Neuroscience 323 (2016) 110–120

REVIEW

GLUCOSE AND HYPOTHALAMIC ASTROCYTES: MORE THAN A FUELING ROLE?

C. LELOUP,* C. ALLARD,† L. CARNEIRO,‡ X. FIORAMONTI, S. COLLINS AND L. PÉNICAUD

Centre des Sciences du Goût de l'Alimentation, CNRS UMR 6265, Dijon, France

Centre des Sciences du Goût de l'Alimentation, INRA UMR 1324, Dijon, France

Centre des Sciences du Goût de l'Alimentation, Université de Bourgogne, Dijon, France

Abstract—Brain plays a central role in energy homeostasis continuously integrating numerous peripheral signals such as circulating nutrients, and in particular blood glucose level, a variable that must be highly regulated. Then, the brain orchestrates adaptive responses to modulate food intake and peripheral organs activity in order to achieve the fine tuning of glycemia. More than fifty years ago, the presence of glucose-sensitive neurons was discovered in the hypothalamus, but what makes them specific and identifiable still remains disconnected from their electrophysiological signature. On the other hand, astrocytes represent the major class of macroglial cells and are now recognized to support an increasing number of neuronal functions. One of these functions consists in the regulation of energy homeostasis through neuronal fueling and nutrient sensing. Twenty years ago, we discovered that the glucose transporter GLUT2, the canonical ''glucosensor'' of the pancreatic beta-cell together with the glucokinase, was also present in astrocytes and participated in hypothalamic glucose sensing. Since then, many studies have identified other actors and emphasized the astroglial participation in this mechanism. Growing evidence suggest that astrocytes form a complex network and have to be considered as spatially coordinated and regulated metabolic units. In this review we aim to provide an updated view of the molecular and respective cellular pathways involved in hypothalamic glucose sensing, and their relevance in physiological and pathological states.

This article is part of a Special Issue entitled: Astrocyte-Neuron Interact.

Key words: hypothalamic glucose sensing, glucose, lactate, connexins 30 and 43, astroglial gap junctions, astroglial hemichannels.

Contents

INTRODUCTION

Energy homeostasis maintains body energy supply and expenditure in a balanced state. This balance is governed by complex communications between different organs where the brain plays a central role. It integrates short-term and long-term peripheral signals such as circulating nutrients, peptides and hormones according

*Correspondence to: C. Leloup, Centre des Sciences du Goût et de l'Alimentation, CNRS UMR 6265, INRA UMR 1324, Université de Bourgogne, 9E boulevard Jeanne d'Arc, 21000 Dijon, France.
E-mail addresses: corinne.leloup@u-bourgogne.fr (C. Leloup), callard@tulane.edu (C. Allard), lionel.carneiro@unil.ch (L. Carneiro), xavier.fioramonti@dijon.inra.fr (X. Fioramonti), stephan.collins@u-bourgogne.fr (S. Collins), luc.penicaud@u-bourgogne.fr (L. Pénicaud).
† Present address: Tulane Health Science Center, Department of Medicine, New Orleans, USA.
‡ Present address: Université de Lausanne, Département de physiologie, Lausanne, Switzerland.

Abbreviations: 2-NBDG, 2-[N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-D-glucose (metabolizable); 4-CIN, alpha-cyano-4-hydroxycinnamate; 6-NBDG, 6-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose; ARC, Arcuate nucleus; BBB, Blood–brain barrier; Cx, connexin; GK, glucokinase; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; GLUT, glucose transporter; MCT, monocarboxylate transporter; pCMBS, p-chloromercuribenzene sulfonate.

http://dx.doi.org/10.1016/j.neuroscience.2015.06.007

to their release and integration: Among macronutrients, carbohydrates exhibit the most rapid gastric emptying and are the first ones to be digested and thus released in the blood. After integration of these signals, the brain, in turn, sets up adaptive responses in order to modulate peripheral organ activity and food intake (Fig. 1). Among all circulating parameters, glycaemia is one of the most tightly regulated. Indeed, maintaining near constant glucose availability is crucial for many cellular activities. Therefore, blood glucose concentration remains stable in physiological conditions (5 mM), and any smallest variations are rapidly and finely counter-regulated. Chronic and pathological variations results in a loss of adequate brain glucose sensing which are likely to worsen the control of glucose homeostasis (Pénicaud et al., 2006; Thorens, 2008; Colombani et al., 2009; Ogunnowo-Bada et al., 2014).

Brain glucose sensing takes place primarily in the most ventral part of the brain, the hypothalamus. This is facilitated by its proximity to the Willis polygon, a vascular system supplying the brain and related structures, making the hypothalamus the first brain area supplied with arterial blood. While the whole brain is considered as partially isolated from the periphery by the blood–brain barrier, the hypothalamus is located in a region where capillaries also appear more fenestrated. For many years, scientific evidences have supported the existence of permeable spaces (ions/nutrients) due to the presence of endothelial, astroglial or tanycyte-specific proteins mostly located in microdomains within these hypothalamic cells in the vicinity of nutrient-sensitive neurons (Ganong, 2000; Yonezawa et al., 2003; Norsted et al., 2008; Ciofi et al., 2009). Consequently, although not directly demonstrated, it is assumed that small-size blood nutrient concentrations (i.e., blood glucose) reaching hypothalamic areas (of which, the arcuate nucleus (ARC) seems to be of crucial importance) could be at or near levels to those present in the blood.

Fifty years after the seminal works on hypothalamic glucose-sensitive neurons (Anand et al., 1962; Oomura et al., 1969), studies have highlighted the participation

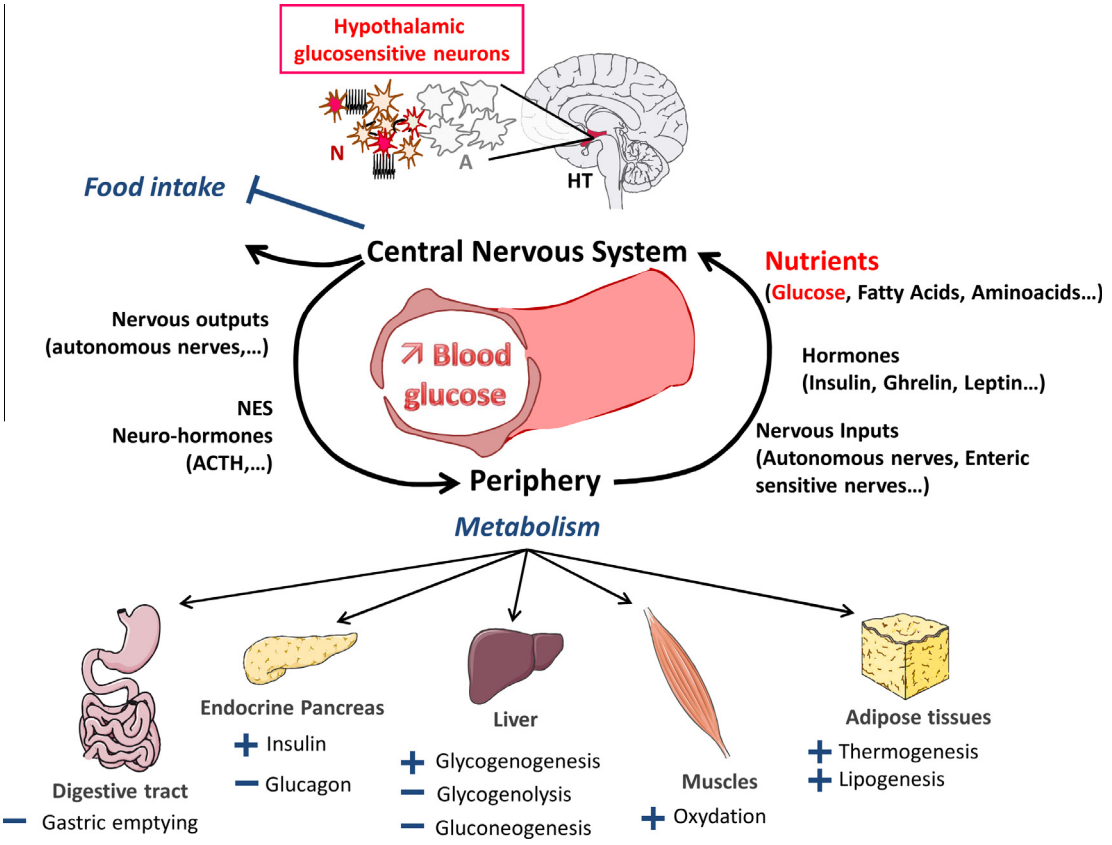

Fig. 1. Physiological responses after hypothalamic glucose detection of increased blood glucose. Blood increase of circulating nutrients (firstly glucose after a meal, then aminoacids and finally lipids) enters the brain, being mostly detected in the hypothalamus (HT) thanks to a fenestrated vasculature. Hormones secreted (increased insulin and leptin, decreased ghrelin after a meal) are also detected, the hypothalamus being highly enriched in their receptors, at both astroglial (A) and neuronal (N) membranes. Hypothalamus also receives multiple indirect inputs from the autonomous and enteric nervous system, mainly stemming from the gastro-intestinal tract. The short-term signal glucose triggers activation or inhibition of some hypothalamic glucosensitive neurons, leading to numerous physiological responses: transient decreased food intake (glucose inhibited food intake exerts maximal effects the first 30 min), while most vagal inputs increase their activity (+) and splanchnic ones decrease (−), finely tuning autonomous activity toward an anabolic status. The neuroendocrine system (NES) modulates the release of several neuro-hormones (for instance ACTH) also implied in the control of metabolism. These direct (nervous) and indirect (hormones) controls lead to multi-organ responses allowing glycemia decline to the basal value (5 mM).