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Regulation of Glucose Homeostasis by Hypothalamic Nuclei

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Abstract: Diabetes mellitus is the most common metabolic disease in humans and is characterized by hyperglycemia and insulin resistance. Although current drug-based and insulin-based therapies bring great benefits to patients, they can only maintain a transient normal blood glucose level and do not fundamentally change the abnormal blood glucose control of the human body. Therefore, a comprehensive understanding of the mechanisms by which the human body maintains glycemic stability is a prerequisite for the treatment of diabetes. At present, a large number of studies have confirmed that the hypothalamus is a key region in the regulation of glucose homeostasis, but its neural mechanism of regulating blood glucose is still not fully elucidated. In this paper, the mechanism of glucose regulation by glucose-sensing neurons and various hypothalamic nuclei and their research progress will be reviewed.

Keywords: Blood glucose; Hypothalamus; Arcuate nucleus; Paraventricular nucleus

Introduction

Diabetes mellitus is a metabolic disease characterized by chronically increased blood glucose levels, and the incidence is increasing year by year worldwide and in China. However, the current treatment of diabetes can only briefly maintain blood glucose at normal levels, and does not completely cure diabetes, so a comprehensive understanding of the mechanism by which the human body maintains blood glucose stability is a prerequisite to conquer diabetes. It has been confirmed that the central nervous system is involved in the regulation of glucose homeostasis, in which multiple nuclei of the hypothalamus have the ability to sense and integrate changes in the corresponding metabolic levels and play an important role in controlling glucose and energy metabolism [1]. In this paper, we will review the research progress of multiple nuclei involved in energy metabolism in the hypothalamus in the mechanism of glucose regulation, and further elaborate the mechanism of glucose regulation in the hypothalamus in order to provide clues for finding new therapeutic targets for diabetes.

1. Central glucose sensing mechanism

Neurons in the hypothalamus can be divided into glucose-excited (GE) neurons and glucose-inhibited (GI) neurons according to their sensitivity to glucose concentration. GE is activated at elevated glucose levels and its firing frequency increases with increasing extracellular glucose concentration; GI is activated at reduced glucose levels and its firing frequency increases with decreasing extracellular glucose concentration. In addition, some scholars have demonstrated that astrocytes are involved in glucose sensing in the central nervous system and systemic glucose metabolism [2], endothelial cells interact with astrocytes and regulate glucose entry into the brain by changing blood-brain barrier permeability, of which glucose transporter-1 (GLUT-1) is highly expressed in astrocytes, and GLUT-1 loss leads to limited glucose transport into the brain. García-Cáceres et al. [2] found that hypothalamic astrocytes co-control central nervous system glucose sensing and systemic glucose metabolism by regulating glucose uptake at the BBB through insulin signaling, and this study also found that astrocyte-specific insulin receptor deletion reduced neuronal glucose sensitivity in proopiomelanocortin (POMC). Thus, non-neuronal cells in the CNS control glucose homeostasis by associating with glucose-sensing neurons.

2. Regulation of glucose homeostasis by hypothalamic nuclei

The hypothalamic nuclei involved in the regulation of glucose homeostasis mainly include the arcuate nucleus (ARC), paraventricular nucleus (PVH), ventromedial hypothalamus (VMH), lateral hypothalamic area (LHA) and suprachiasmatic nucleus (SCN) [3]. In the following, the author will elaborate on the mechanism of action of these nuclei in glucose regulation, respectively.

2.1 Arcuate Nucleus

ARC is located near the median eminence and contains two functionally antagonistic neuronal populations, neuropeptide Y (NPY) neu-

rons/agouti-related protein (AgRP) neurons and proopiomelanocortin (POMC) neurons/neurons with cocaine-amphetamine-regulated transcripts (CART) [4]. The activity of different types of neurons is regulated by glucose levels, and when glucose levels increase, POMC neurons activate and secrete the neurotransmitter α-melanocyte-stimulating hormone (α-MSH), which in turn induces anorexic effects and regulates peripheral glucose metabolism, thereby lowering blood glucose [5]; however, when glucose levels decrease, NPY/AgRP neurons are activated and release NPY and AgRP, and NPY directly stimulates feeding by activating NPY Y Y 1 and Y 5 receptors [6]. In addition, AgRP/NPY neurons can also directly inhibit POMC neurons to regulate feeding through inhibitory γ-aminobutyric acid (GABA) effects [7], and can also inhibit anorexia by inhibiting the release of α-MSH [8]. In addition to diet control, AgRP neurons exert glucose regulatory functions by regulating brown adipose tissue gene expression leading to impaired systemic insulin sensitivity [9]. In addition, endogenous hormones also exert effects on neurons within the ARC, which in turn control blood glucose levels, insulin inhibits AgRP neuronal firing through insulin receptor-dependent signaling, and leptin also exerts hypoglycemic effects by inhibiting AgRP neuronal activity [10 – 12].

In summary, ARC is essential for the regulation of feeding and metabolism [13]. According to the change of extracellular glucose concentration, different types of neurons are activated to achieve the regulation of glucose homeostasis. In addition, hormones can also affect neurons and then regulate blood glucose.

2.2 Ventral Medial Hypothalamic Nucleus

The VMH is located dorsally in the tubercle portion of the hypothalamus and mediolaterally in the intermediate region, which, like the ARC, also contains GE and GI neurons. When extracellular glucose concentration decreases, potassium channels open on GE neurons thereby inhibiting neuronal activity; whereas GI neurons are activated through the opening of chloride channels, thereby increasing blood glucose [14]. In addition to this, SF-1 neurons in the VMH play an important role in the regulation of energy and glucose metabolism through p110β. p110β is the phosphocreatine 3-kinase catalytic subunit and is an indispensable subunit for leptin and insulin to play a role in VMH [15]. Fujikawa et al. [16] found that deletion of p110β in SF-1 neurons disrupts glucose metabolism and confers insulin resistance in mice. Others have found that SF-1 neurons regulate neuronal activity and metabolism through the thrombospondin receptor α2δ-1, mediate sympathetic nerves to promote glucose uptake in peripheral tissues, and achieve glucose homeostasis [17]. On the other hand, PACAP neurons of the VMH secrete PACAP, which acts on their receptors and increases sympathetic activity in peripheral targets, thereby regulating blood glucose, thermogenesis, energy expenditure, and food intake [18].

In summary, the VMH is a heterogeneous nucleus containing many types of neurons that act on their respective receptors through different subunits or by secreting neuropeptides to maintain glucose homeostasis by improving glucose uptake or improving insulin resistance in peripheral tissues, and its regulation of energy expenditure is partially achieved by activating sympathetic nerves; however, the precise neural pathways that connect sympathetic nerves to the VMH have not been precisely identified, and therefore, future studies using emerging technologies may provide further insights into the functional pathways that connect sympathetic nerves to the VMH.

2.3 Paraventricular Nucleus

The PVN, located in the ventral diencephalon immediately adjacent to the third ventricle, is involved in regulating energy homeostasis and is a key site in regulating the endocrine system, which integrates signals from multiple brain regions, such as the suprachiasmatic nucleus, ventromedial hypothalamic nucleus, and arcuate nucleus. In the PVN, α-MSH released from POMC neurons in the arcuate nucleus interacts with melanocortin-4 receptor (MC4R) expressed by MC4R neurons to regulate energy intake [19]. On the other hand, PVN is an important component of autonomic pathways, and activation of PVN neurons can increase blood glucose levels through the sympathetic nervous system [20]. The hypothalamic-pituitary-adrenal (HPA) axis is a major neuroendocrine axis regulating homeostasis in mammals, including glucose metabolism. Small neurons in PVN synthesize corticotropin-releasing hormone, which increases hepatic glycogen synthesis by promoting glucocorticoid release from the adrenal cortex and reduces glycogen utilization and breakdown in tissues, thereby increasing blood glucose. It has also been shown [21] that dopaminergic neurons in the substantia nigra (SN) participate in the regulation of glucose metabolism in vivo through CRH neurons expressing dopamine receptor 2 in the PVN of the hypothalamus. This suggests that SN - PVN dopaminergic pathway regulates HPA axis function, leading to abnormal glucose metabolism. In addition, parvocellular neurons secrete thyrotropin-releasing hormone to control the hypothalamic-pituitary-thyroid axis and then regulate glucose metabolism [22]. Some scholars have also found that BMAL1, a clock gene in PVN, may be involved in circadian changes in blood glucose in healthy subjects, and BMAL1 regulates arginine vasopressin with circadian changes and releases it into the circulation, which alters blood glucose levels by directly activating pancreatic β-cells [23].

In conclusion, PVN is an important brain region regulating energy metabolism and plays a unique role in integrating signals and neuroendocrine in different brain regions.

2.4 Lateral hypothalamic area

The LHA is a subcortical brain region containing two specific neuronal populations that express orexin neurons that stimulate appetite

and neurons that express melanin-concentrating hormone (MCH) [24]. Orexin peptides secreted by orexin neurons not only regulate feeding processes, but also play a role in including arousal, addiction, and metabolism [25]. Central injection of orexin peptide can promote glucose release [26], and similarly, Yi et al. [27] found that orexin peptide injection by ICV induced feeding and drinking behaviors and also increased blood glucose through sympathetic pathways. Inutsuka et al. [28] found that activation of orexin neurons caused a synchronous increase in movement, feeding, and water intake, and affected metabolic factors such as respiratory exchange ratio and blood glucose levels, suggesting that orexin neurons play an indispensable role in regulating feeding behavior and metabolism. On the other hand, it has been shown that MCH neurons lower blood glucose by controlling glucose production in the liver or by increasing glucose uptake in muscle and fat [29].

These findings deepen our understanding of the important role of LHA in the regulation of glucose homeostasis, in which orexin neurons and MCH neurons regulate blood glucose levels through different mechanisms.

2.5 Suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN) of the hypothalamus coordinates circadian behavior in humans and mammals, controls resting activity cycles as well as a range of physiological and endocrine functions. The SCN is mainly composed of GABAergic neurons, and the nuclear receptors REV-ERB-α and REV-ERB-β within GABAergic neurons are key components of the circadian clock mechanism and show robust circadian rhythms in the SCN. Increases in REV-ERB during the late sleep cycle help to reduce GABA neuron excitability during wakefulness, thereby improving insulin sensitivity by enhancing insulin-mediated inhibition of hepatic glucose production [30]. Some scholars have decreased the activity of SCN neurons by local administration of tetrodotoxin to the SCN of rats, resulting in the production of endogenous glucose and systemic glucose uptake [31], a result that is completely consistent with the previous finding that SCN lesions in mice have a significant effect on endogenous glucose [32]. Foppen et al. [31] found that injection of GABA antagonists into the perifornical region resulted in hyperglycemia and increased endogenous glucose, and they speculated that the circadian rhythm of blood glucose concentration was caused by the circadian rhythm of GABAergic neurons projecting to the perifornical region, which provided evidence that GABAergic neurons in the SCN control diurnal blood glucose homeostasis. In addition, it has been further demonstrated that SCN vasopressin neurons control glycemic rhythms by regulating glucose entry into the ARC [33]. These findings provide insights into how the central circadian clock regulates circadian and glucose rhythms in hepatic insulin sensitivity.

In summary, glucose rhythm may be generated by the circadian clock and its autonomic projections in the SCN, but its downstream signaling pathways remain poorly understood, and some studies have found that the SCN does not act directly on autonomic nerves, but transmits signals to other regions of the hypothalamus, which in turn regulates glucose homeostasis.

3. Summary and outlook

In conclusion, the middle hypothalamus of the brain is a key region involved in glucose homeostasis, and current studies have shown that ARC regulates glucose metabolism in vivo through two different glucose-sensing neurons; VMH can regulate peripheral blood glucose by activating sympathetic nerves; PVN regulates glucose homeostasis by regulating neuroendocrine axes; LHA alters blood glucose concentration by regulating appetite; and SCN is a key brain region regulating circadian rhythm of glucose. However, the mechanism of action of hypothalamic nuclei involved in regulating glucose homeostasis has not yet been fully elucidated, and most of these mechanisms are currently explored in animal models and human research data are lacking. In addition, the mechanism of action of other substances and hormones on glucose-sensing neurons, how glucose-sensing neurons and glial cells are regulated by other substances and hormones, and how they interact remain to be explored in a large number of studies.

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