not appear to exert a major role on pancreatic functions under control conditions. In fact, microinjections of ionotropic glutamate receptor antagonist kynurenic acid into the DMV do not affect pancreatic exocrine secretion in control rats (9). However, glutamatergic synapses impinging on pancreas-projecting DMV neurons are subject to modulation by various neurotransmitters and hormones (10). Similar to GABAergic synapses, glutamatergic synapses are modulated by PP, GLP-1 and CCK, as well as by metabotropic glutamate receptors (8, 16, 77-79).

Both GABAergic and glutamatergic synapses impinging on pancreas-projecting DMV neurons express metabotropic glutamate receptors (mGluR), which have also been shown to affect pancreatic functions (8). Unlike the ionotropic glutamate receptors, which couple 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. There are eight known subtypes of mGluRs, which belong to three different groups (group I II and III mGluRs), each of which has unique pharmacological characteristics (10). Both GABAergic and glutamatergic synapses impinging on pancreas-projecting DMV neurons express group II and group III mGluRs and activation of either receptor type decreases inhibitory and excitatory synaptic transmission (8). These observations suggest that

glutamate released from the synaptic terminals in the DMV not only activates pancreas-projecting neurons postsynaptically, but also modulates synaptic transmission onto these neurons. Microinjections of the group II mGluR agonist into the dorsal vagal complex increases pancreatic exocrine secretion and decreases plasma insulin levels, whereas microinjections of the group III mGluR agonist decreases plasma insulin, without affecting pancreatic exocrine secretion (8). These findings further support the suggestion that mGluRs modulate pancreatic functions via actions on pancreas-projecting DMV neurons. Our laboratory has shown that the responsiveness of DMV neurons to the group II mGluR agonist is altered in a rat model of acute pancreatitis, suggesting that these receptors may play a role in the development of pathological conditions of the exocrine pancreas (9).

Pancreatic polypeptide

Pancreatic polypeptide (PP) is released by the cells of the pancreatic islets of Langerhans after ingestion of a meal. The release of PP is vagally mediated and involves activation of post-ganglionic muscarinic acetylcholine receptors (36). Circulating PP inhibits PES, not via direct actions on the pancreatic acini, but rather via actions on the dorsal vagal complex (81). PP receptors are not expressed by acinar or ductal cells, and isolated acini or ducts are not inhibited by PP (62, 81). Instead, PP receptors are expressed in the dorsal vagal complex, in the area postrema, NTS and DMV (21, 60, 81). Microinjections of PP in the dorsal vagal complex inhibit pancreatic exocrine secretion by modulating vagal cholinergic output, but does not affect basal plasma insulin, somatostatin or glucagon secretion (42, 60), suggesting that PP modulates PES, but not endocrine pancreatic secretions. Electrophysiological studies from our laboratory have demonstrated that approximately half of the identified pancreas-projecting DMV neurons respond to PP. In these experiments, PP inhibited both excitatory and inhibitory postsynaptic currents elicited by the stimulation of the NTS and reduced the amplitude of currents stimulated by chemical activation of the area postrema (16). Interestingly, pancreas-projecting DMV neurons that responded to PP did not respond to GLP-1, suggesting that these two peptides affect separate populations of pancreas-projecting neurons.

Cholecystokinin

Cholecystokinin (CCK) is released from enteroendocrine cells in the small intestine in response to ingestion of a meal and exerts various effects along the GI tract, including increased PES, gastric relaxation, decreased gastric acid secretion and reduction of food intake (23, 25). CCK exerts its effects both via paracrine actions on vagal sensory neurons and via actions in the dorsal vagal complex (73). In addition, CCK1 receptors are also present on acinar cells and CCK can therefore directly influence acinar cell function, at least in rodents (reviewed in (20, 80, 82). CCK-1 receptors are expressed on neurons of the dorsal vagal complex and are activated by exogenous administration of CCK. Intraduodenal infusions of casein, a protein known to release endogenous CCK, increased pancreatic exocrine secretion even after vagal afferent fibers were surgically removed, although the response was attenuated. Furthermore, the casein-induced increase in pancreatic exocrine secretion was attenuated after application of CCK-1 receptor blocker in the dorsal vagal complex, suggesting that CCK increases pancreatic exocrine secretion via centrally-mediated mechanisms (76). Electrophysiological studies from our laboratory have shown that CCK excites pancreas-projecting neurons via direct effects on DMV neurons and via effects on excitatory synapses impinging onto these neurons. Neurons that were excited by CCK were also inhibited by PP, suggesting that these peptides affect the same population of pancreas-projecting neurons (78).

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is released from intestinal cells into the circulation, where it binds to receptors on the pancreatic β cells to stimulate insulin release. In addition to its actions on pancreatic βcells, GLP-1 acts via central mechanisms to decrease food intake and increase insulin secretion (24, 30). GLP-1 increases the discharge of fibers from the hepatic branch of the vagus nerve and selective hepatic branch vagotomy attenuated GLP-1-induced increase in insulin secretion (58, 59). GLP-1 administration also increases the expression of c-fos, an intermediate early gene and a marker of neuronal activation, in the NTS (75), providing further evidence for central effects of GLP-1. Studies from our laboratory have shown that GLP-1 increases the frequency of excitatory and inhibitory synaptic inputs to pancreas-projecting neurons in the DMV (8, 77) and that microinjections of exendin-4, a GLP-1 analogue, into the dorsal vagal complex increased plasma insulin levels (8). Taken together, these findings suggest that GLP-1 increases pancreatic endocrine secretions via actions on DMV neurons as well as pancreatic β cells.

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) modulates pancreatic secretions via both direct and indirect actions. Serotonin-containing neurons innervate the pancreas, stomach and small intestine and it has been suggested that serotonin inhibits pancreatic exocrine secretion via activation of presynaptic receptors on cholinergic neurons, although this mechanism has not been fully investigated (51).

Serotonin also modulates pancreatic exocrine secretion via excitation of vagal afferent fibers (44, 85). Vagal deafferentation and serotonin-3 receptor antagonists have been shown to block an increase in pancreatic exocrine secretion induced by intraduodenal carbohydrates or mucosal stimulation (44). It has also been demonstrated that serotonin and CCK have synergistic actions in the regulation of pancreatic secretion. This suggestion is supported by the finding that the CCK-1 receptor antagonists attenuate the ability of serotonergic agonist to excite pancreatic vagal afferent fibers (55). This interaction between serotonin and CCK may provide a means to finely tune the regulation of the neural control of pancreatic functions.

Thyrotropin-releasing hormone

Thyrotropin-releasing hormone (TRH) receptors, as well as TRH-immunoreactive axons that originate from the medullary raphe, the parapyramidal nuclei and the hypothalamus are expressed in the dorsal vagal complex (72). Intracerebroventricular and intra-DVC injections of TRH increase pancreatic exocrine secretion and this effect is prevented by vagotomy, ganglionic blockade with hexamethonium, blockade of post-ganglionic transmission with atropine or by a VIP antagonist (39, 52, 61), suggesting that TRH-induced increase in pancreatic exocrine secretion is vagally mediated.

Acetylcholine

The hypothalamus plays an important role in modulation of pancreatic secretions. Electrical stimulation of the ventromedial anterior hypothalamus increases, whereas stimulation of the posterior hypothalamus decreases pancreatic secretions (28). It has been suggested that hypothalamic nuclei that modulate pancreatic secretions receive cholinergic inputs from higher centers in the CNS. Microinjections of muscarinic receptor antagonists into the lateral hypothalamus or the paraventricular nucleus of the hypothalamus inhibited basal and stimulated pancreatic exocrine secretion and central depletion of neuronal acetylcholine stores had similar effects (47). In contrast, microinjection of muscarinic receptor agonists into the hypothalamus increased pancreatic exocrine secretion (74). Cholinergic inputs to the hypothalamus originate in the lateral septum and

the lateral parabrachial nucleus, which provide a major influence on hypothalamic neurons that project to the dorsal vagal complex (47).

Orexin

Neurons in several regions in the CNS, including the ventromedial hypothalamus, NTS and the DMV, can directly sense changes in glucose levels. The lateral hypothalamic area contains neurons that are activated by hypoglycemia (glucose-inhibited neurons) and those that are activated by hyperglycemia (glucose-excited neurons) and is known to modulate the efferent outflow to the pancreas (53, 84). Orexin-containing neurons in the lateral hypothalamic area project to the parasympathetic and sympathetic preganglionic neurons that innervate the pancreas (18) and microinjection of orexin-A antagonist into the lateral hypothalamic area decreases pancreatic vagal nerve activity (84). These observations suggest that changes in peripheral glucose levels activate glucose-sensitive orexin neurons in the lateral hypothalamic area, which, in turn, activates pancreas-projecting neurons in the DMV.

6. Evidence for distinct regulation of endocrine and exocrine pancreas

Several lines of evidence suggest that vagal circuits that modulate pancreatic exocrine secretion are separate from those that regulate pancreatic endocrine secretions. At the level of the pancreas, vagal innervation shows an anatomical gradient, with innervation being more dense at the head compared to the tail of the pancreas (12). The influence of vagal stimulation on pancreatic exocrine secretion and endocrine secretions depends on either the frequency of vagal stimulation or the frequency of action potentials in DMV neurons (10). Furthermore, although vagal celiac branches innervate 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 (13). This finding suggests that celiac branches innervate targets other than pancreatic α and β cells. Taken together, these observations suggest that vagal circuits are organized in a highly specific manner and that separate circuits may regulate different pancreatic functions.

Further evidence for distinct circuits regulating exocrine and endocrine pancreatic secretions came from recent studies in our laboratory. Pancreas-projecting neurons in the DMV that regulate pancreatic exocrine secretion can be distinguished from those regulating insulin secretion based on their neurochemical and pharmacological properties (7, 8, 77). Electrophysiological studies from our laboratory have shown that pancreas-projecting neurons that respond to GLP-1 do not respond to PP or CCK (7, 76), whereas the majority of neurons that respond to CCK also respond to PP (7). This observation suggested that pancreas-projecting neurons in the DMV comprise at least two distinct neuronal populations, one of which responds to GLP-1 and the other to CCK and PP. This finding also raised the possibility that the two populations of neurons may regulate separate pancreatic functions. In support of this suggestion, CCK and PP have been shown to modulate PES, whereas GLP-1 modulates insulin release (10). We have shown that microinjections of GLP-1 into the DVC increase plasma insulin levels, but have no effect on PES, whereas microinjections of CCK and PP in the DVC increase pancreatic exocrine secretion (8). Furthermore, we have demonstrated that in rats with copper deficiency, which selectively destroys the exocrine pancreas while leaving the islets of Langerhans unaffected, DMV neurons display a diminished responsiveness to CCK and PP, peptides that selectively regulate pancreatic exocrine secretion (7). This evidence further supports the idea that separate neuronal populations within the DMV regulate pancreatic exocrine secretion and insulin release.

DMV neurons that regulate pancreatic exocrine secretion can also be distinguished from those that regulate insulin release based on their responses to metabotropic glutamate receptor

(mGluR) agonists and antagonists (8). Using single-cell patch-clamp, we demonstrated that both group II and group III mGluRs are present on excitatory (glutamatergic) and inhibitory (GABAergic) synapses impinging on identified pancreas-projecting neurons in the DMV (8). Application of a group II mGluR (mGluRII) agonist reduced the frequency of postsynaptic currents in the vast majority of excitatory (89%) and inhibitory (71%) synaptic terminals, whereas application of mGluRIII agonist affected a smaller proportion of excitatory (65%) and inhibitory (58%) synapses. All neurons that responded to the mGluRIII agonist also responded to the mGluRII agonist, whereas another population of neurons responded only to mGluRII agonist. Further analysis revealed that a majority of neurons that responded to the mGluRIII agonist also responded to the GLP-1 analogue exendin-4, but not to CCK or PP. Conversely, neurons that did not respond to the mGluRIII agonist responded to PP and CCK, but not to exendin-4. These findings suggested that group III mGluRs modulate the activity of a specific subpopulation of pancreas-projecting neurons in the DMV that has a unique neurochemical phenotype and raised the possibility that this population of neurons modulates a specific pancreatic function, namely insulin secretion (8).

In order to determine the roles of these neuronal populations in modulating pancreatic functions, we conducted a series of *in vivo* experiments using DVC microinjections while monitoring pancreatic exocrine secretion and insulin secretion. Microinjections of the mGluRII agonist into the DVC dose-dependently increased pancreatic exocrine secretion and decreased plasma insulin levels, whereas microinjections of the mGluRIII agonist decreased insulin levels, but had no effect on PES. Taken together with the patch-clamp data described earlier, these findings suggested that DMV synaptic terminals that express mGluRIII modulate insulin release, whereas terminals that express mGluRII modulate both pancreatic exocrine secretion and insulin release (8).

Further support for the regulation of endocrine and exocrine function by separate pathways came from studies using models of pancreatic disorders. A study from our laboratory has shown that copper deficiency, which selectively destroys the exocrine pancreas while leaving the endocrine pancreas intact, affects DMV neurons that regulate pancreatic exocrine secretion (7). Intraduodenal infusions of CCK or casein, potent stimulators of pancreatic exocrine secretion in control conditions, failed to increase pancreatic exocrine secretion in copper deficient rats. This lack of an effect was accompanied by a reduction in the number of tyrosine hydroxylase-immunoreactive neurons in the DMV, suggesting that there was a reduction in catecholaminergic regulation of pancreatic exocrine secretion (7). Furthermore, electrophysiological evidence showed that fewer pancreas-projecting DMV neurons responded to CCK and PP in copper deficient rats compared to controls. Interestingly, while copper deficiency affected postsynaptic responses to these peptides, it did not affect presynaptic responses, suggesting that copper deficiency selectively affects pancreas-projecting neurons in the DMV, while leaving the sensory synaptic inputs onto these neurons intact (7).

Synaptic inputs to pancreas-projecting DMV neurons are also affected by acute pancreatitis, a severe, and sometimes fatal, disorder of the exocrine pancreas. Acute pancreatitis is characterized by premature activation of zymogens leading to acinar cell injury, release of chemokines and cytokines and an inflammatory response (71). Although early events that lead to the development of acute pancreatitis are initiated in the pancreas, it has also been shown that severity of acute pancreatitis is modulated by the CNS. Our laboratory, for example, has demonstrated that acute pancreatitis alters the sensitivity of pancreas-projecting DMV neurons to group II mGluR agonist, which, in turn, changes the balance of glutamatergic and GABAergic synaptic inputs to DMV neurons. Specifically, we demonstrated that acute pancreatitis decreases the response of glutamatergic synaptic terminals

in the DMV to group II mGluR agonist. In contrast, group III mGluRs do not appear to be affected by acute pancreatitis (9). These findings suggest that acute pancreatitis selectively affects DMV neurons involved in the regulation of pancreatic exocrine secretion and further supports the notion that exocrine and endocrine pancreatic secretions are regulated by separate neuronal populations.

7. Summary

The pancreas plays an important role in the control of nutritional homeostasis. Pancreatic functions are regulated by finely tuned inputs from the sympathetic and parasympathetic branches of the autonomic nervous system, which perform as an integrated neural circuit to adapt exocrine and endocrine secretions to constantly changes environmental and physiological conditions.

An increasing amount of experimental evidence indicates that autonomic pathways involved in regulation of pancreatic function are organized in a highly specific manner, with distinct pathways regulating endocrine and exocrine secretions. It is therefore important to understand how specific neural pathways regulate pancreatic secretions and to identify neurotransmitter and receptor phenotypes involved in regulation of specific pancreatic functions. Data from our laboratory have shown that DMV neurons that regulate exocrine and endocrine secretions can be differentiated by their responses to CCK, PP and GLP-1, as well as their responses to group II and group III mGluRs. Thus, in order to completely understand the role of the central nervous system in the regulation of pancreatic functions, future studies should be aimed at further characterizing neuropeptides and receptors involved in regulation of various pancreatic functions. Data from animal models suggests that pathological conditions that affect the pancreas, including diabetes and acute pancreatitis, induce neurochemical changes in DMV neurons. Therefore, understanding of specific pathways that regulate exocrine and endocrine secretions would provide novel targets for the treatment of these disorders. Further studies of neuropeptides, their receptors and receptor pharmacology in pathological conditions are needed to fully understand the contribution of neural regulation in disorders of the pancreas.

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