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MINIREVIEWS

Neurotransmitters regulate β cells insulin secretion: A neglected factor

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Abstract

β cells are the main cells responsible for the hypoglycemic function of pancreatic islets, and the insulin secreted by these cells is the only hormone that lowers blood glucose levels in the human body. β cells are regulated by various factors, among which neurotransmitters make an important contribution. This paper discusses the effects of neurotransmitters secreted by various sympathetic and parasympathetic nerves on β cells and summarizes the mechanisms by which various neurotransmitters regulate insulin secretion. Many neurotransmitters do not have a single source and are not only released from nerve terminals but also synthesized by β cells themselves, allowing them to synergistically regulate insulin secretion. Almost all of these neurotransmitters depend on the presence of glucose to function, and their actions are mostly related to the Ca^{2+} and cAMP concentrations. Although neurotransmitters have been extensively studied, many of their mechanisms remain unclear and require further exploration by researchers.

Key Words: β cells; Insulin secretion; Neurology; Type 2 diabetes; Islet

Core Tip: β-Cells are the only islet cells in the body that release insulin, and the neurotransmitter is an important factor in regulating insulin secretion. This review systematically describes the release sources of different neurotransmitters and their effects on insulin secretion. There are common mechanisms among different neurotransmitters, which mainly involve neuroanatomy and blood glucose homeostasis in vivo. There are great differences among different species. Although many specific mechanisms remain to be explored, this review provides a certain reference value and direction for subsequent research.

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INTRODUCTION

Islets are important endocrine micro-organs for maintaining glucose homeostasis. In animals, intermittent feeding is an important cause of fluctuations in blood glucose levels, which are precisely controlled within a certain range by various hormones secreted by the islets. Islets are scattered in the exocrine parenchyma of the pancreas and are composed of cells, 65%-80% of which are β cells that secrete insulin (the only hypoglycemic hormone in the body)[1]. In rodents, β cells are located in the center of the islets and are surrounded by α-cells (which secrete glucagon), δ-cells (which secrete growth inhibitory hormone), and PP-cells (which secrete pancreatic polypeptide). In humans, islets are formed by three main cell types in close proximity, allowing more local interactions than in rodents[2]. The blood glucose level is undoubtedly an important factor in the regulation of islet function. In addition, islets are innervated by autonomic nerves; thus, a logical hypothesis is that neurotransmitters act as messengers to regulate the autonomic innervation of islets[1]. Recent studies have found that in addition to neurotransmitters, many neuropeptides located in islets also participate in neuroregulation [3]. The nerves that innervate islets mainly include sympathetic, parasympathetic and sensory nerves; acetylcholine (ACh), vasoactive intestinal polypeptide (VIP), gastric releasing peptide (GRP), 5-hydroxytryptamine (5-HT), pituitary adenylate cyclase activating peptide (PACAP) and nitric oxide (NO) are stored in parasympathetic nerve endings; norepinephrine (NE), dopamine (DA), galanin, calcitonin gene-related peptide (CGRP) and neuropeptide Y (NYP) are stored in sympathetic nerve endings; and sensory neuropeptides, cholecystokinin and substance P are stored in sensory nerve endings[1] (Table 1). Neurotransmitters do not only originate from nerve endings; in addition, β cells, as nonneural sources of neurotransmitters, synergize with nerve endings to secrete neurotransmitters and exert autocrine or paracrine effects locally[1]. These neurotransmitters synthesized by β cells are also released into the bloodstream together with insulin (Figure 1).

Islets are mainly innervated by sympathetic and parasympathetic nerves. Sympathetic preganglionic neurons are located in the mediolateral spinal cord at the T6-L2 levels, and their axons project from the visceral nerves to the superior mesenteric and celiac ganglia and to the pancreas[4]. The preganglionic fibers of parasympathetic nerves originate from the dorsal nucleus of the vagus nerve[5] and possibly from the ambiguous nucleus[6], both of which are under hypothalamic control. It is traditionally believed that sympathetic nerves play the opposite role as parasympathetic nerves in insulin secretion. In mice and humans, sympathetic nerves mainly stimulate the secretion of glucagon by α cells and reduces the secretion of insulin by β cells by regulating the islet vascular system[7]. However, it has been reported that the level of insulin increases slowly when visceral sympathetic nerves are stimulated in anesthetized dogs[8]. Parasympathetic nerves mainly play a role in regulating insulin secretion in the cephalic stage by integrating taste, smell, and visual signals in the hypothalamus, eventually leading to the stimulation of insulin secretion[9]. Dietary hormones such as cholecystokinin and 5-HT can also activate the vagus nerve. Vagal fiber endings release a variety of neurotransmitters, such as ACh and gut GRP[10]. In a previous study, vagotomy was performed in both fed and fasted animals, and it was found that the vagus nerve had no effect on insulin secretion in fasted animals[11] but was involved in insulin secretion in fed animals. Therefore, it is generally believed that the vagus nerve is involved in insulin secretion under high-glucose feeding conditions but has little effect on basal insulin secretion. In addition, many studies have shown that the mode of glucose administration also affects the control of insulin secretion by the vagus nerve; for example, intravenous glucose administration rarely affects basal insulin secretion, while vagotomy substantially reduces insulin secretion when glucose is administered orally[1]. All these studies suggest that glucose is an important stimulus for the regulation of β cells by the vagus nerve in the gastrointestinal tract. Although the sympathetic nerves in the pancreas originate from the lower thoracic and upper lumbar segments of the spinal cord[12], their myelin sheaths form the paravertebral sympathetic chain[1] or cross the viscera to reach the ventral and mesenteric ganglia[12], and the postganglionic fibers emanating from the paravertebral sympathetic chain, ventral ganglia and mesenteric ganglia ultimately innervate the pancreas. Neurotransmitters may be involved in regulating insulin secretion in healthy people as well as in individuals with type 1, type 2, or other types of diabetes, so we do not distinguish between their specific roles in various types of diabetes.

Table 1 Role of neurotransmitters in the islet

Name	Source	Receptor	Effect on pancreatic islet secretion
ACh	Vagus nerve	M3	↑↑↑
NO	Vagus nerve, beta cells	sGC	Low concentration ↑, high concentration ↓
GRP	Vagus nerve	GRPR	↑
VIP	Vagus nerve	VIP-2	↑
PACAP	Vagus nerve, gut-pancreas nerve	PACAP-3	↑
5-HT	Vagus nerve, gut-pancreas nerve, beta cells	Htr1	↑↑
NE	Sympathetic nerves	α2, β2	α2 receptors ↑, β2 receptors ↓↓
Galanin	Sympathetic nerves	GALR1	↓
NPY	Sympathetic nerves	Y2	↓
DA	Sympathetic nerves, beta cells	D2, D3	D2↑, D3↓
CGRP	Sensory nerves	CGRP	↓
SP	Sensory nerves	NK1	↑
Cholecystokinin	Sensory nerves	CCK	↓

"↑" represents the promotion of insulin secretion; "↓" represents the inhibition of insulin secretion. 5-HT: 5-hydroxytryptamine; ACh: Acetylcholine; CCK: Cholecystokinin; CGRP: Calcitoningenerelatedpeptide; DA: Dopamine; GRP: Gastrin releasing peptide; NE: Norepinephrine; NO: Nitric oxide; NPY: Neuropeptide Y; PACAP: Pituitary adenylate cyclase activating polypeptide; SP: Substance P; VIP: Vasoactive intestinal peptide.

NEUROTRANSMITTERS ORIGINATING FROM NERVE ENDINGS

ACh

ACh, an important hormone secreted by the vagus nerve, has traditionally been the focus of research by endocrinologists. However, ACh has been shown to be rapidly hydrolyzed by cholinesterase in the cytoplasm, and thus direct measurement of ACh levels is impossible. Therefore, researchers usually choose to measure plasma PP levels instead of Ach levels. PP also plays a role in regulating insulin secretion. PP acts on the Y4 receptor of delta cells, reducing somatostatin secretion and promoting insulin secretion[13].

ACh promotes insulin secretion, but this effect mainly depends on Ca^{2+} and glucose. After ACh is secreted by the vagus nerve, it acts on M3 receptors in β cells to promote glucose-mediated coupling of phospholipase C (PLC) to G proteins. The coupling of PLC to G proteins results in phosphoinositide (PI) hydrolysis. The hydrolysis of PI leads to the formation of inositol triphosphate (IP3). The binding of IP3 to IP3 receptors promotes the release of Ca^{2+} from the Ca^{2+} pool, thereby increasing the $[Ca^{2+}]_i$. It should be emphasized that the increase in Ca2+ release caused by the ACh-induced IP3 pulse peaks every 5-7 min, and this pattern of release is synchronized with the pulse secretion of insulin[14,15]. When a large amount of Ca^{2+} is released from the intracellular Ca^{2+} pool, the lack of Ca^{2+} in the storage pool leads to an inward flow of extracellular Ca^{2+}, leading to volumetric Ca^{2+} inward flow, a second mechanism by which ACh promotes an increase in Ca^{2+} concentrations. In addition, voltage-dependent Ca^{2+} channels are located in the β-cell membrane, and large amounts of Ca^{2+} enter the cell when they are open.

ACh promotes insulin secretion by increasing the Ca^{2+} concentration in β cells on the one hand and enhances the effect of Ca^{2+} in promoting insulin secretion on the other hand. According to many studies, the PLC-PKC pathway may be involved in the mechanism by which ACh increases the prosecretory effect of Ca^{2+}[10]. PLC activation results in the production of the diglyceride DAG_2, which is a PKC activator that induces the translocation of PKC from the cytoplasm to the cell membrane; however, the mechanism by which PKC increases the effect of Ca^{2+} in promoting insulin secretion remains to be investigated. Further studies are needed to investigate whether phospholipase A2 is involved in this process. In addition, ACh does not regulate insulin secretion in one direction. ACh stimulates insulin secretion directly but simultaneously inhibits insulin secretion by promoting somatostatin secretion from δ-cells[1].

GRP

Enterostatin is a hormone that promotes insulin secretion, and its mechanism of action is closely related to glucose and Ca^{2+}. However, the mechanism has not been fully elucidated. GRP seems to stimulate insulin secretion through direct and indirect mechanisms, and GRP seems to promote glucagon secretion.

GRP does not increase insulin secretion when the extracellular glucose concentration is less than 11.1 mmol/L in β cells, leading to the conclusion that the effect of GRP in promoting insulin secretion depends on the presence of glucose. Likewise, it was found that GRP did not increase the insulin concentration or insulin secretion when the extracellular culture medium was deficient in Ca^{2+}, suggesting that GRP function also depends on extracellular Ca^{2+}[16]. However, in

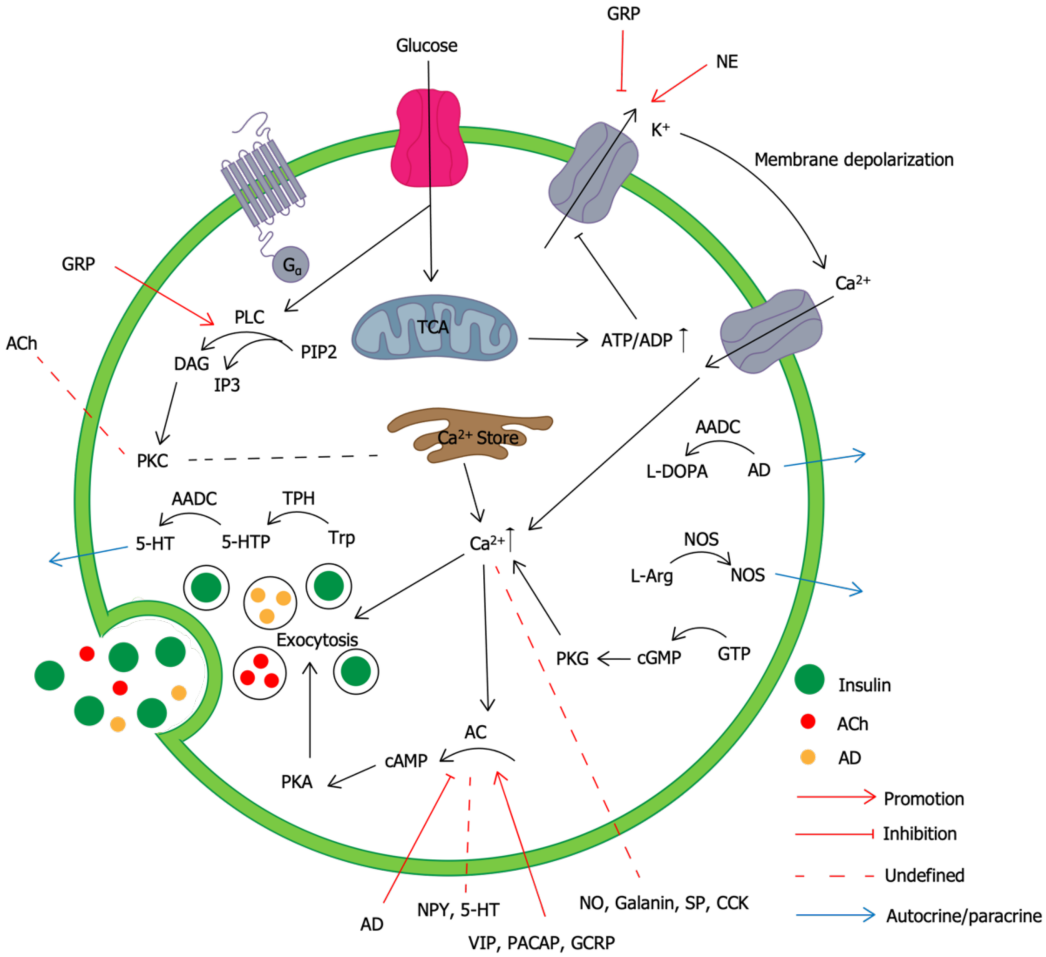

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Figure 1 Regulation of insulin secretion by neurotransmitters. With the increase of glucose concentration, the concentration of adenosine triphosphate (ATP) produced by glucose metabolism also increases correspondingly, and the closure of internal rectifying K^+-ATP channels leads to membrane depolarization, which opens volt-sensitive Ca^{2+} channels, and Ca^{2+} enters intracellularly to mediate insulin secretion in large quantity. Acetylcholine, gastrin releasing peptide, 5-hydroxytryptophan, vasoactive intestinal peptide, pituitary adenylate cyclase activating polypeptide and nitric oxide promote insulin secretion. Dopamine, neuropeptide Y, galanin and norepinephrine inhibit insulin secretion. 5-HTTP: 5-hydroxytryptophan; AADC: Amino acid decarboxylase; ADP: Adenosine diphosphate; cAMP: Cyclic adenosine monophosphate; CCK: Cholecystokinin; cGMP: Cyclic guanosine monophosphate; DAG: Diacylglycerol; GCRP: Calcitoningenerelatedpeptide; GTP: Guanosine triphosphate; IP3: Inositol triphosphate; L-Arg: Levo-arginine; L-DOPA: Levo-dopa; NOS: Nitric oxide synthase; PIP2: Phosphatidylinositol(4,5)bisphosphate; PKA: Protein kinases A; PKC: Protein kinase C; PKG: Protein kinases G; PLC: Phospholipase C; SP: Substance P; TCA: Tricarboxylic acid cycle; TPH: Tryptophan hydroxylase; Trp: Tryptophan; VIP: Vasoactive intestinal peptide.

subsequent experiments, it was found that although GRP acts continuously on β cells, the extracellular secretion of Ca^{2+} is not continuous; thus, GRP promotes insulin secretion by inducing only transient extracellular secretion of Ca^{2+}. GRP stimulates IP3 production[17] but not IP3 hydrolysis[16]. GRP likely promotes PKC production by stimulating DAG production, and PKC promotes insulin secretion[18], suggesting that GRP also indirectly promotes insulin secretion. Overall, the GRP-mediated promotion of secretion depends on the presence of Ca^{2+}. First, GRP stimulates IP3 production, and although it does not promote its hydrolysis, it still substantially increases the intracellular Ca^{2+} concentration. In addition, GRP also seems to inhibit K^+ channels, which accelerates β-cell depolarization and prolongs its duration, which is more favorable for inward Ca^{2+} flow. Many studies have also found that in addition to having direct effects, GRP may act indirectly through cholinergic mechanisms. The muscarinic receptor M3 is involved in the action of GRP in promoting insulin secretion[19].

VIP and PACAP

VIP and PACAP have similar mechanisms of action and are colocalized in rat ganglion neurons, so they are often discussed together. PACAP and VIP share the receptors VIP1 and VIP2, while PAC1 is a specific receptor for PACAP[6]. Of course, PACAP can also be secreted by the enteropancreas. PAC1 is expressed in intrapancreatic ganglia, intestinal neurons, and beta cells[3]. Similar to NO and GRP, VIP and PACAP act in a glucose-dependent manner; when glucose is absent in the extracellular matrix, the effects of VIP and PACAP are almost negligible. Most studies suggest that the mechanisms of action of VIP and PACAP are related to their ability to stimulate increased cyclic adenosine monophosphate (cAMP) production[20], which increases the intracellular Ca^{2+} concentration in β cells. However, when Ca^{2+} is removed from the extracellular matrix, the intracellular Ca^{2+} concentration in β cells does not increase significantly, which

suggests that instead of intracellular Ca^{2+} being released from the storage pool, extracellular Ca^{2+} flows into the cell[20]. VIP and PACAP increase the cAMP concentration, and a peak in the intracellular Ca^{2+} concentration can indeed be detected in β cells[21]. However, in mice, researchers did not observe an association between VIP-stimulated insulin release and increased cAMP levels[22], suggesting that signaling pathways other than the cAMP pathway might also participate in this process. When the VIP- and PACAP-stimulated increase in cAMP levels was reversed, it was found that VIP and PACAP stimulated a transient increase in cAMP and Ca^{2+} concentrations but a persistent increase in insulin levels, which supports the existence of other mechanisms[21].

NE

NE is released into the pancreatic vein mainly by sympathetic excitatory postganglionic fibers[23]. In animal experiments, exogenous NE was found to inhibit glucose-mediated insulin secretion; colistin, an α_2-adrenergic receptor agonist, was found to inhibit insulin secretion[24], as was the β-blocker, propranolol. Therefore, NE is presumed to inhibit insulin secretion. Phentolamine, however, acts as an α-adrenergic receptor blocker and seems to counteract the inhibition of insulin secretion after neuroelectrical stimulation[25]. NE may likewise promote insulin secretion; one pathway might be the direct stimulation of insulin secretion through the activation of β2-adrenergic receptors in pancreatic β cells, and the other pathway may involve signaling directly through α2 and β2-adrenergic receptors in α cells[26], promotion of glucagon secretion by these cells and indirect stimulation of insulin secretion through glucagon. Therefore, the effect of NE on islets seems to be a vector sum of the actions of two receptors.

However, in general, the main effect of NE on β cells is the inhibition of insulin secretion. The mechanism underlying this effect is mainly related to the promotion of K^+-ATP channel opening by NE. The opening of K^+-ATP channels directly affects the Ca^{2+} concentration in β cells[27], and when NE acts on α_2-adrenergic receptors, K^+-ATP channels remain open, β cells are in a hyperpolarized state, and Ca^{2+} does not flow inward, which in turn inhibits insulin release[28]. After NE acts on β_2-adrenergic receptors, it also inhibits the reduction in cAMP production by β cells[29], which inhibits insulin production through another pathway.

NPY

Galanin and NPY are both released by sympathetic nerve fiber terminals, and their role in inhibiting insulin release is well recognized. Although they exert different inhibitory effects in different species, in general, their directions of action are consistent. Although the results of their actions are well understood, their mechanisms remain unclear. Galanin has been shown to inhibit insulin secretion in a variety of animals[30]. Although the mechanism remains unclear, galanin was found to inhibit the glucose-mediated increase in the Ca^{2+} concentration in previous studies[31]. Therefore, we speculate that galanin may inhibit K^+-ATP channel opening to inhibit β-cell membrane depolarization. When researchers induced β-cell depolarization with K^+, galanin did not inhibit insulin secretion[32]; while other mechanisms through which galanin inhibits Ca^{2+} inward flow must exist, they remain unclear. Many studies suggest that NPY may inhibit insulin secretion by inhibiting G protein coupling and adenylate cyclase activity.

Sensory nerves

In addition to parasympathetic and sympathetic nerves, islets are also innervated by a wide range of sensory nerves, which secrete CGRP and SP. The CGRP receptor complex is expressed in mouse β cells, while the substance SP receptor NK-1R is expressed in mouse α cells. CGRP stimulates the release of gastrointestinal growth inhibitory hormone, which inhibits insulin release, and this pathway might be the mechanism by which CGRP inhibits insulin release. CGRP increases blood flow to the pancreas, which leads to a decrease in the insulin concentration due to an increase in blood flow when an increase in the insulin concentration is detected[33]. Several experiments have shown that CGRP inhibits glucose-induced insulin release, but the exact mechanisms involved need to be further investigated. However, there are some species-specific differences in this phenomenon. For example, CGRP does not affect insulin secretion in cattle[34]. The effect of substance P on insulin shows more obvious species-specific differences. While *in vitro* experiments on the effect of substance SP on insulin in rats have yielded inconsistent results, it has been shown that substance SP inhibits glucagon secretion; however, in dogs, substance SP stimulates insulin and glucagon secretion in a concentration-dependent manner[35,36]. *In vivo*, substance SP inhibits insulin secretion in rats but increases insulin and glucagon secretion in pigs[36,37].

CGRP and substance P are also coexpressed with insulin receptors in vagal afferent neurons, but CGRP is predominantly expressed in spinal sensory fibres[6]. In addition, some other neurotransmitters that are secreted by the pancreatic nerve have been identified; for example, cholecystokinin promotes insulin secretion, and its mechanism may be related to the activation of PLC[1].

NEUROTRANSMITTERS ORIGINATING FROM BOTH NERVE ENDINGS AND NONNERVE ENDINGS

5-HT

5-HT is a monoamine derivative that is present in the central nervous system and peripheral tissues[38], and as one of the most intense stimuli of vagal afferent neurons[39], it plays a role not only in neurotransmission in the central nervous system and brain development[40] but also in the physiological control and development of peripheral tissues[41]. In rats, 5-HT is also secreted by enteral neurons in the duodenum and stomach[42]. 5-HT is synthesized by tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AADC) *via* a two-step reaction[43]. Pancreatic β cells

synthesize 5-HT de novo and release it *via* vesicular monoamine transporter 1/2 (VMAT1/2) as an autocrine and paracrine signal[44]. 5-HT is released from β cells along with insulin and ATP[45], and 5-HT secretion is regulated by the blood glucose concentration[46]. The 5HT3 receptor is a 5-HT receptor that is highly expressed on vagal afferent neurons. Antagonism of 5-HT receptors inhibits the response of vagal sensory neurons to β-cell stimulation[47], although the exact mechanism is unclear. In addition, intracellular 5-HT in β-cell granules acts as a substrate for the production of secretion-related proteins, which enhances insulin granule secretion[43]. However, differences in the effects of exogenous and endogenous or redistributed 5-HT on insulin secretion have been identified. Extracellular 5-HT is usually presumed to attenuate insulin release by stimulating Htr1a receptors in islet tissue, possibly through 5-HT receptor subfamily members (Htr1) that are coupled to Gαi and thus inhibit cAMP formation.

5-HT effectively inhibits insulin and glucagon secretion in islets under nondiabetic conditions. Surprisingly, this inhibition is lost in the islets of individuals with T2D[48], suggesting that functional 5-HT signaling is essential for normal β-cell function. Furthermore, 5-HT has recently been shown to play a role in β-cell expansion and compensatory insulin secretion during pregnancy[45].

DA

DA, an excitatory neurotransmitter secreted by sympathetic nerves, plays an important role in insulin secretion. β cells, which are important sites for nonneuronal DA synthesis and utilization, also secrete DA and coregulate insulin secretion with sympathetic nerves. β cells convert DA precursors (*e.g.*, L-DOPA) to DA mainly through the actions of AADC[49], and newly synthesized DA is subsequently released in response to high glucose stimulation. The increase in DA secretion by β cells in response to glucose stimulation may be due to increased L-DOPA uptake and subsequent DA synthesis, resulting in a larger pool of releasable DA[50]. Synthesized DA is stored in β cells and is consecrated with insulin *via* VMAT2[38]. This endogenous DA signals in an autocrine/paracrine manner in insulin-secreting cells that express D2-like receptors. When DA is bound, it activates the Gα subunit to negatively regulate cAMP production, thereby decreasing protein kinase A activity[51] and subsequently activating PLC and reducing intracellular Ca^{2+} levels by affecting intracellular stores and L-type calcium channels[52]. In addition, D2-like receptors regulate G protein-coupled inward rectifying K^+ channels[53]. Plasma concentrations of glucose and insulin are usually tightly linked, and alterations in glucose levels may result in rapid alteration in insulin levels in an attempt to bring glucose levels back to normal. Psychotropic drugs such as tiapride have a potent antagonistic effect on D2 receptors. Therefore, in previously reported patients, these counterregulatory mechanisms may not have worked, as they may have resulted in continuous insulin release even in the presence of normal or low glucose levels[54]. Furthermore, a certain rhythmicity in the regulation of insulin secretion by DA was found. When L-DOPA is coadministered with the D2 receptor antagonist sulpiride, the decrease in the circadian rhythm amplitude produced by the L-DOPA treatment was reversed, and the amplitude was restored to the level in carrier-treated cells. Based on these results, the D2 receptor modulates the effect of L-DOPA on circadian rhythm amplitude[55]. In contrast, the D2 receptor agonist bromocriptine significantly reduces the circadian rhythm amplitude in a concentration-dependent manner.

NO

NO is a stable and effective gaseous mediator that has become a hot topic in medical research in recent years, and a consensus on its role in vasodilation has been achieved. However, controversy exists regarding the role of NO in glucose-induced insulin secretion, as both inhibitory and facilitatory effects have been reported; whether glucose inhibits or promotes insulin secretion may be related to the NO concentration.

NO is secreted not only by vagal nerve terminals but also by HIT-T15 in hamster islet β cells stimulated with glucose [56]. L-arginine, a precursor of NO, is present in β cells, and L-arginine was shown to enhance the effect of glucose in promoting insulin secretion as early as 1966. NO synthase (NOS) was also detected in large quantities in β cells. Therefore, it can be inferred that L-arginine is likely to exert its insulin secretion-promoting effect after the conversion of NOS to NO. N-methyl-L-arginine (NMMA) is an NO inhibitor, and in the presence and absence of NMMA, researchers stimulated β cells with glucose and measured the concentration of NO in the extracellular culture medium. Glucose stimulated the release of NO from β cells in a concentration-dependent manner[57], but the mechanism underlying this effect is not clear at present. Based on this information, it can be concluded that glucose stimulates NO production in β cells in a concentration-dependent manner and that L-arginine and NOS are involved in NO production; however, the cytotoxicity of NO should not be ignored. When the glucose concentration exceeds a certain range, excess NO production in β cells reduces insulin release, potentially due to the cytotoxicity of NO. When β cells are stimulated with sodium nitroprusside (SNP, an extracellular NO donor) alone or both sodium nitroprusside and glucose, glucose is still the main factor that induces insulin secretion; NO alone does not induce insulin secretion but only enhances glucose-induced insulin secretion. The mechanism underlying this effect is not clear, but one hypothesis suggests that it may be related to NO-mediated stimulation of transient Ca^{2+} release[58].

The results of many studies have shown that NO exerts a negative effect on insulin secretion. Sodium nitroprusside inhibits glucose-induced insulin secretion, and hemoglobin, as a scavenger of NO, attenuates this inhibitory effect[59]. Due to the paradoxical effect of NO on glucose-induced insulin secretion, researchers studying islets have shifted their focus to changes in Ca^{2+} concentrations. Hemoglobin reduces the intracellular Ca^{2+} concentration in β cells, while high concentrations of NO reduce the intracellular Ca^{2+} concentration, which may explain the paradoxical effect of NO[60].

CONCLUSION

As an organ that regulates blood glucose levels in the body, the pancreas mainly functions by secreting various hormones. Insulin secreted by β cells is the only hormone that lowers blood glucose levels in the body, and neurotransmitters play an important role in β cell-mediated insulin; thus, the regulatory effect and mechanism of action of β cells are hot research topics. Insulin secretion mainly depends on the Ca^{2+} concentration in β cells, and when the glucose concentration increases, the concentration of ATP produced by glucose metabolism also increases accordingly. Glucose and other substances that produce ATP after being metabolized induce inwardly rectifying K^+-ATP channel closing, subsequently leading to membrane depolarization[61]. Glucose produces a large action potential peak during β-cell depolarization, allowing voltage-sensitive Ca^{2+} channels to open and Ca^{2+} to enter the cell in large quantities to mediate insulin secretion[62].

Parasympathetic nerves play a predominant role in promoting insulin secretion, and ACh stimulates IP3 hydrolysis to increase the Ca^{2+} content in β cells. ACh enhances Ca^{2+}-mediated insulin release *via* the PLC-PKC pathway, but the mechanism involved is unclear. Some studies also indicate that ACh affects the β-cell membrane potential and promotes β-cell membrane depolarization in the presence of glucose. GRP increases the intracellular Ca^{2+} concentration to stimulate insulin secretion from β cells. VIP and PACAP have similar mechanisms of action, binding to VIP-2 and PACAP-3 receptors, respectively, to increase cAMP production and stimulate insulin release from β cells. Sympathetic nerves mainly inhibit insulin secretion from β cells. NE promotes K^+-ATP channel opening to inhibit cell membrane depolarization and reduce the inward flow of intracellular Ca^{2+}, thus inhibiting insulin release from β cells. Both glycopeptide and NYP inhibit insulin secretion by β cells, and glycopeptide may block inward Ca^{2+} flow through an as-yet unknown mechanism; moreover, NPY inhibits insulin secretion from β cells by inhibiting cAMP signaling.

While some neurotransmitters are released solely from nerve terminals, many transmitters are released by β cells in conjunction with nerve terminals. 5-HT is synthesized by the conversion of tryptophan to the intermediate product 5-HTP by TPH and AADC followed by the conversion of 5-HTP to 5-HT. The generated 5-HT is released *via* VMAT1/2, and it functions as an autocrine and paracrine signal to promote insulin secretion. DA precursors (such as L-DOPA) are converted to DA by AADC-dependent enzymes, and as L-DOPA uptake and DA synthesis increase, a releasable DA pool is generated in β cells. DA is then cosecreted with insulin through VMAT2. This endogenous DA acts in an autocrine/paracrine manner on insulin-secreting cells that express D2-like receptors. When DA is bound, it activates the Gα subunit to negatively regulate cAMP production, thereby decreasing protein kinase A activity and inhibiting insulin secretion. In addition, a large amount of NOS exists in β cells, and L-arginine promotes insulin secretion after its conversion to NO. However, the effect of NO on insulin secretion is controversial, as studies reporting its effects in promoting and inhibiting insulin secretion have been published; this suggests that the functions of NO may be related to its concentration. NO does not promote insulin secretion from β cells alone, and NO plays a facilitating role only in the presence of glucose. However, due to the cytotoxicity of NO, high NO concentrations may damage β cells and affect glucose metabolism, leading to a decrease in insulin release.

In previous studies, the effects of neurotransmitters on insulin secretion were initially identified, and it was found that neurotransmitters mainly act during the last step of insulin release, *i.e.* on cytosolic insulin. The general direction of the sympathetic and parasympathetic effects on insulin secretion has been determined, but many unresolved questions remain. The current research can't answer these questions, but we hope that future researchers can investigate these directions: (1) Do differences in the release of peri-islet neurotransmitters exist under normoglycemic and hyperglycemic conditions? (2) Does glucose increase neurotransmitter secretion by stimulating nerve endings under hyperglycemic conditions? (3) Do any stimulatory conditions excite the peri-islet vagus nerve and promote insulin secretion by increasing neurotransmitter secretion? (4) Why does ACh promote insulin secretion for a short period but inhibit insulin secretion upon prolonged stimulation? (5) Do neurotransmitters originating from dual sources play a more important role in regulating insulin secretion than those from a single source (*i.e.* nerves)? (6) Are neurotransmitters involved in insulin synthesis and transport? (7) Are the concentrations of neurotransmitters in human blood altered by drugs used to regulate blood glucose levels? Do neurotransmitters affect the first and second phases of insulin secretion? (8) Does neurotransmitter release decrease in response to peri-islet nerve ending lesions during the development of diabetes mellitus? (9) Is the effect of sympathetic nerve radiofrequency ablation in alleviating type 2 diabetes related to neurotransmitters? And (10) Whether the brain itself affects insulin secretion through neurotransmitters?

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FOOTNOTES

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