Relationships Between the Autonomic Nervous System and the Pancreas Including Regulation of Regeneration and Apoptosis

Recent Developments

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Abstract: Substantial new information has accumulated on the mechanisms of secretion, the development, and regulation of the gene expression, and the role of growth factors in the differentiation, growth, and regeneration of the pancreas. Many genes that are required for pancreas formation are active after birth and participate in endocrine and exocrine cell functions. Although the factors that normally regulate the proliferation of the pancreas largely remain elusive, several factors to influence the growth have been identified. It was also reported that the pancreas was sensitive to a number of apoptotic stimuli. The autonomic nervous system influences many of the functions of the body, including the pancreas. In fact, the parasympathetic nervous system and the sympathetic nervous system have opposing effects on insulin secretion from islet β cells; feeding-induced parasympathetic neural activity to the pancreas stimulates insulin secretion, whereas stress-induced sympathetic neural activity to the pancreas inhibits insulin secretion. Moreover, it has been reported that the autonomic nervous system is one of the important factors that regulate pancreatic regeneration and stimulate the carcinogenesis. The present review focuses on the relationships between the autonomic nervous system and the pancreas, and furthermore, presents evidence of the autonomic nervous system–related pancreatic regeneration and carcinogenesis.

Key Words: pancreas, regeneration, apoptosis, the autonomic nervous system

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Many genetic factors required for pancreas formation are active after birth and participate in endocrine and exocrine cell functions (Fig. 1). The mouse pancreas, an immature organ at birth, reaches its adult size and morphology after weaning (3 weeks of age).

In pancreatic regeneration after cholecystokinin analog cerulein-induced acute pancreatitis, 2 separate peaks of DNA synthesis have been reported. The first peak corresponded with duct cell and mesenchymal cell proliferation, and the second peak was associated with acinar cell proliferation.[1] However, in this model, islet cells did not regenerate. Formation of new β cells can take place via 2 pathways: replication of already differentiated β cells and neogenesis from putative islet stem cells. It is generally admitted that neogenesis mostly takes place during fetal and neonatal life. In adulthood, little increase in the β-cell number seems to occur. For as yet unknown reasons, the β cell has a remarkably limited proliferative potential, and the production of new β cells by division normally is about 3% per day. However neogenesis from the ductal epithelium is feasible in the adult gland after partial pancreatectomy, ligation, or cellophane wrapping or in transgenic mice whose β cells are induced to express interferon-gamma.[2–4] Moreover, in pregnancy, a marked hyperplasia of the β cells is observed both rodents and humans. On the contrary, the high incidence of gestational diabetes, around 1%, may be due to a lack of compensatory increase in the β-cell mass.[5] The most usual substances to induce diabetes in the rat are alloxan and streptozotocin.[6] Clarifying the pattern of β-cell neogenesis in the alloxan-perfused, β cell–depleted segment of glucose-intolerant mice, first duct cells proliferated in the perfused segment, then cells coexpressing multiple islet hormones and transcription factors such as pancreatic duodenum homeobox protein-1 (Pdx-1), Nkx2.2, Islet1, and paired box gene (Pax-6) were observed in duct cells, and newly formed islet-like cell clusters containing β cells were recognized. In residual β cell–depleted islets, glucagon or somatostatin and Pdx-1 double-positive immature endocrine cells were recognized.[7] Glucagon or somatostatin, insulin, and Pdx-1 triple-positive cells then appeared, and these cells appeared to undergo terminal differentiation into β cells. It was demonstrated by at least 2 different processes of β-cell neogenesis, ie, formation of new

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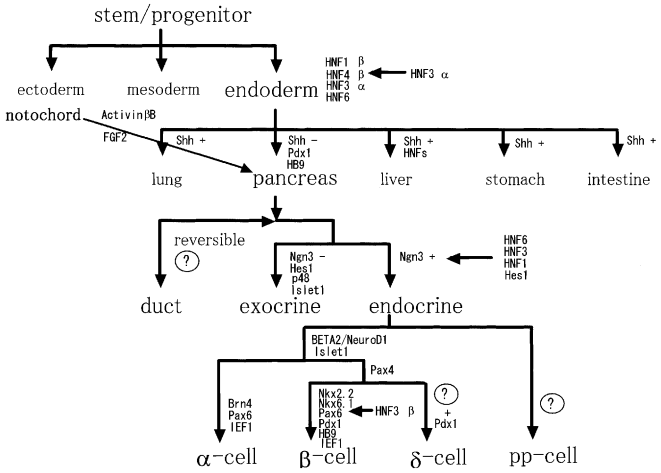

FIGURE 1. The hierarchy of transcription factor in the developing pancreas. Brn-4, Brain-4; HNF, hepatocyte nuclear factor; Ngn3, neurogenin 3; Pdx-1, pancreatic duodenum homeobox protein-1; Shh, sonic hedgehog Hes-1, hairy/enhancer of split 1; Pax6, paired box gene 6.

islet-like cell clusters from ductal epithelium and redifferentiation of residual non–β islet cells occurred in this model. In addition, transcription factors that appear in the processes of endocrine cell development may also play essential roles during β-cell neogenesis from duct cells.

Apoptosis is a highly regulated process of cell death that plays a major role in normal tissues, both in embryogenesis and in mature tissue homeostasis and in the pathogenesis of a wide variety of diseases.[8] Pancreatic β cells are sensitive to a number of apoptotic stimuli. Fas signaling represents a final common pathway responsible for β-cell apoptosis and impaired β-cell proliferation in response to elevated glucose concentrations and to cytokines.[9] Moreover, human islets normally express Fas ligand (Fas L) but not the Fas receptor. Upregulation of the Fas receptor by elevated glucose levels may contribute to β-cell destruction by the constitutively expressed Fas L independent of an autoimmune reaction.[9] Apoptosis also plays a significant role in acinar loss in chronic pancreatitis. Consistent with this, the expression of the Fas/FasL system is also involved in acinar cell apoptosis.[10] A supramaximal dose of the cerulein leads to edematous pancreatitis with subsequent acinar cell destruction predominantly by apoptosis.[11] Moreover, estradiol dose-dependently attenuates acinar cell apoptosis and development of chronic pancreatitis.[12]

As mentioned above, substantial new information has accumulated on the mechanisms of the secretion, the development and regulation of the gene expression, and the role of growth factors in the differentiation, growth, and regeneration of pancreas. However, in recent years, there has been increasing interest in the relationships between the pancreas and the autonomic nervous system. Here, the current status of studies aimed at understanding these relationships are reviewed. The present review focuses on the evidence of the autonomic nervous system–related pancreatic regeneration and carcinogenesis.

THE AUTONOMIC NERVOUS SYSTEM AND PANCREAS

The autonomic nervous system influences many of the functions of the body, including those of the cardiovascular system, kidneys, liver, pancreas, gastrointestinal tract, and glands.[13] Moreover, it is well known that autonomic abnormalities and neuropathy tend to increase with age.[14] Classically, the autonomic nervous system uses 2 interconnected neurons to control effector functions and is divided into 2 systems, the sympathetic and the parasympathetic nervous systems, according to the location of the preganglionic cell bodies. However, there are indications suggesting that these 2 systems are not always independent of each other but display anatomic interactions[15] or share similar neurotransmitters.[16]

The mammalian pancreas embryologically develops from an outgrowth of the primitive foregut and is richly innervated, being composed of a variety of myelinated or unmyelinated nerve fibers, thick nerve bundles, and aggregates of neural cell bodies known as intrapancreatic ganglia. These ganglionic structures are randomly scattered throughout the pancreatic parenchyma and represent the intrinsic neural component of the pancreatic nerve supply.[17] The 2 main extrinsic components are anatomically identified in the vagus nerves (anterior and posterior branches) and the splanchnic nerve trunks (Fig. 2). The vagus nerves reach the pancreas directly or, alternatively, they pass across the preaortic chain of the sympathetic ganglia. Postganglionic sympathetic fibers, whose neural cell bodies are located in the superior mesenteric and celiac gan-

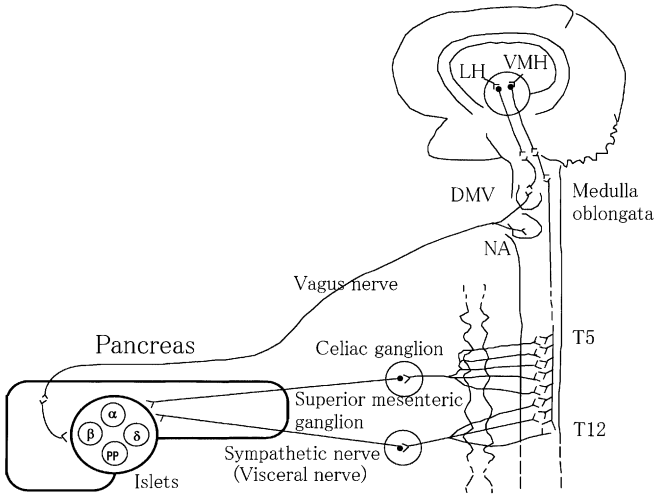

FIGURE 2. Relationships between pancreatic autonomic nervous system and central nervous system. DMV, nucleus dorsalis nervi vagi; LH, lateral hypothalamus; NA, nucleus ambiguus; VMH, ventromedial hypothalamus.

glia, run with the splanchnic nerves. The afferent system, primarily involved in sensory/pain transmission to the central nervous system, is composed of thin unmyelinated fibers running with either the parasympathetic pathways (vagi) or the sympathetic inputs (splanchnic nerves) (Fig. 3).[17]

Comparable with the enteric nervous system, an intrapancreatic nervous system exists to enable a degree of independence of the pancreas when cut off from the central nervous system and the gut. The morphologic equivalent is an intrapancreatic ganglionated plexus with terminal axons supplying both the endocrine and exocrine portions of the organ.[18] The pancreatic ganglia are the nervous integration centers of the pancreatic exocrine (and endocrine) secretion. They receive input from vagal preganglionic, sympathetic postganglionic, sensory, and enteric fibers. Postganglionic nerve fibers surround almost every acinus, forming a periacinar plexus containing cholinergic, noradrenergic, peptidergic, and nitrergic fibers, which in majority terminate at the acinar cells.[18]

Parasympathetic Nerve

The parasympathetic nerve fibers innervating the pancreas originate mainly from the dorsal vagal nucleus and partly from the nucleus ambiguous of the brain stem[19] (Figs. 2 and 3). Most of these fibers run within the posterior vagal truncus[20] near the small curvature of the stomach and the pylorus to the pancreas.[21] Some of the fibers run intramurally along the pylorus and the proximal part of the duodenum before joining the pancreas.[22] The majority of the vagal preganglionic fibers terminate on the pancreatic ganglia, performing interneuronal

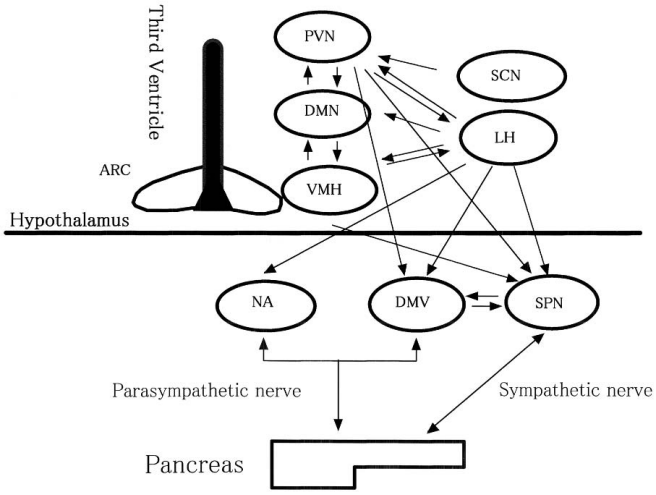

FIGURE 3. Simplified schema of the putative neural network in pancreas and hypothalamus. ARC, arcuate nucleus; DMV, nucleus dorsalis nervi vagi; LH, lateral hypothalamus; PVN, paraventricular nucleus of the hypothalamus; NA, nucleus ambiguus; SCN, suprachiasmatic nucleus; SPN, spinal cord neuron; VMH, ventromedial hypothalamus.

synapses. Pancreatic ganglia were most abundant in the head/neck region within 1–2 cm of the walls of the antrum, pylorus, and duodenum but were also readily found in the main body of the pancreas located adjacent to the celiac–superior mesenteric plexus. They enter the pancreas along the vessels and terminate at intrapancreatic ganglia, from which the postganglionic nerves pass to the islets; these nerves penetrate the islets to terminate close to the endocrine cells.[23] That parasympathetic nerves innervate the islets has been verified in a number of species by light and electron microscopy after staining pancreatic sections with cholinesterase.[23] Preganglionic vagal fibers release acetylcholine (ACh) that binds to nicotinic receptors on intraganglionic neurons. Postganglionic vagal fibers release several neurotransmitters: ACh, vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), nitric oxide (NO), and pituitary adenylate cyclase-activating polypeptide (PACAP).[24] The importance of the cholinergic innervation of the endocrine pancreas is attested to by the presence of 10-fold higher activity of choline acetyltransferase and acetylcholinesterase (the enzymes involved, respectively, in the synthesis and the degradation of ACh) in the islets than in the surrounding exocrine tissue.[25] Cholinergic synapses with endocrine cells have been observed in some species.[26]

ACh, a major neurotransmitter from the autonomic nervous system, regulates the cholinergic stimulation through interactions with muscarinic receptors. Cholinergic agents elicit pancreatic secretion via stimulation of muscarinic receptors that comprise 5 distinct subtypes (M1–M5). Iwatsuki et al,[27] in a study on anesthetized dogs, showed that bethanechol-stimulated pancreatic secretion is mediated by the M3 type of muscarinic receptors. The study of Kato et al[28] on rat pancreatic acini also suggests that M3 muscarinic receptors play an important role in pancreatic exocrine secretion. In a study on conscious, neonatal calves, it was shown that the specific M3 muscarinic receptor antagonist 4-diphenylacetoxy-N-methylpiperidine-methiodide (4-DAMP) significantly decreased the interdigestive outflow of pancreatic juice and diminished periodic pancreatic secretion.[29] Miguel et al[30] reported that, by measuring insulin release from insulin-secreting BRIN BD11 cells treated with ACh in the presence of various muscarinic receptor antagonists, muscarinic toxin-3 (M4 antagonist) and methoctramine (M2 antagonist), increased ACh-stimulated insulin secretion and that pirenzepine (M1 antagonist) and hexahydro-sila-difenidol p-fluorohydrochloride (M3 antagonist) inhibited ACh stimulation. Therefore, ACh may act on different receptor subtypes producing both a stimulatory and an inhibitory action on insulin release. Although prominent smooth muscle contractions are important for autonomic organs, the role of each subtype has not been characterized precisely because of the poor selectivity of the currently available muscarinic ligands. By generating a mutant mouse line ($M2^{-/-}M3^{-/-}$ mice) lacking M2 and M3 receptors, the relative contributions of M2 and M3 receptors in

vitro was approximately 5% and 95% for the detrusor muscle contraction and approximately 25% and 75% for the ileal longitudinal muscle contraction, respectively.[31] Thus, M1, M4, or M5 receptors do not seem to play a role in such contractions. Despite the complete lack of cholinergic contractions in vitro, $M2^{-/-}M3^{-/-}$ mice were viable, fertile, and free of apparent intestinal complications. Thus, cholinergic mechanisms are dispensable in gastrointestinal motility. The receptor for the major pancreatic ACh belongs to the superfamily of G protein–coupled or 7 transmembrane domain receptors. ACh binding protein is a homopentamer of α-like subunits that are 24% homologous to the neuronal α7 subunit.[32] Moreover, ACh binding protein contains many of the structural cornerstones that give nicotinic receptors their unique signature.

Cholecystokinin (CCK) binds to CCK-A receptors on afferent neurons, stimulating pancreatic exocrine secretion via a vagovagal loop.[33] However, some investigators observed that human pancreatic acini did not respond to CCK agonists and did not express high levels of CCK receptors, suggesting that CCK stimulation of human pancreatic acinar cells is likely regulated by an indirect mechanism of stimulation of afferent neurons.[34] When plasma CCK does not increase during bile and trypsin infusion, a mechanoreceptor of the vagal afferent nerve responds to the increased ductal pressure, inhibiting pancreatic protein secretion as a mechanism of self-protection.

The basal exocrine secretion of the pancreas is maintained at a constant level in conscious rats.[35] Chen et al[36] showed that islets from young obese mice release more insulin than islets from their lean littermates at different glucose concentrations and that this effect may be mediated by increased pancreatic cholinergic stimulation. Meyer et al[37] reported that continuous intraduodenal infusion of amino acids stimulates pancreatic secretion in the dog. Such results indicate that a reflex increase in efferent activity has occurred in the pancreatic branch of the vagus. Moreover, it has been thought that the vagus nerve–mediated regulation of insulin secretion is composed of the vagal hepatic and vagal pancreatic efferents systems. Under starvation, vagal hepatic afferent impulses tonically suppressed the efferent vagal system in the central nervous system, which promotes insulin release.[38] This concept is supported by a report that electrical stimulation of the cut end of the afferent hepatic vagal branch decreases plasma insulin levels and that an acute section of the hepatic vagus nerve increases plasma insulin concentration.[39] Furthermore, electrical stimulation of the vagal trunks in animals[40] and efferent vagal activation induced by insulin hypoglycemias in humans[41] or by administration of the glucose antagonist 2-deoxyglucose in dogs[42] have been shown to cause strong stimulation of pancreatic enzyme output.

The enteric peptides capable of inhibiting pancreatic exocrine secretion include peptide YY (PYY), oxyntomodulin, glicentin, glucagon-like peptide-1 (GLP-1), somatostatin, and pancreatic polypeptide (PP). Most of these substrates suppress pancreatic enzyme secretion in vivo but do not act directly on the acinar cells to suppress enzyme release. All these peptides appear to inhibit pancreatic secretion by modulating vagal parasympathetic outflow.[34] PYY administration reduces meal-stimulated pancreatic exocrine secretion in various species. PYY receptors have been localized to the dorsal vagal complex in the brain stem,[43] but the location of PYY inhibition of pancreatic exocrine secretion has only recently been elucidated. Oxyntomodulin and glicentin inhibit pancreatic secretion via a vagal-dependent pathway,[44] and GLP-1 mediates its inhibitory effects via central GLP-1 receptors or via receptors associated with afferent pathways to the brainstem.[43] The activation of the GLP-1 receptor has been shown to have an important role in the functional activity of islet β cells and in the expansion of the islet cell mass. GLP-1 receptor signaling also directly modifies the susceptibility to apoptotic injury and provides a new potential mechanism linking GLP-1 receptor activation to preservation or enhancement of β-cell mass in vivo.[45] Furthermore, GLP-1 upregulates expression of β-cell genes (glucose transporter-2, glucokinase, insulin, and Pdx-1) and promotes β-cell neogenesis and differentiation of ductal cells into insulin-secreting cells.

Gastrin-releasing peptide (GRP), a neurotransmitter and a paracrine factor, has been localized to nerve fibers innervating pancreatic acini and has been shown to dose-dependently increase secretin-evoked pancreatic fluid and amylase secretion.[46] Flowe et al[47] demonstrated that GRP stimulated amylase release in a dose-dependent manner from rat pancreatic lobules in vitro, and this effect was inhibited by treatment with tetrodotoxin and atropine. Therefore, there is a possibility that GRP regulates amylase secretion by a neurally mediated mechanism involving ACh release from intrapancreatic neurons.

Sympathetic Nerve

Sympathetic innervation of the pancreas originates from preganglionic perikarya located in the thoracic and upper lumbar segments of the spinal cord[48] (Figs. 2 and 3). The myelinated axons of these cells traverse the ventral roots to form the white communicating rami of the thoracic and lumbar nerves that reach the paravertebral sympathetic chain.[49] Preganglionic fibers either communicate with a net of ganglion cells within the paravertebral sympathetic chain or pass through the sympathetic chain, travel through the splanchnic nerves, and reach the celiac[48] and mesenteric ganglia.[48] Ganglia within the paravertebral sympathetic chain and the celiac and mesenteric ganglia give off postganglionic fibers that eventually reach the pancreas. Some sympathetic fibers run within the pancreatic parenchyma, directly terminating on acinar cells. The sympathetic innervation of the exocrine pancreas, however, is modest compared with the islets and the pancreatic blood vessels.[50] The existence of intrapancreatic sympathetic ganglia has also been reported.[51]

The sympathetic nervous system exerts profound effects on the secretion of the hormones. In fact, glucagons and PP secretions are stimulated by sympathetic nerve activation,[52] whereas somatostatin secretion is inhibited.[53] Moreover, epinephrine stimulates glucagon secretion in vivo and in vitro.[54] The sympathetic nervous system serves to maintain or increase glycemia with various conditions of stress such as neuroglycopenia, hypovolemia, or physical exercise. Activation of sympathetic nerves increases circulating glucose and inhibits insulin release from the islet β cells, which might contribute to stress-related diabetes. However, in contrast to cholinergic inhibition, sympathectomy does not perturb the development of chemically induced diabetes in mice.[55] Moreover, it was found that the pretreatment of such rats with reserpine, thereby markedly depleting the pancreatic content of catecholamines, did not affect insulin secretion.[56] Nevertheless, it was found that insulin gene expression was reduced in association with increased islet size after sympathectomy, as judged by in situ hybridization, suggesting that islet sympathetic nerves are of importance for the long-term regulation of islet function.[55]

Adrenoceptors are known as α-1 (α-1A, α-1B, α-1D), α-2 (α-2A, α-2B, α-2C), and β (β-1, β-2, β-3). The localization of adrenoceptors regulating pancreatic secretion is still debated, but some data indicate that β adrenoceptors could be located peripherally on duct cells,[57] whereas α-2 adrenoceptors would be mainly located in the central nervous system.[58] Moreover, α adrenoceptors are more likely neural, certainly present peripherally in intrapancreatic ganglia or preganglionic fibers. The stimulatory effect of β adrenoceptors in water and bicarbonate secretion in the pancreatic juice agrees with previous data[57] as well as the inhibitory effect of α adrenoceptors.[59] In the rat, activation of adrenoceptors thus produces 2 opposite effects on water and bicarbonate secretion, whereas activation of both α and β adrenoceptors inhibit protein secretion. These observations differ from those obtained in the dog, rabbit, and guinea pig, in which adrenergic agonists all inhibit pancreatic secretion.

It is interesting to know about the reinnervation of transplanted organs. Korsgren et al[60] reported that the transplanted rat pancreas becomes reinnervated by mainly sympathetic nerve fibers.

Central Nervous System

To reveal brain regions and transmitter systems involved in control of pancreatic hormone secretion, Buijs et al[61] reported the combined specific vagal and sympathetic denervation with injection of a retrograde transsynaptic tracer, pseudorabies virus, into the pancreas. Consequently, after sympathetic or vagal transsection, first-order neurons were revealed in the dorsal motor nucleus of the vagus (DMV) or in preganglionic spinal cord neurons (SPN), respectively (Fig. 3). A far larger number of cell groups are involved in the control of DMV than of SPN neurons. Examples are given of a high level of interaction between the sympathetic and parasympathetic nervous systems. Several cell groups project to both branches of the autonomic nervous system, sometimes even though the same neurotransmitter is used, eg, oxytocin neurons in the paraventricular nucleus and melanin-concentrating hormone and orexin neurons in the lateral hypothalamus project to both the DMV and SPN. Moreover, the appearance of third-order neurons located in the sympathetic SPN after complete sympathectomy and in the DMV after complete vagotomy illustrates the possibility that motor neurons of the sympathetic and parasympathetic systems may exchange information by means of interneurons. The presence of second-order neurons in prefrontal, gustatory, and piriform cortex may provide an anatomic basis for the involvement of these cortices in the cephalic insulin response. The observation that second-order neurons in both vagal and sympathetic control of the pancreas contain neuropeptides that are known to play a role in food intake indicates a direct association between behavioral and autonomic functions. Finally, the observation of third-order neurons in the suprachiasmatic nucleus (SCN) and ventromedial hypothalamus (VMH) shows the modulatory action of the time of the day and metabolic state, respectively. In addition, electrical stimulation of the SCN also results in an increase in insulin secretion[62] (Fig. 3). Moreover, it has been reported that the VMH does indeed not have detectable projections to the dorsal vagus complex and mainly has major projections within the hypothalamus and to melanin-concentrating hormone neurons located in the dorsal part of the lateral hypothalamus (LH).[61] These anatomic observations indicate that the VMH serves to integrate hypothalamic and peripheral information of the metabolic state without the possibility of transmitting this information directly to the autonomic neurons that control pancreatic hormone secretion.

A study by Bereiter et al[63] on the central nervous system modulation of pancreatic endocrine function and its multiple modes of expression concluded the following: (1) one source of vagal efferent fibers capable of facilitating insulin secretion originated in the rostral half of the nucleus ambiguous; (2) acute lesions of the VMH results in hyperinsulinemia that could be abolished by acute vagotomy; (3) chronic lesions of the VMH increased the secretion of insulin and glucagons and decreased the secretion of somatostatin when the pancreas was subsequently isolated and perfused. These changes were attributed to altered cholinergic activity related to previous VMH lesions because they could be reversed toward normal by atropine infusion or mimicked by the cholinergic agonist methacholine; (4) electrical stimulation of the LH in anesthetized rats produced with an inhibitory component of insulin secretion, probably related to adrenergic stimulation, and a stimulatory component, probably resulting from the release of factor(s) that promote insulin secretion into the blood; and (5) the anatomic organization of the brain of the genetically obese

mouse is abnormal. These abnormalities could be involved in the endocrinological disturbances of these animals.

Calcitonin gene-related protein (CGRP) is widely distributed in the central nervous system and was shown to inhibit pancreatic exocrine via a central vagal site.[64] Central administration of thyrotrophin-releasing hormone (TRH) has been demonstrated to stimulate pancreatic exocrine via excitation of vagal efferent nerves. Moreover, Masuda et al[65] reported that centrally administered somatostatin inhibited TRH-induced pancreatic secretion in a dose-dependent manner. This depends on the fact that central somatostatin selectively inhibits vagal excitation induced by TRH. Furthermore, Miyasaka et al[66] showed that centrally administered somatostatin also diminishes central CGRP-induced inhibition of basal pancreatic exocrine secretion in rats. Masuda et al[65] also investigated the role of centrally administered dopamine on basal pancreatic exocrine secretion in rats. Central dopamine inhibited basal pancreatic secretion in a dose-dependent manner, and pretreatment with a dopamine D1 receptor antagonist blocked this inhibitory effect. Moreover, bretylium, an inhibitor of norepinephrine release, also blocked the inhibitory effect of central dopamine, but vagotomy had no effect. These observations suggest that central dopamine inhibits basal pancreatic secretion via dopamine D1 receptors and by a mechanism involving sympathetic innervation. Furthermore, cocaine- and amphetamine-regulated transcript (CART) peptide is a recently described neuropeptide that has been localized to areas of the central and peripheral nervous systems. CART peptide has stimulatory effects on pancreatic exocrine secretion.[67]

THE AUTONOMIC NERVOUS SYSTEM AND PANCREATIC REGENERATION AND APOPTOSIS

A decreased proliferation rate in pancreatic islet cells 2 and 3 weeks after vagotomy in obese hyperglycemic mice has been demonstrated.[68] A reduced islet mass was observed 150 days after surgery despite similar weight gain as in sham-operated animals.[69] No difference in islet proliferation was observed between vagotomized and sham-operated lean mice.

Experimental hyperactivity of the vagal nerve, induced by lesioning the VMH, produces an increased β-cell proliferation in rats,[70,71] and vagotomy reduces islet proliferation rate in ob/ob mice.[68] However, whether sympathetic nerves affect islet proliferation is not known. As mentioned above, increased islet size and β-cell mass can theoretically also be produced by neogenesis of islets from pancreatic duct cells, which are thought to be the "stem cells" of endocrine islet precursors.[72] To which extent this process is augmented by sympathectomy remains to be studied. It is not unconceivable, though, that the increased islet size after sympathectomy is partially due to elimination of negative regulator of β-cell growth. Moreover, this author recently reported that VMH lesions induce apoptosis in the liver thorough the cholinergic mechanisms,[73] but in the pancreas, apoptosis was not detected by terminal deoxynucleotide transferase-mediated dUTP nick end labeling (TUNEL) methods (unpublished data). Therefore, there is a possibility that the mechanisms be which apoptosis occurs might be different in the liver and in the pancreas of the VMH-lesioned rats. Further investigations are needed to clarify this matter.

It is interesting to know the mechanisms and what physiological role that the autonomic nervous system has in the pancreatic regeneration by comparing with other factors. The author previously reported that the cholinergic mechanism was involved in the pancreatic β cell and exocrine cell proliferations.[71] Therefore, it is possible that transcription factors that appear in the processes of endocrine and exocrine development may play essential roles during these cells proliferations.

THE AUTONOMIC NERVOUS SYSTEM AND CARCINOGENESIS

A possible role for the autonomic nervous system in the mechanism of chemical carcinogenesis has been suggested.[51] It was found that enhanced activity of the sympathetic nervous system stimulates gastric carcinogenesis.[74] Moreover, it was found that chemical sympathectomy with 6-hydroxydopamine significantly reduces the norepinephrine concentration in the gastric wall and the BrdU-labeling index of gastric mucosa and significantly decreases the incidence and number of gastric cancers.[75] Moreover, it was reported that the sympathetic nervous system may have an important effect on pancreatic carcinogenesis.[76]

Gastrin is one of the neuropeptides associated with potent cellular mitogens for a variety of cell types. Previous studies demonstrated that pancreatic carcinoma in rodents express receptors for the peptide hormone gastrin that are not present in normal adult pancreas. In view of abundant literature suggesting that gastrin may promote growth of various gastrointestinal tissues and tumors, the effect of hypergastrinemia on the process of pancreatic carcinogenesis was evaluated. However, McDonald et al[77] reported that hypergastrinemia stimulated an increase in pancreatic weight but did not stimulate development of premalignant lesions or progression to cancer in the azaserine model of rat pancreatic acinar cell carcinoma. Moreover, to determine whether gastrin receptors mediate pancreatic growth or promote carcinogenesis or both, Yen et al[78] created a transgenic mouse that constitutively expresses gastrin receptors in the exocrine pancreas. In both female and male transgenic mice, the expression of the gastrin receptor in the exocrine pancreas is associated with a significant increase in pancreas weight, but it does not appear to promote the development of spontaneous pancreas tumors. On the other hand, to explore the pancreatic function of CCK2/gastrin receptor, Clerc et al[79] reported that ElasCCK2 transgenic mice expressing the human receptor in pancreatic exocrine cells. The transgenic CCK2/gastrin receptor was demonstrated to mediate enzyme release and protein synthesis. Moreover, the

authors suggested a key role of the CCK2/gastrin receptor in the development of pre- and neoplastic lesions of the pancreas. ElasCCK2 mice provided a model for carcinogenesis by transformation and dedifferentiation of acinar cells.

CONCLUSIONS AND FUTURE STUDIES

The current literature indicates that the various factors including the autonomic nervous system regulate the secretion, regeneration and carcinogenesis of the pancreas. Moreover, the central nervous system modulates the regeneration through the autonomic nervous system. Recently, there has been increasing interest in the relationship between the pancreas and autonomic nervous system. However, the specific mechanisms of changes of pancreatic enzymes and increased pancreatic cell proliferation and carcinogenesis caused by the autonomic nervous system including the central nervous system have not yet been clarified. In regard to this matter, future studies should outline a more complete mechanism.

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