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Neuropeptidergic Regulation of Pancreatic Hormones, a Therapeutic Approach for Type 2 Diabetes Mellitus

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Abstract

A number of factors are considered responsible for type 2 diabetes, which has become epidemic. Apart from regular modulators (insulin and glucagon) of glucose metabolism, brain has also been observed to be involved in regulating pancreatic hormone release. Hypothalamic neuronal interactions are involved in insulin and leptin regulation as these neurons are very sensitive to insulin levels. Many neuropeptides have also been studied in the recent years to play a role in the maintenance of pancreatic hormone secretions. In this review, roles of some neuropeptides in the regulation of pancreatic hormones are reviewed. Substantial data signifies the involvement of neuropeptides in regulating food intake, glucose metabolism and energy expenditure. Studies indicate that acetylcholine and other neuropeptides are diffused to the endocrine islet cells and stimulate insulin and glucagon release upon activation of their specific receptors. Studies in dogs, mice and pigs showed that gastrin releasing peptides (GRP) stimulate insulin secretion via ganglionic GRP receptor activation. A positive correlation was found between plasma insulin and plasma 26RFa in healthy, obese and type 2 diabetic patients. An *in vitro* direct action of neuropeptide Y (NPY) on insulin release from pancreatic islets is inhibitory, but *in vivo* effect of NPY increases plasma insulin. A thorough knowledge of these neuropeptides in glucose signaling points out towards the major therapeutic role of neuropeptides in diabetes.

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Introduction

Secretion of hormones (insulin and glucagon) by pancreatic islet is regulated by nutrients (free fatty acids, glucose, amino acids and gut hormones like glucagon-like peptide 1 (GLP-1)) and autonomic nerves innervating the islets [1]. Islet cells are in close apposition to autonomic nerve terminals whose vesicles contain several neuropeptides and classical neurotransmitters (noradrenaline and acetylcholine), which are released from nerves upon activation. Neurotransmitters diffuse along the islet α and β-cells, causing inhibition or stimulation of secretion of islet hormone [1]. The autonomic nerves also affect islet function through changes in blood flow by innervating the islet blood vessels [1]. Neuropeptides can play a role in the control of the mechanism of hormone release and appetite. Neuropeptides such as leptin, neuropeptide Y (NPY), beta-endorphin and galanin may affect hormone release. NPY levels were observed high in obese hypertensive and diabetic patients in comparison with normal individuals [2]. The loss of NPY's inhibitory action was observed to elevate basal and glucose-stimulated insulin secretion [3]. Type 2 diabetes is characterized by insulin resistance. Glucose metabolism in healthy individuals is maintained by balanced insulin secretion. An unbalanced glucose-insulin metabolism leads to type 2 diabetes. An increase in insulin release is mediated by many signals, including lipids and glucose [1]. Neurotrophic factors from efferent nerves may modulate glucagon secretion [4, 5]. The objective of this review was to study a link between specific neuropeptides, pancreatic hormones and diabetes disease.

Brain regulation of glucose metabolism

The brain regulates food intake through the hypothalamus. The arcuate nucleus (ARC) within the hypothalamus senses peripheral metabolic signals [6]. Peripheral metabolic hormones, insulin, leptin and ghrelin act on first-order neurons, orexigenic (neuropeptide Y (NPY) and agouti-related peptide (AgRP)) and anorexigenic (proopiomelanocortin (POMC)) in the arcuate nucleus [7]. First order neurons like POMC communicate with second-order neurons, such as the lateral hypothalamus (LH) and paraventricular nucleus (PVN) [8]. α-MSH, which is transcribed form of POMC causes reduced food intake and mutation of its receptor causes obesity in humans [9, 10]. This signifies its role in the maintenance of normal body weight.

NPY infusion stimulates food intake through Y1 and Y5 receptors [11] and is required for the rapid stimulation of feeding [12]. The ventromedial hypothalamus (VMH) neurons sense leptin and glucose. The VMH communicates with the dorsomedial nucleus (DMN) and arcuate nucleus [13, 14]. Removal of the VMH and DMN causes hyperglycemia and obesity [15, 16] indicating their role in glucose homeostasis maintenance. Insulin is secreted from β-cells in response to energy flux. Plasma insulin concentrations increase in proportion to the amount of stored fat [17]. When insulin is administered directly into the central nervous system, it induces a dose-dependent reduction in food intake. Studies about hypothalamic glucose sensing neurons have strengthened our idea of glucose metabolism by central regulation [18, 19]. Change in glucose concentration in extracellular fluid alters the excitability of neurons, which are involved in glucose metabolism [20].

Acetylcholine regulation of endocrine islets

Acetylcholine (ACH**)** is released by nerve cells to send signals to other cells. Acetylcholine and other neuropeptides from autonomic nerves affect islet hormone secretion but little is known about the physiologic conditions that activate these nerves [21]. Meals activate islet parasympathetic nerves and also initiate and increase the early insulin response to meals. Studies of mice with either β-cell overexpression or β-cell deletion of acetylcholine receptors highlight the acetylcholine mediation of islet hormone secretion for glucose homeostasis. They have high glucose tolerance and increased insulin secretion, whereas β-cell acetylcholine receptor knockout mice have low glucose tolerance and reduced insulin secretion. The β-cell acetylcholine receptor overexpressing mice are also resistant to hyperglycemia and food-induced low glucose tolerance [22]. Studies indicate potential effects of the autonomic neurotransmitters on insulin secretion. Activation of neurotransmitter receptors has been shown to increase insulin secretion. For example, activation of the cholinergic receptors induces insulin secretion [23]. Acetylcholine and neuropeptides

are diffused to the endocrine islet cells and stimulate insulin and glucagon release upon activation of their specific receptors. This regulation is important in cephalic phase of meal-induced insulin secretion as well as for the first few minutes of food ingestion, but before nutrients stimulation of islet insulin secretion [24]. These parasympathetic islet nerves may also stimulate glucagon secretion during hypoglycemia [25].

Gastrin-releasing polypeptide (GRP)

Gastrin-releasing peptide is a human peptide that increases gastrin release and regulates gastric acid secretion [26]. Activation of different signaling mechanisms may contribute to insulin secretion by GRP such as increased cytoplasmic calcium has been found to stimulate GRP [27]. Also, phospholipase D and protein kinase C (PKC) contribute to the GRP-induced insulin secretion [28, 29]. GRP is localized to nerve terminals in the pancreatic ganglia, and is released from the isolated pig pancreas during vagal nerve activation [30]. Experimental studies in dogs, mice and pigs showed that GRP stimulates insulin secretion via ganglionic GRP receptor activation [31-33].

A possible effect of GRP on glucagon secretion is not determined. Studies in dogs showed no effect of GRP on glucagon secretion while only one study demonstrated GRP role in stimulating glucagon secretion in mice [1]. A fair number of genetic animal model studies have suggested that the brain, specifically the hypothalamus, plays an important role in the regulation of glucose and energy metabolism. It is well documented that the brain controls food intake, energy expenditure and insulin secretion. Glucose metabolism is maintained by interactions between the peripheral metabolic organs and brain. Any abnormality in these interactions causes the development of type 2 diabetes and obesity [34].

26RF amide regulation of glucose metabolism

The 26RF amide is a 26-aa neuropeptide belongs to the RFamide peptide family and is a potent orexigenic peptide in mice [35]. Studies suggest a role of hypothalamic neuropeptides in the control of glucose metabolism [36]. In this regard, 26RFa has been studied to play a potential role in regulating the glucose metabolism. 26RFa/43RFa has been found to regulate the glucose metabolism [37]. Studies show that pancreatic islets and rodent insulin-secreting cell lines INS-1E and MIN6 express 6RFa/43RFa and GPR103 [38, 39]. 43RFa promotes glucose uptake by β cells, whereas 26RFa does not [38]. Variable effects of 26RFa were studied on insulin and glucagon secretion by rat perfused pancreas [40]. In mice, 26RFa attenuates glucose-induced hyperglycemia but enhances insulin sensitivity and increases insulin production by the MIN6, suggesting its direct action on pancreatic β cells. Prévost et al. [39] reported a positive correlation between plasma insulin and plasma 26RFa in healthy, obese and type 2 diabetic patients.

Glucose metabolism dysregulation in diabetes

Normal body weight involves a balance of energy expenditure and energy intake. Pathological weight gain impairs ability and of the brain to maintain energy homeostasis. A number of defects have been demonstrated in the negative-feedback pathway in energy.

Diabetes mellitus results from abnormal pancreatic insulin secretion and is characterized by hyperglycemia [41, 42]. Studies suggest that defective metabolic sensing in hypothalamic neurons may lead to dysregulation of glucose homeostasis and diabetes [43]. Hypothalamic insulin–PI3K signaling is affected in rats with streptozotocin-induced diabetes. Insulin signaling in the hypothalamus has been found to be disrupted by fat-rich diet and may contribute to the development of diabetes [44]. Altered secretion of insulin and leptin may cause weight gain. Plasma leptin concentrations increase in relation to body mass index. However, plasma leptin concentrations are much increased than that of cerebrospinal fluid in obese individuals [45]. Leptin acts on hypothalamus neurons to regulate the energy balance, so leptin transfer to the brain can be important for its action [8]. Hypothalamic expressions of leptin receptors are reduced in rats with diet-induced obesity [46].

Role of neuropeptide Y in control of insulin secretion

The intracerebroventricular (ICV) microinjection of NPY in wild-type mice markedly increased insulin level after 30 min of treatment [47, 48].

Polymorphisms of the NPY gene affected glucose tolerance and diabetes [49]. Studies showed that when isolated islets of the mouse were treated with NPY, it significantly stimulated beta-cell replication by activating extracellular kinases and inhibited glucose-stimulated insulin secretion [50, 51]. NPY gene deletion in islet cells increased insulin secretion [52]. NPY decreases energy and stimulates food uptake [53]. NPY also regulates insulin and glucose metabolism via leptin [54]. An *in vitro* direct action of NPY on insulin release from pancreatic islets is inhibitory, but *in vivo*, NPY increases plasma insulin [55].

Concluding remarks

Accumulated evidence is demonstrating that central nervous system is playing an important role in the control of glucose metabolism via neuronal interactions and release of its neuropeptides and neurotransmitters. Acetylcholine, NPY and RF amide regulate the glucose metabolism both *in vivo* and *in vitro* islet cells. Some of them have both inhibitory and stimulatory roles in insulin release depending on their activities which may be *in vivo* and *in vitro*. Acetylcholine has been found to have a stimulatory role in insulin secretion and thus a positive role in glucose metabolism. Together, they act as strong regulators of food intake and glucose metabolism and hence can be potential targets in diabetes therapeutics. Clinical and preclinical studies will be needed to prove the efficacy and safety of new drugs aimed at these new targets. Although good amount of data can be found on the neuropeptide regulation of pancreatic hormones, more research is needed for better understanding of the role of neuropeptides in the pancreatic hormonal regulation for a therapeutic development of diabetes.

Conflict of Interest

The authors declare that they have no conflict of interest.

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