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Basic study

Central glucose sensing

Détection centrale du glucose

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Abstract

Since concentrations of blood glucose represent an important aspect of systemic energy homeostasis, we postulate that fluctuation of glycemia must not be only detected by pancreatic β-cells, and central neuron system (CNS) could monitor and regulate the plasma glucose levels in some stilled undefined mechanisms. In this review, we will summarize recent progress focused in the identification and characterization of actions of central glucose in the regulation of systematic energy homeostasis and glucose homeostasis, which may provide new insights into the prevention and treatment of diabetes.

Keywords: CNS; Glucose sensing

Résumé

La concentration plasmatique en glucose est un élément important de l'homéostasie énergétique systémique. Cette revue a pour postulat que les fluctuations de glycémie pourraient ne pas être détectées seulement par les cellules bêta du pancréas, et que le système nerveux central (SNC) pourrait détecter et réguler le niveau de glucose plasmatique selon des mécanismes encore non définis. La revue résume les progrès récents concernant l'identification et la caractérisation des actions du glucose au niveau central dans la régulation de l'homéostasie énergétique systémique et de l'homéostasie du glucose, ce qui pourrait fournir de nouvelles perspectives dans la prévention et le traitement du diabète.

Mots clés : Système nerveux central (SNC) ; Détection du glucose

1. Introduction

Diabetes as well as related complications are among the most challenging health problems and the World Health Organization (WHO) projects that diabetes will be the 7th leading cause of death in 2030 [1], generating an urgency for the scientific community to explore the underlying mechanisms. In the pathological conditions of diabetes, glucose homeostasis is severely disturbed. Despite that the complex mechanisms underlying the progress of diabetes remain elusive, increasing literature suggests that central glucose, fatty acids and amino acids play a role in the modulation of glycemia, the physiological significance of which may be underscored until recently. Carbohydrates, lipids and amino acids are three principal resources of extra glucose production, the availability of which represents crucial signals of organismal survival. Therefore, the ability of the organs to cope with alterations in circulating nutrients levels is key to maintain healthy. The hypothalamus of the human body was postulated to a main sensor to integrate multiple nutrient-related signals and contribute a lot in the regulation of energy and glucose homeostasis [2]. Within the arcuate nucleus (ARC) of the hypothalamus, both proopiomelanocortin (POMC) neurons, the anorexigenic neurons releasing a-MSH, and the orexigenic agouti-related protein (AgRP)/neuropeptide Y (NPY) coexpressing neurons, have been indicated in controlling homeostatic

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Table 1
Arcuate nucleus (ARC) glucosensing neurons.

Glucosensing neurons	Glucose response		Mechanism involved
	Glucose sensitivity range < 5 mmol/L	Glucose sensitivity range > 5 mmol/L	
Glucose change	5 to 0.5 mmol/L	5 to 15 mmol/L	
GE	Inhibition	No effect	K_{ATP}
GI	Excitation	No effect	CFTR
HGE	No effect	Excitation	K_{ATP} independent non-selective cationic conductance [40]
HGI	No effect	Inhibition	?

GE: glucose excited; GI: glucose inhibited; HGE: high glucose excited; HGI: high glucose inhibited; CFTR: cardiac cystic fibrosis transmembrane regulator; ?: unknown.

functions in the mammal. These neurons appear to be involved in mediating actions of nutrients sensing in the brain, which then send efferent signals to peripheral organs, for example liver and pancreas, to regulate the endogenous glucose production [3], glucose stimulated insulin release (GIIS) [4]. In this review, we will focus on recent insights relating the identification and characterization of central glucose sensing pathway in the regulation of energy homeostasis and glucose homeostasis.

2. Glucose sensing neurons in the brain

In contrast to most neurons in the brain that fuel glucose to facilitate their metabolic needs, selective groups of neurons serve as glucose sensors via altered firing rates in response to ambient glucose levels [5]. Evidence has been provided that four distinct populations of glucosensing neurons were reportedly existing in the ARC (Table 1). Glucose is capable of exciting POMC neurons and inhibiting NPY neurons. Moreover, Adenosine 5′-triphosphate (ATP)-dependent sensitive potassium (K_{ATP}^{+}) channels are widely expressed in POMC and NPY neurons [6]. The presence of Kir6.2, sulfonylurea receptor 1 channel subunits and glucosekinase in the POMC neurons, strongly highlights that these neurons may be sensitive to metabolic inhibition, which was verified by the varied firing rate in response to changes in glucose availability [7,8]. On the contrary, POMC neurons were also found insensitive to glucose alterations greater or less than 5 mM, and glucosensing neurons were among no-POMC-GFP-recorded ARC cells [9]. Besides, glucose transporter type 2 (Glut2) expressing neurons in the lateral hypothalamus, the dorsal vagal complex, and the basal medulla is necessary for central glucose to facilitate leptin's control of thermoregulation [10]. Therefore, other types of glucose sensing neurons within or outside hypothalamus cannot be excluded.

3. Peripheral actions of central glucose sensing

As it is known, the endocrine pancreas is richly innervated by both parasympathetic and sympathetic inputs, the former stimulates, whereas the latter inhibits insulin secretion [11,12]. Although insulin secretion stimulated by glucose is thought mainly mediated by peripheral action of β-cells, intracerebroventricular (icv) glucose infused rats displayed improved glucose handling during the first 10 mins of the intravenous glucose tolerance tests (IVGTTs), with a significant lower area under the excursion curve ($AUC_{0\sim10}$) relative to control urea infused animals, highlighting that the hypothalamic glucose sensing participates in the regulation of insulin secretion [13]. Since impaired first-phase glucose-stimulated insulin release is a major pathological hallmark of the early stages of type 2 diabetes [14], impaired glucose sensing in the brain may contribute to the early development of type 2 diabetes in prone population. Therefore, the effectiveness of central glucose sensing in the regulation of insulin secretion in diabetic models merits further investigation. Moreover, in β-cells there are microdomains (alternatively referred as "excitosomes", "Ca^{2+} microdomains", or "secretory microdomains"), where the submembrane is in close proximity to voltage-gated calcium channels [15–18]. Since these microdomains seem to be especially important for the early phase insulin secretion, we ask could the underlying molecular mechanisms is linked to regulation of microdomains in β-cells? Effective hypothalamic glucose sensing was reported to low hepatic glucose production (HGP), which was impaired under pathological conditions of sustained hyperglycemia [19]. This data indicates that control from central glucose sensing is required for normal hepatic glucose production. In diabetes, counter regulatory (epinephrine and glucagon) responses against hypoglycemia induced by intensified glucose-lowering regimens are disrupted. In normal rats, the closure of brain K_{ATP}^{+} channels by icv perfusion of sulfonylurea suppressed counter regulatory response to brain glucopenia and systemic hypoglycemia [19,20], pointing that glucose sensing in the brain may also be responsible for detection of hypoglycemia. Central glucose was also demonstrated to enhance the leptin sensitivity of NPY and POMC neurons on the control of thermoregulation, dependent of Glut2 in the lateral hypothalamus, the dorsal vagal complex, and the basal medulla but not in the arcuate nucleus [10].

To summerize, recent work is primarily focused on the modulation of central glucose on HGP, GSIS, counter regulatory responses against hypoglycemia as well as thermoregulation, more is needed to clarify whether or not it may influence other aspects of blood glucose regulation. For instance, extrahepatic gluconeogenesis stemming from the kidneys and intestine were