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**Autonomic control of pancreatic beta cells: what is known on the regulation of insulin
secretion and beta-cell proliferation in rodents and humans**

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ABSTRACT

Insulin secretion and pancreatic beta-cell proliferation are tightly regulated by several signals such as hormones, nutrients, and neurotransmitters. However, the autonomic control of beta cells is not fully understood. In this review, we describe mechanisms involved in insulin secretion as well as metabolic and mitogenic actions on its target tissues. Since pancreatic islets are physically connected to the brain by nerves, parasympathetic and sympathetic neurotransmitters can directly potentiate or repress insulin secretion and beta-cell proliferation. Finally, we highlight the role of the autonomic nervous system in metabolic diseases such as diabetes and obesity.

KEYWORDS: Insulin, Autonomic nervous system, Muscarinic, Adrenergic.

ABBREVIATIONS

A alpha

Ach acetylcholine

ANS autonomic nervous system

B beta

CNS central nervous system

DMNX dorsal motor nucleus of the vagus

GABA gamma-amino butyric acid

GLP-1 glucagon-like peptide 1

GLUT glucose transporter

GPCR G-protein coupled receptor

GRP gastrin-releasing peptide
GSIS glucose-stimulated insulin secretion
IGF insulin-like growth factor
IR insulin receptor
MR muscarinic receptor
NOD non-obese diabetic
NorE norepinephrine
NTS nucleus of the solitary tract
PACAP pituitary adenylate cyclase-activating polypeptide
PKA protein kinase A
PNS parasympathetic nervous system
PP pancreatic polypeptide
SNS sympathetic nervous system
SSTR somatostatin receptor
T1D type 1 diabetes
T2D type 2 diabetes
TRPV transient receptor potential vanilloid-1
VIP vasoactive intestinal polypeptide

1. Introduction

Secreted by pancreatic beta cells, insulin plays a major role in maintaining energy homeostasis. Insulin secretion is finely regulated to maintain glycaemia within a physiological range, essentially by stimulating glucose utilization by the liver, muscles and, adipose tissue and by inhibiting hepatic glucose synthesis. Dysregulation of insulin secretion and/or action contributes to the development of insulin resistance leading to type 2 diabetes (T2D) over time.

The central nervous system (CNS) is a key player in the regulation of energy homeostasis (Luquet and Magnan, 2009), islet hormone secretion, and cell proliferation (Thorens, 2010). Specialized hypothalamic neurons detect local variations in nutrients which modify their firing rates and more globally the nervous tone (Magnan et al., 2015; Thorens, 2012). In addition, the autonomic nervous system (ANS) through the parasympathetic and the sympathetic tones participates in the regulation of insulin secretion and beta-cell proliferation and is sensitive to several signals detected by the brain. Via the nerves, the response is extremely fast to tightly modulated insulin secretion.

Hundred years after insulin discovery by Frederick Grant Banting, Charles Best and, John James Rickard Macleod in Toronto in 1921 (Vecchio et al., 2018), and the awarding of the Nobel Prize in Physiology or Medicine by Banting and Macleod in 1923, several questions remain. How does the autonomic control of pancreatic beta-cells regulate insulin secretion? What is the importance of the ANS in the regulation of beta-cell proliferation? How is the modulation of autonomic tone involved in diseases? In this review, we specifically focused on the role of the autonomic nervous system on insulin secretion and beta-cell proliferation mainly in animal models since literature in humans is relatively less developed, and how deregulation of the autonomic tone can participate in insulin-related diseases.

2. Mechanisms of insulin secretion

Glucose is the main stimulus for insulin secretion. In beta cells, GLUT2, also known as solute carrier family 2 member 2 (SLC2A2), is a facilitative glucose transporter located in the plasma membrane of the liver, pancreatic, intestinal, and kidney cells as well as in the portal and the hypothalamus region (Berger and Zdziebło, 2020). Once in the cell, glucose is rapidly phosphorylated by the rate-limiting enzyme glucokinase. This low-affinity enzyme allows a significant variation in activity within the range of physiological glucose concentrations (Moullé et al., 2017). Intracellular glucose metabolism generates several molecules of ATP, increasing ATP/ADP ratio and promoting closure of ATP-sensitive K⁺ channels (Figure 1) which leads to depolarization of the plasma membrane and the opening of voltage-dependent Ca²⁺ channels. The rise of intracellular Ca²⁺ triggers several pathways that reinforce insulin exocytosis and contribute to the regulation of beta-cell proliferation (Moullé et al., 2017; Prentki et al., 2013).

Several other signals can trigger intracellular pathways and enhance GSIS (Prentki et al., 2013). At the surface of beta cells, G-protein coupled receptors (GPCR) mediate the effects of numerous regulators of insulin secretion such as neurotransmitters (e.g. acetylcholine, noradrenaline), fatty acids (e.g. oleate, palmitate), and hormones (e.g. somatostatin, glucagon-like peptide 1 (GLP-1)). They generate metabolic coupling factors involved in intracellular calcium increase and insulin exocytosis. Amino acids such as glutamine and leucine can enhance GSIS directly or through their capacity to increase blood levels of glucagon, GLP-1, and gastric inhibitory peptide (GIP) (Fu et al., 2013).

2. Autonomic innervation of pancreatic beta-cells

The first observations on islet innervation were made by Paul Langerhans in the late 1800s. He identified, on rabbit and cat pancreas, pale non-myelinated nerve fibers which were connected to

intrapancreatic ganglia and which formed a rich neural plexus joining islets of Langerhans (Langerhans, 1869). Thus, mammalian islets receive abundant nerve supply, as reported by silver impregnation stains and light microscopy experiments. Complexes formed by islet secretory cells and nerve cell bodies were initially observed in the developing pancreas of many mammals and called “*complexe sympathetico-insulaire*” by Van Campenhout (Van Campenhout, 1927, 1925). They were later observed in human adult pancreas and named “*complexe neuro-insulaire*” or neuro-insular complex (NIC) (Simard, 1937, 1935). Two types of NIC, differing by the presence of either nerve cell bodies or nerve fibers with islet cells were described by (Fujita, 1959). The utilization of electron microscopy has revealed the nature of the neural elements contained within the islets, allowing to categorize them as cholinergic or adrenergic neuron terminals (Woods and D Porte, 1974). Since then, a lot of work has been done to understand how pancreatic islets are innervated and the role of autonomic innervation on pancreatic islet function, *i.e.* hormone secretion and cell proliferation.

2.1. Organization of the autonomic nervous system in pancreatic beta cells

The ANS is formed by the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) which govern multiple essential functions independent of voluntary control. Both systems have globally opposite effects. For example, SNS increases cardiac frequency, reduces intestinal peristalsis, and induces mydriasis whereas PNS decreases cardiac frequency, increases intestinal peristalsis, and provokes miosis. These 2 systems differ anatomically by the localization of their ganglia and their neurotransmitters (Li et al., 2019; Rodriguez-Diaz and Caicedo, 2014). The sympathetic ganglia are mainly located in the spinal cord, where pre-ganglia fibers meet post-ganglia fibers to relay the nervous information through a cholinergic signal. At the post-ganglia level, *i.e.* inside the organs, it is an adrenergic signal mostly driven by

norepinephrine. Parasympathetic ganglia are mainly located in close vicinity or even inside innervated organs. Like many organs, the exocrine and endocrine parts of the pancreas receive both SNS and PNS innervations (Ahrén, 2000).

Pancreatic islets are physically connected to the brain via the ANS as evidenced by multiple experiments using anterograde and retrograde tract-tracing (Rodriguez-Diaz and Caicedo, 2014). These experiments allow a better understanding of the physical neural map between the pancreas and brain. Preganglionic parasympathetic and sympathetic afferent fibers have been identified in the nodose ganglion and the dorsal root ganglion, respectively (Figure 2). They project to the nucleus of the solitary tract (NTS) and the spinal cord laminae I and IV, respectively (Li et al., 2019). Afferent signals are integrated from the NTS, the major relay of visceral afferents, to other partially unknown brain areas. Recent work has shown that the activity of both PNS and SNS outflow to the pancreas is regulated by neural input from multiple overlapping hindbrain, midbrain, and forebrain structures (Faber et al., 2020). Preganglionic parasympathetic efferent fibers originate from the dorsal motor nucleus of the vagus (DMNX) and form synapses with postganglionic parasympathetic efferent fibers in intrapancreatic ganglia (Rinaman and Miselis, 1987). Preganglionic sympathetic efferent fibers project from the spinal cord to paravertebral and prevertebral sympathetic ganglia (Llewellyn-Smith, 2009) or directly to intrapancreatic ganglia (Havel and Taborsky, 1989).

The innervation of the endocrine part, *i.e.* the pancreatic islets, varies across species (Abdulreda et al., 2013). In mice, the sympathetic axons are located on the periphery of the islets, near the alpha cells (Dolenšek et al., 2015), whereas in humans, these types of axons are rare and generally localized around the blood vessels, inside the islets (Rodriguez-Diaz and Caicedo, 2014). Concerning the PNS, mice islets seem to be strongly innervated inside the islet while the

human islets are barely innervated while the human fetal pancreas is strongly innervated (Taborsky, 2011). Like innervation, the cytoarchitecture of pancreatic islets varies between humans and rodents (Dolenšek et al., 2015; Rodriguez-Diaz and Caicedo, 2014). In rodents, beta cells represent around 70% of the total endocrine cells and form the core of the islet. The alpha cells are located at the periphery of the islet so that a minority of beta cells are juxtaposed to alpha cells. In humans, beta cells form a smaller percentage of the endocrine population than in rodents. They are mixed with alpha cells within the islet, with more than 70% of beta cells in contact with non-beta cells (Unger and Orci, 2010). Therefore, neural regulation of pancreatic endocrine function may be different between species.

2.2. Cellular mechanisms of ANS in pancreatic beta cells

Acetylcholine is the main neurotransmitter released from both preganglionic parasympathetic and sympathetic fibers. In addition to acetylcholine, postganglionic parasympathetic fibers also secrete vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), pituitary adenylate cyclase-activating polypeptide (PACAP), and nitric oxide (NO). On the contrary, postganglionic sympathetic neurons release norepinephrine, galanin, and neuropeptide Y (Li et al., 2019). Beta cells express specific receptors for these peptides (Ahrén, 2000; Li et al., 2019; Ruiz de Azua et al., 2012). In this section, we will describe the molecular mechanisms triggered by acetylcholine and norepinephrine through their action on muscarinic and adrenergic receptors, respectively.

2.2.1. Intracellular pathways activated by acetylcholine and epinephrine

Muscarinic and adrenergic receptors are GPCR. Regarding the type of G protein, different intracellular pathways are activated leading or not to insulin release or not (Figure 1). The G_q protein upregulates phospholipase C (PLC) which PLC cleaves phosphatidylinositol 4,5-

bisphosphate (PIP₂) into 1,2- diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP₃). DAG activates protein kinase C, which activates downstream proteins and causes calcium influx. IP₃ causes an increase of intracellular calcium stores (Ahrén, 2000). The G_{i/o} protein inhibits adenylyl cyclase decreasing intracellular AMPc levels and activates potassic ATP-dependent channels via beta-gamma subunit increasing potassic efflux (Zhao et al., 2010). Hyperpolarization of the membrane blocks insulin release in part via the closure of voltage-dependent calcium channels. The G_s protein activates adenylyl cyclase leading to an increase in intracellular AMPc levels. It activates protein kinase A (PKA), the exchange protein directly activated by cAMP (Epac), and cyclic AMP response elements and other proteins in the nucleus which participate in insulin exocytosis independently of potassic ATP-dependent channels (Straub and Sharp, 2012). Thus, the regulation of pancreatic beta cells by acetylcholine and epinephrine is very complex and depends on the type of GPCR which is activated.

2.2.2. Muscarinic receptor expression

Acetylcholine is the specific ligand for muscarinic receptors of which there are 5 subtypes, M1 to M5. M1, M3, and M5 are coupled with G_q protein while M2 and M4 are coupled with G_{i/o} protein. The M3 subtype represents the major muscarinic receptor functional in pancreatic beta cells (Boschero et al., 1995; Karlsson and Ahrén, 1993). The important role of the M3 receptor in the maintenance of proper blood glucose homeostasis has been highlighted using genetically modified animal models (Ruiz de Azua et al., 2012). M3 receptors knock-out mice have impaired glucose tolerance and glucose-induced insulin secretion (GSIS) in vivo as well as a reduced response to oxotremorine-M, a muscarinic agonist, in islets isolated (Gautam et al., 2006). On the opposite, overexpression of the M3 receptor improves glucose tolerance and increases GSIS in vivo. The response to oxotremorine-M is also enhanced (Gautam et al., 2006).

2.2.3. Adrenergic receptor expression

Norepinephrine and epinephrine, bind adrenergic receptors. There are 2 subtypes, alpha (A) and beta (B), divided into other subtypes which are associated with different G proteins. The classification of these subtypes has been done according to their sensitivity to epinephrine, norepinephrine, and isoprenaline, an agonist of adrenergic receptors (Ritter et al., 2018). A1-adrenergic receptors are coupled with G_q protein while A2-adrenergic receptors are coupled with G_{i/o} protein. B-adrenergic receptors are coupled with G_s protein independently of the subtype 1,2 or 3. A2- and B-adrenergic receptors are expressed in humans (Lacey et al., 1996) and rodent islets (Santulli et al., 2012; Straub and Sharp, 2012). Norepinephrine intracellular signaling has been extensively described in a review by Straub and Sharp (Straub and Sharp, 2012). Activation of adrenergic receptors by norepinephrine acts at several levels of the intracellular cascade of insulin exocytosis. It activates K⁺ channels to hyperpolarize the cell, inhibits adenylyl cyclase, and prevents exocytosis by a distal effect. In addition, the activation of G protein by norepinephrine releases the beta-gamma subunit which is responsible for the inhibition of insulin granule exocytosis by binding and blocking soluble N-éthylmaleimide-sensitive-factor attachment protein receptor (SNARE) function and decreasing the number of exocytic events without affecting vesicle size or fusion pore properties (Zhao et al., 2010).

2.3. Role of ANS on insulin secretion and beta-cell proliferation

A part of the insulin secretion is controlled by the CNS. In particular, the PNS plays a major role in the cephalic phase of insulin release (i.e., first phase) defined by the release of gut hormones and digestive enzymes before the systemic hormonal response induced by the ingested nutrients (Ahrén and Holst, 2001; Guemes et al., 2019). Besides, the SNS is essential to maintain blood glucose levels during stressful situations by decreasing insulin and increasing glucagon secretion.

The PNS also plays an important role in pancreatic exocrine secretions whose peptide secretions such as cholecystokinin or pancreatic polypeptide are vagally mediated (Ahrén, 2000). However, the action of SNS on exocrine pancreases remains controversial (Babic and Travagli, 2016). More recently, the active participation of ANS in the regulation of pancreatic beta-cell proliferation has been demonstrated in pancreatic regeneration models and vagotomized or nutrient-infused animals (Berger et al., 2016; Das et al., 2006; Moullé et al., 2019).

Non-cholinergic activated-pathways mediated by neuropeptides such as VIP and GRP have also been reported in humans and pigs. However, it is still unclear to what extent non-cholinergic mechanisms are involved in hormonal secretion during the cephalic phase. On the other hand, the sympathetic innervation is unlikely to affect insulin secretion because it mainly inhibits insulin secretion during the hypoglycemia state (Thorens, 2010).

2.3.1. ANS and insulin secretion

Activation of PNS increases insulin secretion whereas activation of SNS inhibits it via the A-adrenergic branch which is predominant (Peterhoff et al., 2003) (Figure3). As the pancreas is connected to the brain, electrical stimulation of certain brain areas or nerves can trigger insulin secretion. The stimulation of the lateral hypothalamus inhibits insulin secretion, which is abolished by a continuous infusion of phentolamine, a competitive sympathetic A-adrenergic competitive antagonist suggesting an adrenergic influence on beta-cell function (Berthoud et al., 1980). Likewise, sympathectomized rats have a weaker GSIS in vivo (Prates et al., 2018). Conversely, the electrical activation of parasympathetic fibers stimulates insulin secretion while vagotomy inhibits it (Ahrén, 2000). In normal rats, celiac vagotomy does not influence plasma insulin levels or GSIS (Lausier et al., 2010; Moullé et al., 2019) and truncal vagotomy in obese rats completely restored insulin sensitivity suggesting that the reduction of cholinergic action on

the endocrine pancreas is sufficient to normalize plasma insulin levels and insulin action (Balbo et al., 2016).

Administration of cholinergic agonists, acetylcholine, carbachol, and pilocarpine, leads to an increase in plasma insulin levels followed by a fall in blood glucose levels in rodents (Lundquist, 1982; Moullé et al., 2019; Zawalich and Zawalich, 2002). Muscarinic blockade by atropine blocks carbachol-induced insulin secretion (Lundquist, 1982). In rats, atropine injection twice a day reduces plasma insulin levels without affecting plasma blood glucose (Moullé et al., 2019). In isolated islets, carbachol treatment enhances GSIS at low (5.5 mM) and high (16.7 mM) glucose levels (Moullé et al., 2019). Acetylcholine stimulates insulin secretion in MIN6-K8 cells, a beta-cell line, isolated mouse islets, and perfused human islets (Cabrera et al., 2008; Zhu et al., 2019). Isolated islets from sympathectomized rats have a weaker GSIS *ex vivo* (Prates et al., 2018).

Treatment with epinephrine, an adrenergic agonist, decreases media insulin levels in response to glucose (Moullé et al., 2019) and also reduces GSIS (Prates et al., 2018) in isolated rat islets. Co-treatment with yohimbine, a specific A₂-antagonist, or prazosin, a specific A₁-antagonist, reverses epinephrine-inhibited insulin secretion only at high glucose concentration (Moullé et al., 2019). When co-infused in saline-infused rats for 3 days, epinephrine does not significantly reduce plasma insulin levels and results in a small but significant rise in plasma blood glucose (Moullé et al., 2019). In humans, epinephrine infusion reduces the acute insulin response during intravenous glucose tolerance tests in young and old subjects. Even the smallest dose of epinephrine, which results in only a two- to threefold increase in plasma epinephrine levels, can affect determinants of glucose tolerance (Morrow et al., 1993). Adra2a knockout mice show reduced circulating glucose levels and increased insulin levels (Savontaus et al., 2008). The

decrease in beta-cell A₂-adrenergic receptor function stimulates insulin secretion (Das et al., 2006).

Although epinephrine has more affinity for A-adrenergic receptors, the B-adrenergic effect predominates at low doses, resulting in the potentiation of insulin secretion. B-adrenergic stimulation by isoproterenol at low glucose concentration is not sufficient to stimulate insulin secretion (Hermann and Deckert, 1977). Furthermore, even when testing several low doses, isoproterenol does not alter insulin secretion in isolated rat islets treated with glucose and lipids (Moullé et al., 2019).

The involvement of ANS in the regulation of insulin secretion is no longer in question. Innervation of the endocrine pancreas is quite well-established and recent works identified brain areas involved in both PNS and SNS outflow to the pancreas. The effects of pharmacological treatment with cholinergic and adrenergic agonists and antagonists are pretty clear and well-described at least in rodent and human islets. Models of denervation or vagotomy show more variable effects that could be explained by species- or strain-related differences as well as variations in surgical protocols. Moreover, most of the studies have been done on rodent islets while human islets, by their specific organization and innervation, may respond differently to autonomic stimuli. The effects of acetylcholine produces in the human islet are different and more complex than expected from studies conducted on cell lines and rodent islets (Molina et al., 2014). Finally, ex vivo and in vitro studies might limit discoveries on autonomic regulation of insulin secretion because it is not an integrated physiology model but have the advantage of being able to study fine mechanisms of inter-cell communication, especially to study paracrine communication within the islet.

2.3.2. ANS and beta-cell proliferation

Regarding beta-cell proliferation, literature is more limited. Vagal hyperactivity caused by ventromedial hypothalamic lesions increases pancreatic cell proliferation (Kiba et al., 1996). Inversely, in adult rats, celiac vagotomy reduces (Lausier et al., 2010) or does not affect beta-cell proliferation (Moullé et al., 2019). However, vagal innervation is required for the compensatory beta-cell proliferation in *ob/ob* mice (Yamamoto et al., 2017) and rats infused with glucose and lipids through the brain during 3 days (Moullé et al., 2019).

Carbachol treatment increases beta-cell proliferation at low (5.5 mM) and high (16.7 mM) glucose levels in isolated rat islets (Moullé et al., 2019) and rat pancreas (Yoshimura et al., 2006). Despite that atropine injection twice a day in rats reduces plasma insulin levels, it does not affect beta-cell proliferation in a rat model of nutrient excess (Moullé et al., 2019). Conversely, beta-cell proliferation is blocked by atropine administration in a rat pancreatic duct ligation model in which beta-cell neogenesis and proliferation are increased (Medina et al., 2013).

Epinephrine decreases beta-cell proliferation in isolated rat islets independently of glucose concentration (Moullé et al., 2019). Co-treatment with yohimbine, a specific A₂-antagonist, or prazosin, a specific A₁-antagonist, reverses epinephrine-reduced beta-cell proliferation specifically when islets are treated with glucose and lipids (Moullé et al., 2019). The same observation has been made when epinephrine is co-infused with glucose and lipids (Moullé et al., 2019). Decreased beta-cell A₂-adrenergic receptor function stimulates beta-cell proliferation during pancreatic regeneration in post-weaning pancreatectomized rats (Das et al., 2006). Furthermore, the loss of *adra2a* increases beta-cell proliferation in neonatal mice (Berger et al., 2016) while A₂-agonists inhibit it in adult mouse islets *ex vivo* (Sjöholm, 1991).

Isoproterenol, a B-agonist, also increases beta-cell proliferation in a pancreatic cancer cell line (Lin et al., 2012) but not in isolated rat islets at least after 3 days of treatment at low glucose levels (5.5 mM), high glucose levels (16.7 mM), and high glucose+lipids (Moullé et al., 2019).

The regulation of beta-cell proliferation by the ANS is less described in the literature (Figure 4). As for insulin secretion, models of vagotomy show variabilities in the effect of vagotomy that could be explained by the method used. Further, beta-cell proliferation is known to be weak in adults. The majority of animal models are adults or isolated islets from adults. Vagal control of beta-cell proliferation may play a more important role in pathological models such as compensatory beta-cell proliferation. The degree of insulin resistance associated with compensation might also contribute to the variations observed. Increasing the knowledge on the regulation of beta-cell compensation may offer the opportunity to proliferate islets *ex vivo* and increase the pool of islets available for transplantation.

2.3.3. Non-adrenergic non-cholinergic inhibitory pathway

As mentioned above, other neuropeptides are liberated inside the islets by nervous autonomic fibers. Non-adrenergic non-cholinergic transmitters often function as co-transmitters, which are released together with acetylcholine or noradrenaline. Vasoactive intestinal peptide (VIP) can stimulate glucagon and insulin secretion. Since VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) have similar structures, they bind to the same receptors, VIP1 and VIP2 both present on beta and alpha cells (Kirchgessner and Liu, 2001). Alpha cells are more sensitive to VIP, as demonstrated in dogs where nerves containing VIP are found very close to alpha cells (Havel et al., 1997). Gastrin-releasing peptide (GRP) regulates insulin secretion by activating postganglionic cholinergic nerves and directly by acting on islets without affecting the secretion of glucagon or somatostatin (Hermansen and Ahrén, 1990). Pituitary adenylate cyclase-

activating polypeptide (PACAP) acts through the PAC1 receptor to potentiate pancreatic secretion (Kirchgessner and Liu, 2001). Its action on beta cells as a G_s-signaling activator could reinforce G_q signaling to potentiate insulin secretion and beta-cell proliferation (Yamamoto et al., 2017).

Islets also receive sensory afferent fibers from small primary neurons in dorsal root ganglia which mainly expressed transient receptor potential vanilloid-1 (TRPV1) cation channel (Tsui et al., 2007). These neurons release neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (Rodriguez-Diaz and Caicedo, 2014). The destruction of sensory fibers by capsaicin, an agonist for the TRPV1 channel, leads to an increase in insulin secretion (Karlsson et al., 1994) suggesting that sensory nerve activation in islets inhibits insulin secretion. However, it is not known whether these axons or their neuropeptides are involved in the regulation of islet hormone secretion.

2.4. Role of ANS on other pancreatic hormones

Briefly, ANS can modulate the secretion of glucagon, somatostatin and, pancreatic polypeptide secreted by alpha, delta and, pancreatic polypeptide cells, respectively (Figure 4). However, this response varies across species. In conscious calves, the stimulation of the peripheral ends of both vagus nerves below the heart causes a prompt increase of pancreatic glucagon and pancreatic polypeptide in the arterial plasma, blocked by pretreatment with atropine (Bloom and Edwards, 1981). In isolated chicken pancreas-duodenum, acetylcholine stimulates glucagon and somatostatin secretion which is blocked by atropine pre-infusion (Honey and Weirf, 1980). In isolated rat perfused pancreas with vagal innervation, electrical vagal stimulation produces a decrease in somatostatin secretion which is enhanced by atropine infusion (Nishi et al., 1987). More recently, it has been shown that acetylcholine also stimulates the somatostatin-secreting

delta-cell via M1 receptors in human islets suggesting that cholinergic input to the delta-cell indirectly regulates beta-cell function since somatostatin is a strong inhibitor of insulin secretion (Molina et al., 2014). In dogs, electrical stimulation of the thoracic vagal nerve increases somatostatin secretion (Ahren et al., 1986) while the stimulation of the splanchnic nerve stimulates glucagon secretion (Kaneto et al., 1975). In pigs and humans, SNS enhances PP secretion while it is inhibited in the dog pancreas. In dogs, electrical stimulation of the thoracic vagal nerve increases PP secretion which is partially inhibited by atropine pretreatment (Ahren et al., 1986). Other experiments on isolated human pancreas show that activation of parasympathetic nerves increases plasma levels of PP (Brunicardi et al., 1988). The variability of ANS effects on pancreatic hormones could be explained by the species-related differences in the distribution and innervation of islet endocrine cells, as described above between rodents and humans (Brissova et al., 2005; Cabrera et al., 2006; Dolenšek et al., 2015).

The regulation of pancreatic hormone secretion at the level of the islet is tightly regulated by multiple signals, both from outside and inside of the islet (Figure 3). For example, both SNS and PNS can stimulate glucagon secretion via activation of B2-adrenergic and muscarinic receptors respectively, both expressed on islet alpha cells, which are further regulated by insulin secreted from adjacent beta cells (Ahrén, 2000). Glucagon is also a strong amplifier of insulin secretion in rodents and humans when the local concentration is probably not strong enough to reach the systemic circulation and induce hyperglycemic response but large enough to amplify insulin secretion (Rodriguez-Diaz et al., 2020). The cytoarchitectural organization of islets supports the possibility of paracrine interactions in rodents and humans. Indeed, as insulin is a powerful glucagon suppressor, the insulin spike is always accompanied by a reciprocal decrease in glucagon, which is consistent with the possibility of a paracrine suppressive effect on alpha cells.

Conversely, the decrease in insulin levels in response to a decrease in glucose reciprocally increases glucagon levels (Unger and Orci, 2010). Delta cells are also important paracrine regulators of alpha and beta-cell function (Hauge-Evans et al., 2009; Vivot et al., 2015) and inhibit their activity by secreting somatostatin in response to paracrine or circulating stimuli (Arrojo e Drigo et al., 2019; Molina et al., 2014). Finally, insulin and glucagon can modulate somatostatin secretion (Svendsen and Holst, 2021).

Despite the limited information available on the regulation of beta-cell proliferation by the ANS, this is a topic of growing interest to the scientific community. At the islet level, insulin is known to have proliferative properties through its autocrine action in multiple situations (Kulkarni et al., 1999; Okada et al., 2007). But there is much less information on a potential role for glucagon, somatostatin, and other neurotransmitters and neuropeptides released by the islet cells. Some recent evidence has demonstrated a role for somatostatin in the proliferation and survival of mouse beta cells (Damsteegt et al., 2019; Vivot et al., 2015). Glucagon receptor antagonism increases mouse pancreatic delta-cell mass in part through cell proliferation (Gu et al., 2019). More research is needed in this field, especially in human islets in where paracrine communications can be different than in rodent models commonly used.

3. Modulation of the autonomic tone in diseases: involvement of ANS in islet transplantation?

Since ANS plays an essential role in energy homeostasis, deregulation of the autonomic tone could alter important physiologic functions and lead to metabolic diseases. As mentioned above, glucose homeostasis especially insulin secretion is finely regulated by the ANS. How the autonomic tone is modulated is not completely understood. Several hypotheses have been proposed. The autonomic tone could be modulated at several levels, either by the number of

neurotransmitters released by neurons or by the expression levels of cholinergic and adrenergic receptors that increase or limit the sensitivity to neurotransmitters. Indeed, short-term exposure to nutrients either through a high-fat diet in rats (Cruciani-Guglielmacci et al., 2005) or through lipid infusion in rats and humans (Magnan et al., 2001, 1999) augments insulin secretion by increasing parasympathetic and decreasing sympathetic firing rates. Glucose infusion for 2 days in rats deeply alters parasympathetic and sympathetic nerve activities and induces hyperresponsiveness of the beta cell to glucose, which is partially blunted by subdiaphragmatic vagotomy or A2-adrenergic agonist administration (N'Guyen et al., 1994). Reduction of norepinephrine turnover in the heart, pancreas, and several hypothalamic nuclei was observed in obesity-prone rats (Levin, 1995). Finally, nutritional status can affect the response to agonists or antagonists of insulin secretion, as has been demonstrated for cholinergic modulation of glucose-induced insulin secretion in fasted vs. non-fasted mice injected with atropine (Lundquist, 1982). Thus, small deregulation of autonomic tone, both PNS and SNS, might be responsible in the long term for the development of insulin-related diseases such as diabetes or obesity.

3.1. Type 1 diabetes

Loss of islet sympathetic nervous input has also been identified as a potential mechanism for autoimmune diabetes and from human type 1 diabetes (T1D). Sympathetic innervation of islets demonstrates important plasticity during the evolution of diabetes. It is strongly increased in islets of streptozotocin-injected mice and deeply remodeled in early insulinitis prior to the loss of islet sympathetic nerves with the progression of diabetes (Chiu et al., 2012). In autoimmune non-obese diabetic (NOD) mice, loss of sympathetic nerves and insulinitis are negatively associated indicating that the severity of diabetes is related to a higher degree of nervous deregulation (Taborsky et al., 2009). Plasma glucagon response to tyramine, an indirect sympathomimetic, is

decreased in NOD mice but not in non-obese diabetes resistant mice with alloxan-induced diabetes that have neither invasive insulinitis nor loss of islets sympathetic nerves (Taborsky et al., 2009). Several studies have highlighted the possible involvement of pancreatic sensory innervation on autoimmune diabetes. The deletion of TRPV1-expressing pancreatic sensory fibers prevents islet inflammation and insulin resistance in a model of diabetes-prone NOD mice (Taborsky et al., 2009). In Zucker diabetic rats, the suppression of primary afferents expressing CGRP by capsaicin treatment prevents the decline of glucose homeostasis through increased insulin secretion (Gram et al., 2007). Thus, signals derived from sensory fibers could regulate endocrine function and facilitate access to immune cells.

In addition to a direct decrease of innervation, the destruction of beta cells largely replaced by alpha cells in T1D reduces drastically or even completely the tonic inhibition normally provided by the high local level of insulin from juxtaposed beta cells. The consequence is inappropriate hyperglucagonemia (Unger and Orci, 2010). Autonomic neuropathy in T1D participates also in the impairment of the adrenergically mediated component of the alpha cell response to glucopenia (Tominaga et al., 1987). A potential way to improve glycemic regulation might be to limit the contribution of glucagon to hyperglycemia in T1D. The feasibility to directly do that in vivo appears challenging since it means to target intra-islet communication. However, it might be possible to change the paracrine communication on ex vivo islets before transplantation.

3.2. Type 2 diabetes

Dysregulation of the autonomic tone is thought to participate in the development of type 2 diabetes (T2D) (Thorens, 2011). Pancreatic islets from monosodium glutamate (MSG)-obese rats, a model of prediabetes, secrete more insulin at increasing glucose concentrations but fail to fully respond to potassium, carbachol, forskolin, and 3-isobutyl-1-methylxanthine (Ribeiro et al.,

2013). Expression of the M3 receptor is decreased, as well as PKC alpha and PKA alpha. This could participate in the early development of beta-cell dysfunction in this model.

A plausible explanation for the development of T2D is the excessive inhibition of insulin secretion which would enhance the bad response to blood glucose level increase. Since overexpression of the A2-adrenergic receptor resulted in tonic inhibition of insulin secretion in clonal beta cells (Rodriguez-Pena et al., 1997), abnormalities in the expression or function of these receptors could contribute to the impairment of insulin secretion in T2D. Similarly, the *Adra2a* locus encoding the A2-adrenergic receptor has been identified as being overexpressed in the Goto-Kakizaki rat, a congenital diabetic strain, and responsible for default in insulin secretion as shown by pharmacologic antagonism and genetic silencing of this receptor (Rosengren et al., 2010). In humans, the single-nucleotide polymorphism rs553668 has been identified in the human ADRA2A gene. Carriers of the risk allele show an overexpression of the A2-adrenergic receptor, reduced insulin secretion, and increased T2D risk (Rosengren et al., 2010). This observation has been confirmed in several studies highlighting a potential therapeutic target to alleviate adrenergic tone on pancreatic beta cells (Bo et al., 2012; Talmud et al., 2011).

At the level of the islet, communications between cells are important. As mentioned above, insulin spike may be a key paracrine signal for prompt glucagon suppression by glucose. But first-phase insulin secretion is markedly impaired or lost in T2D (Skyler et al., 2017). The absence of glucagon suppression may lead to the stimulation of alpha cells by glucose conducting to plasma glucagon increase, observed in T2D. Alterations of intra-islet communication could participate in the development of T2D. But the involvement of the ANS in the paracrine actions of the islet cells has not been demonstrated to date. The secretion of non-

neuronal neurotransmitters by islet cells may participate in the regulation of insulin secretion and beta-cell proliferation independently of the ANS (Figure 3). Acetylcholine, glutamate (the major brain excitatory neurotransmitter), gamma-amino-butyric acid (the major brain inhibitory neurotransmitter) act as paracrine and autocrine signals differentially on beta, alpha, and delta cells (Hauge-Evans et al., 2009; Menegaz et al., 2019; Purwana et al., 2014; Rodriguez-Diaz et al., 2011; Tian et al., 2013). Thus, deregulation of the autonomic tone might affect the capacity of islet cells to release neuropeptides affecting paracrine and autocrine signals, if this release depends on the ANS. Morphological and/or functional adaptations of cells might preserve paracrine regulation of the beta cell as morphological changes which are undergone by delta cells in pre-diabetes (Arrojo e Drigo et al., 2019).

3.3. Obesity

Obesity is a multifactorial disease, characterized by environmental and genetic predisposition, and resulting in a multitude of obesity-related disorders. The imbalance of ANS has been identified as a key player in its development and maintenance. High parasympathetic activity associated with low sympathetic tone is usually observed, especially in organs involved in energy metabolism (Barella et al., 2015).

In a mice model of obesity, the liver-brain-pancreas axis participates in the compensatory beta-cell proliferation during obesity development. Activation of the FoxM1 pathway by vagal factors combining carbachol, PACAP, or VIP increases beta-cell proliferation to maintain a proper glucose metabolism (Yamamoto et al., 2017). In MSG-obese rats, vagotomy prevents islet morphofunctional and whole-body nutrient metabolism alterations suggesting that increased PNS activity in the endocrine pancreas of MSG rats could be responsible for the hyperinsulinemia that promotes fat storage or glucose homeostasis deregulation (Lubaczeuski et al., 2015). In

hyperphagic ob/ob mice, the increase in beta-cell mass is compromised after vagotomy (Edvell and Lindström, 1998). Likewise, hepatic activation of extracellular regulated kinase signaling triggers beta-cell proliferation through a neuronal relay involving the vagus nerve in mice (Imai et al., 2008; Yamamoto et al., 2017). The involvement of ANS in the compensatory beta-cell proliferation is necessary to counterbalance the increase of blood glucose and the insulin resistance state. The modulation of the autonomic tone might help to limit the impact of ANS imbalance. However, many organs are under the control of autonomic inputs, therefore more research is necessary to potentially imagine improving metabolic syndrome by regulating autonomic tone (Buijs et al., 2013).

3.4. Therapeutic approaches for beta-cell dysfunction

Insulin treatment is the only therapy for T1D and is also used in T2D in combination with biguanides. One of the major inconveniences with insulin monotherapy of T1D is glycemic volatility. Therefore, new approaches are under investigation to find an alternative to insulin injections.

Islet transplantation is used for treating T1D but not all T1D patients are good candidates for transplantation in part because of the immunosuppressive treatment. Pancreatic islets are transplanted in macro-encapsulation devices to protect them from immune attack but must be permeable to nutrients and insulin secreted by the islets. However, these devices are faced with insufficient transport of oxygen, glucose, and insulin because of the reliance on passive diffusion. For now, the long-term survival and function of macro-encapsulated stem cell derivatives in humans have not yet been reported (Kieffer et al., 2018). Another limitation of islet transplantation is the limited supply of islets for transplantation. Porcine and human islets from cadaveric donors are historically used for transplantation. A lot of research has been

directed towards pluripotent stem cells as new sources of beta cells, and important efforts are underway to further optimize current differentiation protocols. How ANS can intervene and enhance functions and survival of newly transplanted pancreatic islets? Encapsulation of pancreatic islets appears as a physical barrier to the reinnervation of transplanted islets inside the patient body. However, it has been shown recently that antagonization of dopamine D2 receptor repressed apoptosis and dedifferentiation, leading to enhanced proliferation and increased beta-cell mass (Sakano et al., 2016) and fetal innervation is important in humans (Proshchina et al., 2014). Since ANS can modulate beta-cell proliferation as described above, it might be interesting to explore the intracellular pathways involved in beta-cell proliferation and triggered by neuropeptides to identify new potential ways to generate beta cells from pluripotent stem cells.

A more recent research area is the paracrine action of insulin on juxtaposed islet cells including at least alpha and delta cells. This area has been underappreciated, probably because of the difficulty to demonstrate the local action of islet hormones and neuropeptides. Insulin injections are not further sufficient to correct the paracrine insulin deficiency. The evolution of techniques and technologies might improve this research area and contribute to the development of new therapies.

4. Conclusion

Autonomic control of pancreatic beta cells is complex and depends on a horde of neurotransmitters themselves regulated by numerous nutritional, hormonal, or nervous signals. For several decades, researchers have identified nervous and chemical pathways, providing a better understanding of pancreatic islet innervation as well as neural regulation of insulin secretion and beta-cell proliferation. In addition to the nervous system, the paracrine actions of endocrine cells including beta, alpha, and delta cells might be an important mechanism for

regulating pancreatic hormone secretion (Arrojo e Drigo et al., 2019; Rodriguez-Diaz et al., 2020). However, research is still needed to increase our knowledge of these determinants of glucose homeostasis, especially as obesity and diabetes continue to increase year after year in developing and developed countries. The development of new techniques and technologies will likely increase the possibility of detecting low levels of signaling molecules within the islet cell, released from the islet cell, or for which the targeted islet cells express a specific receptor. A better understanding of neural regulation and fine mechanisms at the pancreatic islet level could allow new perspectives and strategies for treatments to cure diseases involving insulin and islet-related hormones.

Furthermore, although this has not been discussed above, ANS plays a vital role in pancreas development during embryonic and postnatal life. The inactivation of GLUT2 in the nervous system of mice induces lower beta-cell proliferation rates during the early postnatal period leading to a lower beta-cell mass. This can be the cause of the development of a late-onset glucose intolerance due to reduced insulin secretion (Tarussio et al., 2014). A dysregulation of hormonal fetal signals during embryonic life can also disturb the establishment of neuronal circuitries as it has been shown in ob/ob embryos (Croizier et al., 2016). The nervous system-endocrine pancreas axis is thus critical for beta-cell mass establishment from the embryonic life and long-term maintenance of beta-cell function.

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FIGURE LEGENDS

Figure 1. Glucose enters pancreatic beta cells through glucose transport 2 (GLUT2). Intracellular glucose metabolism increases the ATP/ADP ratio to block ATP-dependent potassic channels leading to membrane depolarization and opening of voltage-dependent calcium channels. The increase of intracellular calcium triggers insulin secretion. The activation of G_q protein activates the phospholipase C (PLC) which hydrolyzed the phosphatidylinositol-4,5-biphosphate (PIP2) in inositol-3-phosphate (IP3) and diacylglycerol (DAG). IP3 opens IP3-gated ion channels that release calcium ions from endoplasmic stores. DAG activates the protein kinase C (PKC) pathway participating in calcium influx in the cytosol. Both pathways trigger insulin secretion. The activation of G_s protein activates adenylyl cyclase (AC) increasing intracellular cyclic AMP (cAMP). It activates the protein kinase A (PKA) and the exchange protein directly activated by cAMP (Epac) which participate in insulin exocytosis. The activation of $G_{i/o}$ protein inhibits AC and activates ATP-dependent potassic channels via beta-gamma subunit increasing potassic influx that hyperpolarizes the membrane and blocks insulin secretion.

Figure 2. Afferents from the islets to the brain have been identified in the nodose ganglia for the parasympathetic nervous system (PNS) and in the dorsal root ganglia for the sympathetic nervous system (SNS). Parasympathetic afferents project to the nucleus of the solitary tract (NTS) while sympathetic afferents project to the spinal cord laminae I and IV. From the dorsal motor nucleus of the vagus (DMNX) parasympathetic efferent fibers project to intrapancreatic ganglia which relay the information to islets. Regarding the SNS, efferences come from the spinal cord via the paravertebral ganglia, from enteric ganglia, or directly into intrapancreatic

ganglia. Black arrows represent SNS. Green arrows represent PNS. Dotted arrows represent afferents. Continuous arrows represent efferences.

Figure 3. The ANS can participate in insulin, glucagon, and somatostatin secretion by beta, alpha, and delta cells, respectively. Liberated by parasympathetic fibers, acetylcholine (Ach) increases insulin, glucagon, and somatostatin secretion whereas norepinephrine (NorE) and epinephrine released from sympathetic fibers inhibit it. These neurotransmitters activate muscarinic receptors for Ach and adrenergic receptors for NorE and epinephrine. Glucagon can potentiate insulin and somatostatin secretion through the activation of glucagon (GR) and glucagon-like peptide 1 (GLP-1) receptors. Conversely, somatostatin reduces insulin secretion through the activation of its receptor (SSTR). Alpha cells also release glutamate and Ach which contribute to paracrine actions. Ach can potentiate insulin and somatostatin secretion whereas glutamate act as an autocrine positive signal on glucagon release. Its paracrine actions are still debated. Beta cells also release gamma-amino-butyric acid (GABA) which increases somatostatin secretion and inhibits insulin and glucagon release. Black arrows represent SNS. Green arrows represent PNS. Continuous arrows represent ANS action. Dotted arrows represent paracrine and autocrine actions.

Figure 4. Some evidence has demonstrated that the ANS can participate at least in beta-cell proliferation. Acetylcholine (Ach) from parasympathetic nerves increases beta-cell proliferation whereas epinephrine and norepinephrine (NorE) block it. Insulin can act as an autocrine signal to stimulate beta-cell proliferation via its receptor (IR). As a paracrine signal, somatostatin released by delta cells participate also in beta-cell proliferation and survival at least in mice. Black arrows

represent SNS. Green arrows represent PNS. Continuous arrows represent ANS action. Dotted arrows represent paracrine and autocrine actions.

FIGURES

Figure 1

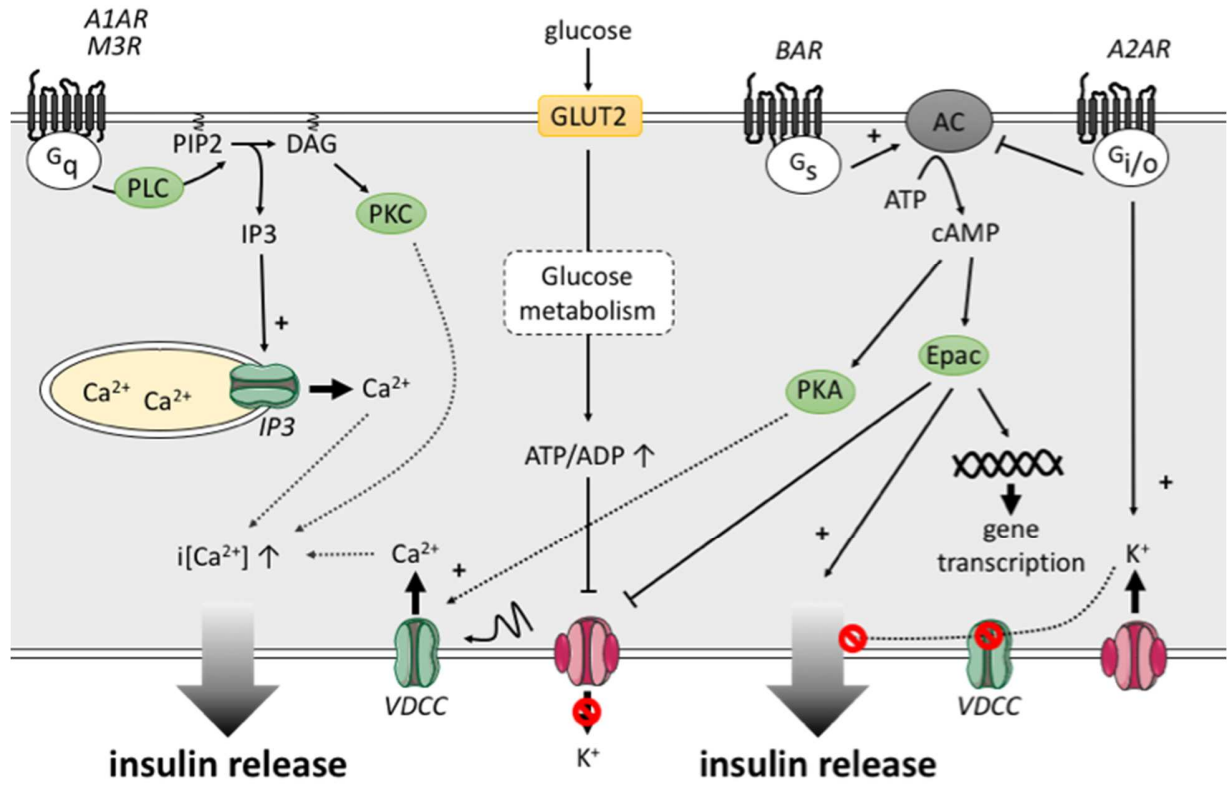


Figure 2

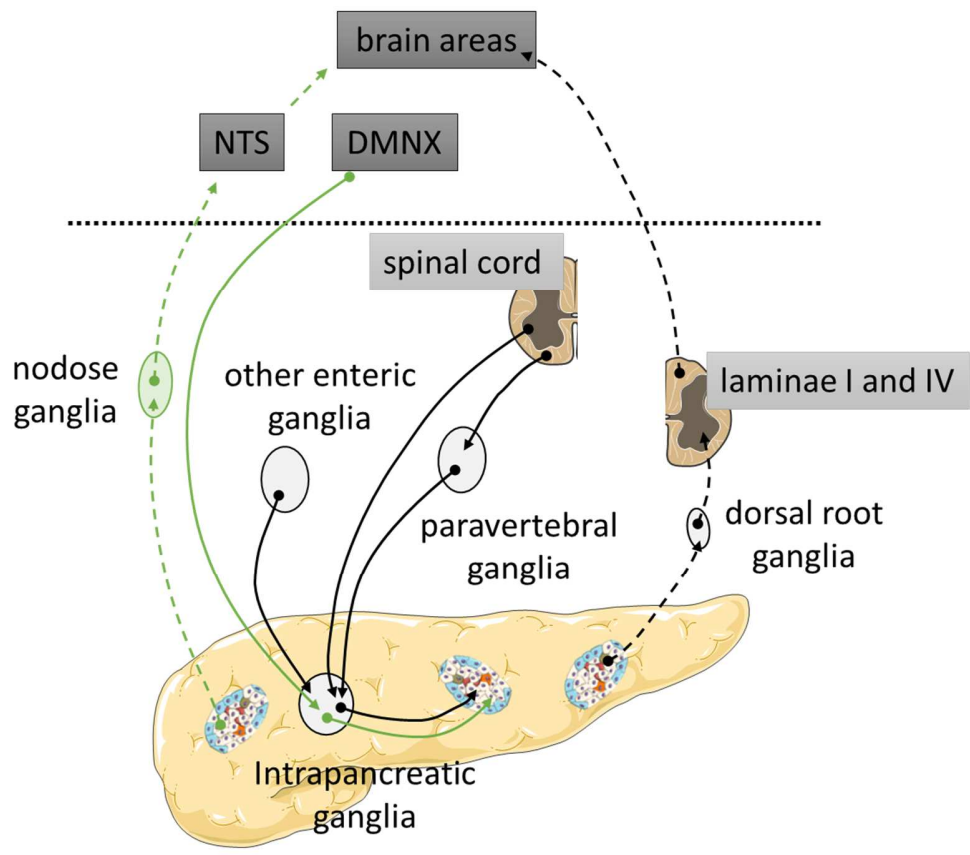


Figure 3

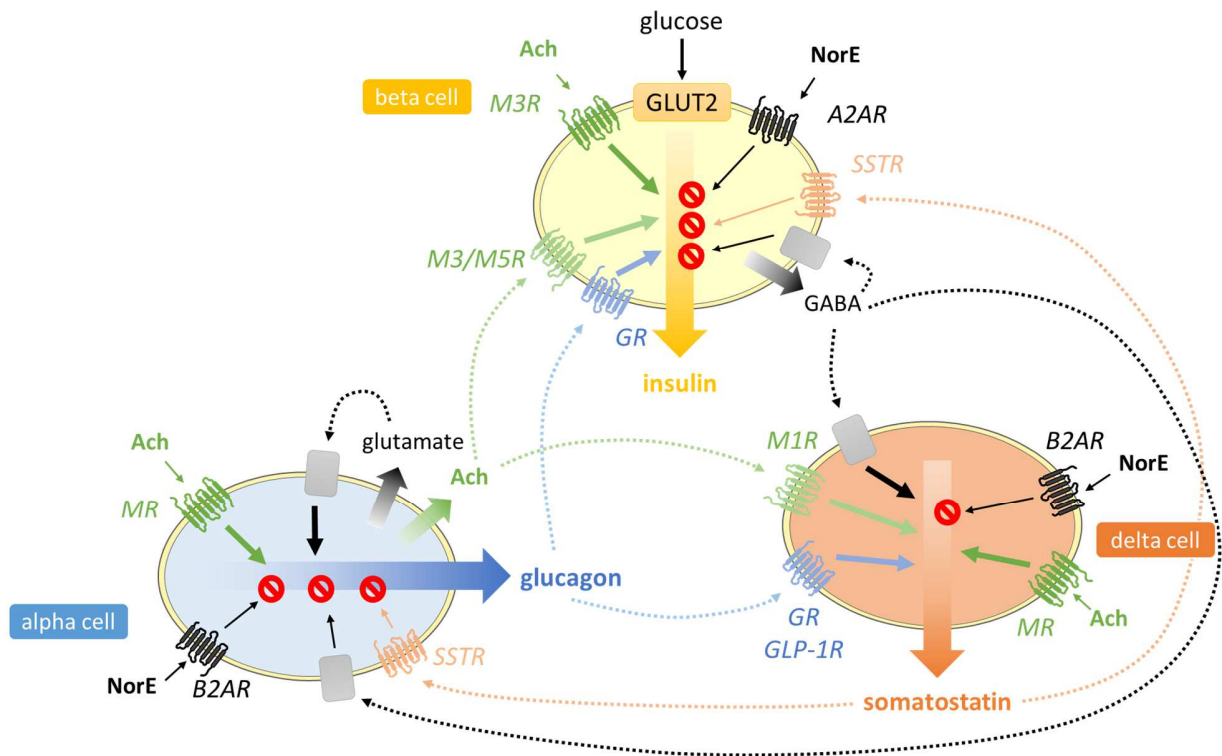


Figure 4

