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Central leptin action on euglycemia restoration in type 1 diabetes: Restraining responses normally induced by fasting?

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ABSTRACT

Leptin monotherapy is sufficient to restore euglycemia in insulinopenic type 1 diabetes (T1D), yet the underlying mechanism remains poorly understood. Accumulating evidence demonstrates that the brain mediates the leptin action on euglycemia restoration. Here, we first review evidence supporting that symptoms in T1D resemble an uncontrolled response to fasting. Then, we discuss recent research progress on brain neurons and their neurotransmitters that potentially mediate the leptin action. Finally, peripheral effective pathways, which are normally involved in fasting responses and associated with leptin action on euglycemia restoration in T1D, will also be discussed. This summary complements several previous excellent reviews on this topic (Meek and Morton, 2016; Perry et al., 2016; Fujikawa and Coppari, 2015). A deep understanding of neurocircuitry and the peripheral effective pathways that mediate the leptin action on euglycemia restoration will likely lead to novel targets for an insulin-independent therapeutics against T1D.

1. Introduction

Insulinopenic type 1 diabetes mellitus (T1D), an escalating disease around the world, is caused by insulin deficiency following destruction of insulin-producing pancreatic β cells. To date, exogenous insulin treatment remains the only option for T1D patients. However, insulin treatment, although effective, is associated with unwanted side effects of obesity development and life-threatening hypoglycemia, and with hypoglycemia unawareness caused by frequent insulin-induced hypoglycemia (Cryer, 2005; Polsky and Ellis, 2015). Thus, an alternative insulin-independent treatment is highly desired. Excitingly, accumulating data have recently established that monotherapy of leptin, the master regulator for energy homeostasis, is sufficient to restore euglycemia and promotes survival in T1D independently of insulin action (Chinookoswong et al., 1999; Yu et al., 2008; Kojima et al., 2009; Wang et al., 2010; Fujikawa et al., 2010, 2013; Xu et al., 2016; Perry et al., 2014). Of note, unlike those associated with insulin administration, the glucose-lowering effect of leptin accompanies less risk of hypoglycemia and improved lipid profiles (Yu et al., 2008; Wang et al., 2010; Fujikawa et al., 2010; Denroche et al., 2011). Importantly, the leptin action on insulin-independent euglycemia restoration is also independent of its action on feeding and body weight (Wang et al., 2010; Fujikawa et al., 2010). Collectively, these findings raise the potential that leptin alone or its combination with insulin could be a very reliable therapeutic choice for T1D treatment. However, although it is accepted that the brain mediates the leptin action on euglycemia restoration, the underlying mechanism remains unclear despite intensive research on this topic. Several recent excellent reviews have discussed the research progress toward the understanding of neural pathways underlying the leptin action (Meek and Morton, 2016; Perry et al., 2016; Fujikawa and Coppari, 2015). The current review offers a complementary discussion on the mechanism of the leptin action with integration of some of our own published as well as unpublished results.

2. Type 1 diabetes resembles an uncontrolled fasting response

Animals and humans have evolved an efficient homeostatic regulation of energy balance. In response to fasting, an array of counter-regulatory responses are initiated to maintain glucose homeostasis and to ensure sufficient glucose supply for key glucose-dependent organs like the brain for survival (Tesfaye and Seaquist, 2010; Beall et al., 2012). To achieve this, several adaptive responses are initiated in a coordinated fashion. The insulin

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Table 1
Common features shared between fasting conditions and type 1 diabetes (T1D) symptoms and their reversal in T1D upon leptin treatment.

	Fasting Compared to controls	T1D Compared to controls	T1D + leptin
Serum insulin	very low	very low/undetectable	very low/undetectable
Serum leptin	very low	very low	increased
Serum glucagon	increased	increased	restored
HPA axis	activated	activated	suppressed
hepatic glucose output	increased	increased	reversed
Glucose utilization	reduced	reduced	largely reversed
Lipolysis	increased	increased	restored
AgRP/NPY expression	increased	increased	restored
Appetite	increased	increased	reversed

concentration will be reduced to limit glucose utilization in peripheral organs like fat and muscle tissues (Sprague and Arbelaez, 2011). Leptin levels will also be reduced to increase the drive for feeding (Ahima et al., 1996). During the initial phase of fasting, glycogen in liver, muscle and other tissues will be utilized to supply blood glucose. With further fasting, fat in adipose tissues and protein in muscle tissues will be mobilized and converted to glucose for the maintenance of glucose homeostasis. This glucose mobilization process is largely driven by a coordinated hormonal response (Tesfaye and Seaquist, 2010; Felig et al., 1979). The glucose homeostasis during fasting is achieved through mobilization of counterregulatory hormones including glucagon, catecholamines, corticosterones and growth hormones in a hierarchical way (Cryer, 1997). All these changes will reduce glucose utilization in peripheral organs and increase hepatic glucose output. It has been well established that this coordinated response is controlled by brain neurons (Beall et al., 2012). Within the brain, especially in the hypothalamus, a subset of neurons can sense and are activated by reduced glucose levels, which will initiate the above-mentioned hormonal responses (Fujikawa et al., 2013; Beall et al., 2012; Meek et al., 2016; Chan and Sherwin, 2013). Supporting this, central administration of 2-deoxy-glucose, a non-metabolizable glucose analogue and an inhibitor of glucose kinase, to non-fasting animals, induces a similar counter-regulatory response to fasting, and renders hyperglycemia (Salter and Watts, 2003).

Despite a stark difference in blood glucose levels between fasting-induced responses and T1D, it is striking that many of fasting responses resemble the symptoms in T1D. Both conditions share a series of common features (Table 1), which include: 1) low insulin and leptin (Havel et al., 1998; Roden et al., 2000; Boden et al., 1996; Chan et al., 2002); 2) increased drive for feeding; 3) increased counter-regulatory responses including increased glucagon levels, hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) (Xu et al., 2016; Perry et al., 2014; Denroche et al., 2011; Beer et al., 1989; Norrelund et al., 2001); 4) increased hepatic glucose output and reduced glucose utilization in adipocytes and muscle tissues; 5) increased lipolysis and protein metabolism; and 6) elevated hypothalamic agouti-related protein (AgRP) and neuropeptide Y (NPY) expression, but reduced hypothalamic proopiomelanocortin (POMC) production (Sindelar et al., 1999; Makimura et al., 2003; Hahn et al., 1998; Mizuno et al., 1998); and 7) suppression of the growth hormone(GH)-insulin-like growth factor (IGF)-1 axis (Norrelund et al., 2001; Russell-Jones et al., 1992; LaPaglia et al., 1998). These similarities strongly suggest that T1D is in a state of fasting-response. Supporting this, leptin, a fasting responsive hormone, when administered, can reverse counter-regulatory responses including the HPA and hypothalamus-pituitary-gonadal axis to fasting (Ahima et al., 1996) and can also reduce heightened counter-regulatory responses including the HPA axis in T1D (Wang et al., 2010; Fujikawa et al., 2010). Thus, the effect of leptin on euglycemia restoration is, at least, associated with its ability to suppress typical responses that are initiated by fasting. Compared to fasting-induced responses, T1D has an exaggerated counter-regulatory response even in face of higher glucose levels, suggesting that T1D is in a state of uncontrolled fasting-induced response. Therefore, it is imperative to study the mechanism underlying fasting-induced responses to understand the leptin action on euglycemia restoration in T1D.

3. Leptin levels in T1D

Leptin is markedly reduced in both T1D and fasting (Yu et al., 2008; Ahima et al., 1996). Administration of leptin back to T1D or fasting reverses the heightened counter-regulatory responses in both conditions, and effectively restore euglycemia in T1D (Yu et al., 2008; Wang et al., 2010; Fujikawa et al., 2010; Ahima et al., 1996). Thus, it is desirable to therapeutically increase leptin levels for the treatment of T1D. However, the mechanism underlying reduced leptin levels in both conditions remains unclear. Of note, reduction in blood leptin levels following insulin reduction in T1D is prior to and unrelated to body weight changes (Denroche et al., 2011; Hidaka et al., 2001), arguing that at least in short term circulating leptin levels are un-proportional to body fat but is controlled by insulin signal. In support of this notion, many reports have demonstrated that insulin directly stimulates leptin secretion (Saladin et al., 1995; Saad et al., 1998; Pagano et al., 1997), which at least in part explains that leptin is reduced in fasting and T1D where insulin is reduced. Given the fact that the leptin level is controlled by insulin and that leptin effectively restores euglycemia in an insulin-independent fashion, it appears that leptin functions as a downstream brain mediator for the insulin action on glucose hemostasis. Supporting this, mice with deficiency in leptin, leptin receptors or other leptin signaling pathways, even with higher levels of insulin, exhibit impaired glucose homeostasis (Bates et al., 2003; Zhang et al., 1994; Lee et al., 1996). However, the mechanism underlying the insulin action on leptin expression and secretion is unknown. However, it is unlikely that a direct action is involved since insulin receptor deletion in fat tissues leads to higher levels of leptin (Bluher et al., 2002). Revealing this mechanism is imperative to identify novel factors that can increase leptin expression and secretion in an insulin-independent manner, potentially leading to an effective and novel treatment for T1D.

4. Leptin action in the brain on insulin-independent glucose homeostasis

Growing evidence indicates that leptin's antidiabetic action is mediated by a central mechanism. Thus, the leptin action is mediated, in principle, by a diverse group of LepR-expressing neurons in the brain including the hypothalamus and many extrahypothalamic brain regions (Schwartz et al., 1996; Myers et al., 2009). The brain sites and neuronal subtypes that are involved in the leptin action have been extensively reviewed by others (see for example (Meek and Morton (2016), Coppari and Bjorbaek (2012)), and will not be discussed. Generally, LepR neurons can be broadly divided into two major subsets that release either fast-acting neurotrans-

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