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Review

Brain GLP-1 and insulin sensitivity

Darleen Sandoval [a], Stephanie R. Sisley [b, *]

[a] Department of Surgery, University of Michigan, Ann Arbor, MI, United States
[b] Department of Pediatrics, Division of Nutrition, Baylor College of Medicine, Houston, TX, United States

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ABSTRACT

Type 2 diabetes is often treated with a class of drugs referred to as glucagon-like peptide-1 (GLP-1) analogs. GLP-1 is a peptide secreted by the gut that acts through only one known receptor, the GLP-1 receptor. The primary function of GLP-1 is thought to be lowering of postprandial glucose levels. Indeed, medications utilizing this system, including the long-acting GLP-1 analogs liraglutide and exenatide, are beneficial in reducing both blood sugars and body weight. GLP-1 analogs were long presumed to affect glucose control through their ability to increase insulin levels through peripheral action on beta cells. However, multiple lines of data point to the ability of GLP-1 to act within the brain to alter glucose regulation. In this review we will discuss the evidence for a central GLP-1 system and the effects of GLP-1 in the brain on regulating multiple facets of glucose homeostasis including glucose tolerance, insulin production, insulin sensitivity, hepatic glucose production, muscle glucose uptake, and connections of the central GLP-1 system to the gut. Although the evidence indicates that GLP-1 receptors in the brain are not necessary for physiologic control of glucose regulation, we discuss the research showing a strong effect of acute manipulation of the central GLP-1 system on glucose control and how it is relevant to type 2 diabetic patients.

Contents

Abbreviations: ARC, arcuate nucleus; AP, area postrema; CRH, corticotropin-releasing hormone; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; GTT, glucose tolerance test; NS, nucleus of the solitary tract; PVN, paraventricular nucleus; VMH, ventromedial hypothalamus.

* Corresponding author. Department of Pediatrics, Division of Nutrition, Baylor College of Medicine, 1100 Bates Ave., Houston, TX 77459, United States. Tel.: +1 713 798 0391; fax: +1 713 798 7057.
E-mail address: sisley@bcm.edu (S.R. Sisley).

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1. Introduction

The rising incidence of type 2 diabetes and the side effects of available therapies have led to searches for new more effective drug targets. One of these targeted systems that has met with good success is the glucagon-like peptide-1 (GLP-1) system. Decades ago, researchers observed that orally given glucose resulted in a smaller glucose excursion than intravenously administered glucose and the lower glucose excursion was associated with a greater rise in insulin. This difference was referred to as the incretin effect and the physiology suggested that it was due to a nutrient-induced intestinal secretion that then acted on the pancreas to stimulate insulin secretion. GLP-1 was discovered as an incretin in humans in 1987 (Kreymann et al., 1987). GLP-1 is made in the L-cells of the intestine and has only one known receptor, the GLP-1 receptor (GLP-1R) (Baggio and Drucker, 2007). Not surprisingly, GLP-1Rs are located on the insulin producing cells of the pancreas (Richards et al., 2014) and long-acting analogs to activate GLP-1Rs have been effective as antidiabetic therapies (Buse et al., 2013). However, GLP-1 also is produced within the brain and its receptors are in key regions associated with both food intake and glucose control (to be discussed later). Thus, much research has sought to answer if brain GLP-1 signaling is necessary for the effects of GLP-1 on glucose tolerance. This review will focus on the glucose homeostatic effects of GLP-1 in the brain, both pharmacological and physiological.

2. Glucose control by the brain

Glucose is a tightly regulated nutrient in the body and is affected by nutrient ingestion, tissue uptake, new synthesis by the liver, and release of stored glucose (in the form of glycogen). Glucose levels are remarkably stable throughout the day despite changes in feeding or activity status. The stability of glucose levels, also referred to as glucose homeostasis, is a result of several physiological processes. For many years after the discovery of insulin, glucose homeostasis was thought to be regulated only by peripheral processes. Insulin, produced by the beta cells of the pancreas, has well known actions within fat and skeletal muscle cells to stimulate glucose uptake and within the liver to suppress glucose output. However, within the brain, distinct regions have also proven to be important in regulation of glucose homeostasis (Sisley and Sandoval, 2011), specifically the arcuate nucleus of the hypothalamus (ARC), the ventromedial hypothalamus (VMH), the nucleus of the solitary tract (NTS) as well as cell bodies for the vagus nerve. Several hormones and cellular signaling systems including insulin, leptin, the melanocortin system, K-ATP channels, and mTOR have all been shown to have effects on glucose homeostasis through brain mechanisms (Grayson et al., 2013).

3. Characteristics of GLP-1 action in the brain

GLP-1 is made in the periphery but the extent to which peripherally secreted GLP-1 reaches CNS-located GLP-1Rs is debated. GLP-1 is rapidly degraded in the circulation by proteases rendering a half-life of only a couple of minutes (Baggio and Drucker, 2007). Despite this, radiolabeled GLP-1 and GLP1R agonists can cross the blood–brain barrier after peripheral administration (Hassan et al., 1999; Hunter and Hölscher, 2012). GLP-1 is also synthesized by the hindbrain in a discrete set of neurons within the nucleus of the solitary tract (NTS) in rats (Larsen et al., 1997) and similarly in non-human primates (Vrang and Larsen, 2010). These neurons have wide projections to hypothalamic, thalamic and cortical areas (Göke et al., 1995; Llewellyn-Smith et al., 2011). Overall, there is evidence for high conservation of GLP-1 positive cells in the CNS across multiple species (Ghosal et al., 2013). However, little is known about the neurophysiology of these neurons and whether it is peripheral or central secretion of GLP-1 that activates CNS GLP-1 receptors. Thus, critical questions remain unanswered regarding the source of GLP-1 that activates CNS GLP-1 receptors.

Much of what is known about the activation of CNS GLP-1 receptors is via exogenous administration of GLP-1 or its antagonist directly into the CNS. When administered centrally, GLP-1 induced c-fos expression, a marker of neuronal activation, in specific brain areas including distinct regions of the paraventricular nucleus (PVN), supraoptic nuclei, ARC, NTS, and area postrema (AP) (Larsen et al., 1997). GLP-1R agonists, albumin-exendin-4 conjugate, and peripheral exendin-4 increased c-fos in the AP, NTS, and PVN as well (Baggio et al., 2008). Within the PVN, central GLP-1 administration has been shown to cause c-fos expression in corticotropin-releasing hormone (CRH) neurons (Sarkar et al., 2003). Thus, GLP-1 or its analogs can directly activate regions of the brain shown to be important for glucose control.

GLP-1R mRNA was found in the human brain (Wei and Mojsov, 1995) and autoradiography showed that it bound to multiple sites in both rat and mice brains, including the thalamus, hypothalamus, AP, amygdala, hippocampus, and NTS (Göke et al., 1995; Scrocchi et al., 1996). GLP-1R mRNA was found in micropunches of the rat NTS, AP, ARC, VMH, PVN and lateral hypothalamus, with highest expression in ARC and AP (Li et al., 2003). More recent genetic tools have demonstrated that fluorescent reporter strains showed abundance of GLP-1R expressing cells in mouse AP, ARC, PVN, and VMH (Richards et al., 2014). Much is to be learned regarding the phenotype of these neurons but it has been demonstrated that GLP-1R nerve fibers have been shown to synapse on rat CRH neurons (Sarkar et al., 2003) which has implications for glucose control under stressful stimuli. In addition, the ARC is an extremely important loci for CNS regulation of glucose homeostasis and GLP-1R mRNA co-localizes with ARC POMC but not AgRP cells in rats (Sandoval et al., 2008). Thus, it is clear that the ability of GLP-1 to signal through its receptor is present in multiple areas of the brain.

4. Measuring glucose homeostasis

Since glucose homeostasis is affected by several processes, including glucose uptake (insulin and non-insulin mediated), glucose production (mainly by the liver), and insulin secretion, we will briefly review the techniques to assess these different processes.

4.1. Glucose tolerance

A glucose tolerance test (GTT) measures the body's ability to clear glucose from the blood. GTTs are performed by rapidly administering a bolus of glucose and performing serial glucose measurements. Glucose can be administered orally (OGTT), intraperitoneally (IpGTT), or intravenously (IVGTT). Oral administration of glucose will evoke the gut to respond and secrete hormones to aid in the clearance of glucose (e.g. incretin effect). Intraperitoneal glucose administration bypasses the intestine and instead gets rapidly absorbed from the peritoneal cavity into the portal vein. The overall result from a GTT describes how quickly the body can respond and clear glucose from its system but not the underlying processes responsible. Although pairing a GTT with a measurement of insulin can be informative, the differing glucose excursions between groups and the difficulty in timing the measurements with the glucose dose only provide for a gross comparison of glucose and insulin responses to a given glucose load. To study insulin secretion, one strategy is to use an IVGTT. With this technique, a small amount of glucose is infused intravenously which then directly stimulates