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Hypothalamic GLP-1: the control of BAT thermogenesis and browning of white fat

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Brown adipose tissue (BAT) is a specialized organ responsible for thermogenesis, a process required for maintaining body temperature. Since the discovery that BAT and brite/beige cells are functional in adult humans, many studies have been focusing on the physiology and functionality of this organ. The brain is controlling the maintenance of body temperature through a complex neuronal network. One of the candidates to modulate thermogenesis at central level is glucagon-like peptide-1 (GLP-1), with GLP-1 receptors widely expressed throughout the brain. Our group has recently reported that stimulation of brain GLP-1 receptors in the ventromedial nucleus of the hypothalamus is essential for the activation not only of BAT thermogenesis, but also browning of white fat. Notably, both actions are mediated by specific inhibition of the energy sensor AMP-activated protein kinase (AMPK). In this commentary, we summarize the latest results on this topic, as well as the potential clinical relevance of the brain GLP-1 system to treat obesity.

Keywords: hypothalamus, GLP-1, brown adipose tissue, sympathetic nervous system

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The physiological relevance of the brown adipose tissue (BAT) in humans has been a matter of controversy during decades. Initially, it was thought that BAT was relevant only in rodents, hibernating mammals, and newborn humans.[1–4] However, novel evidence has clearly demonstrated that BAT is located in dispersed areas of the body in adult humans.[2,5–8] Recently, 2 reports indicated that both classical brown and recruitable brite/beige adipocytes may be contained in adipose tissue,[9,10] with the latter initially reported to appear in response to thermogenic stimuli in white adipose tissue (WAT) due to the so-called 'browning' process.[11-13]

The brain plays an essential role in the maintenance of temperature.[14,15] Among the numerous brain areas involved in this function, the hypothalamus occupies a key position. The arcuate nucleus (ARC), dorsomedial nucleus (DMH), lateral hypothalamic area (LHA), paraventricular nucleus (PVH) and the ventromedial nucleus (VMH) have all been demonstrated to modulate BAT.[14,15] Indeed, these hypothalamic areas are not directly connected to the BAT, and a network of other brain sites, such as the preoptic area (POA) and rostral raphe pallidus (rRPa), is also involved in this regulation. The fact that the network involved in thermoregulation is large and complex indicates its physiological relevance and that a wide range of factors will be able to affect BAT function. Among those factors we can find neurotransmitters, glucose and different hormones.[14,15]

One of those factors is the hormone glucagon-like peptide 1 (GLP-1), a post-translational product of proglucagon, that is endogenously released mainly from the ileum after the ingestion of nutrients. When postprandial GLP-1 increases it augments glucose-induced insulin release.[16,17] In line with this, the secretion of GLP-1 is impaired in patients with type II diabetes mellitus and obesity.[18,19] In addition to its role in insulin secretion, GLP-1 has many other biological actions, and the GLP-1 receptor (GLP1-R) is expressed in organs like pancreatic islets, kidney, lung, heart, stomach, intestine, pituitary, or skin.[18] GLP-1 is also

expressed in the brain, where GLP-1 receptors are also abundant.[20,21] Recent evidence has shown that brain GLP-1 modulates different metabolic actions, of which one is the regulation of BAT thermogenesis.[22] Intracerebroventricular (ICV) injection of GLP-1 reduced body weight and increased BAT thermogenesis independent of changes in feeding and insulin responsiveness. Consistently, the expression of genes involved in the activation of the thermogenic program, such as those coding for peroxisome proliferator-activated receptor-gamma co-activator-1alpha (PGC1α) and uncoupling protein-1 (UCP1), were up-regulated in the BAT of wild type mice centrally treated with GLP-1 receptor agonists.[22] In contrast, mice lacking the GLP-1 receptor did not show any alteration in BAT temperature or BAT gene expression after the stimulation of the brain GLP-1 system. The connection between the brain and the BAT seems to be the sympathetic nervous system, since acute central injection of GLP-1R and glucagon receptor agonists increases electrophysiological activity of the sympathetic fibers that innervate the iBAT.[22]

The neuroanatomical organization of the core thermoregulatory network involved in the actions of GLP-1 remains largely unknown, but a recent study from our group intended to show the first clues in this aspect. By doing an acute central injection of a GLP-1 receptor agonist, namely liraglutide, we confirmed previous results indicating that the brain GLP-1 system increases the thermogenic activation of BAT independently of feeding behavior.[23] In addition, we also observed that the central injection of liraglutide increased browning of WAT. As it is well known that within the central nervous system (CNS), numerous neuronal populations express GLP-1R, including hypothalamic nuclei crucial for the regulation of energy balance,[21,24] we next investigated which hypothalamic area was mediating the central effects of liraglutide on BAT and WAT. Thus, we specifically injected liraglutide into the following hypothalamic nuclei in rats; arcuate nucleus (ARC), LHA, PVH, DMH, or VMH, all of which express GLP-1R in a greater or lesser extent. Interestingly, only the specific stimulation of the GLP-1 system within the VMH was able to recapitulate the effects found after ICV injection of liraglutide.[23]

A role of the VMH is in thermoregulation is supported by anatomical data, demonstrating a link between the VMH and BAT.[25] VMH neurons relay to modulate the sympathetic nervous system in brainstem areas such as the raphe pallidus (RPa) and inferior olive (IO), 2 nuclei which have been functionally linked to the regulation of BAT thermogenesis.[26–28] Gene-modulation studies also support a role for the VMH in thermoregulation, with VMH-specific knockout of steroidogenic factor-1 (SF-1) displaying lower energy expenditure and expression of UCP1 in BAT.[29,30] In this sense, our group and others have previously reported that AMPK in the VMH is a key negative regulator of sympathetically activated BAT thermogenesis, integrating peripheral signals, such as thyroid hormone, estradiol, leptin, and bone morphogenetic protein 8b (BPM8b), as well as drugs such as nicotine.[31-34] Liraglutide is now a new member of this list, because mice treated centrally with liraglutide showed lower levels of hypothalamic pAMPK and its downstream target pACC in comparison to saline-treated mice.[23] Consistently, both the pharmacological AMPK activator AICAR and an adenoviral vector encoding constitutively active isoforms of the catalytic subunit AMPKα injected into the VMH, were able to completely blunt the actions of liraglutide on BAT and WAT. Altogether these results indicate that brain GLP-1 actions on BAT thermogenesis and WAT browning are mediated by a reduction in hypothalamic AMPK, specifically within the VMH.[23]

It is important to highlight that these results indicate that GLP-1 activation in the VMH not only modulates BAT thermogenesis (an effect shown for several other factors, such as thyroid hormones, estrogens, leptin BMP8b, nicotine, etc.), but also controls the thermogenic program in WAT (not demonstrated for the other factors). So far, not many studies have assessed the central control of browning of white fat. In one study, the brain SIRT1 was demonstrated to play an important role. The lack of SIRT1 in POMC neurons caused a reduction in sympathetic nerve activity, brown-fat-like characteristics and UCP-1 expression in perigonadal WAT.[35] Another recent and elegant study also indicated that O-GlcNAc transferase (OGT) in agouti-related peptide (AgRP) neurons within the ARC suppress browning of white fat.[36]

A key question is if the mechanistic aspects related to brain GLP-1 and thermogenesis will be of potential clinical relevance. Liraglutide improves glycemic control in type 2 diabetic patients with the additional benefits of weight loss and a low risk of hypoglycemia.[37,38] As GLP-1R agonists start to be included in treatment guidelines, they are generally being recommended as second- or third-line therapies after the failure of one or more oral antidiabetic drugs.[39] Besides its well-known anti-diabetic properties, liraglutide has been recommended for approval by the US Food and Drug Administration (FDA) committee also for the treatment of obesity. The specific proposed indication is *"for chronic weight management in individuals with a body mass index of 30 kg/m2 or greater, or 27 kg/m2 or greater in the presence of at least 1 weight-related comorbidity."* In an analysis involving 3731 patients, the liraglutide group lost an average 8% of body weight vs 2.6% with placebo at 56 weeks, thereby meeting the FDA benchmark for weight-loss drugs of a 5% difference between active treatment and placebo. Whether this decrease in body weight is linked to decreased food intake or increase energy expenditure is not yet clear in human subjects.[40] As a pilot study, we provided data from a cohort of obese patients with T2D who had been treated for 1 y with the antidiabetic drugs metformin and metformin in combination with the GLP-1R agonists exenatide and liraglutide. As expected, after 1 y of antidiabetic treatment, all study groups showed a decrease in fasting plasma glucose and insulin concentrations. In addition, the groups treated with metformin combined with exenatide or liraglutide showed a significant decrease in BMI and in total body fat percentage and a significant increase in fat free mass.[23] Accordingly, resting energy expenditure adjusted for fat free mass was significantly increased in patients treated with

metformin in combination with exenatide or liraglutide; but not in patients treated only with metformin. Although it is still too early to state that the hypothalamic stimulation of the GLP-1 receptors is, at least partially, responsible of the anti-obesity effects of this drug, we cannot rule out the possibility that an increase in resting energy expenditure might be mediated by peripheral stimulation of GLP-1 receptors. Anyhow, taking into account all our findings, rats and humans, it is tempting to suggest that in addition to its anorexigenic effect, liraglutide works through specific central pathway to increase energy expenditure that ultimately lead to a further reduction in body weight. Rodent studies assessing the same drug combinations used in patients using both wild type mice and brain specific GLP-1 receptor knockout mice will be needed to solve this question. The relevance of the central effects of GLP1-agonists is highlighted by the findings that liraglutide treatment of mice lacking GLP-1 receptors in the brain improved glucose metabolism, which occurred without any major changes in food intake or body weight in animals fed a chow diet or high fat diet.[41] However, the actions of liraglutide on the browning of white fat were not tested in this experiment.

Whether the same mechanisms are shared between liraglutide and new peptides that are agonists to both GLP-1- and other related hormone receptors remains to be fully established. Initial reports using this strategy showed very promising results. A peptide with agonism at the glucagon and GLP-1 receptors reduced body weight gain, improved glucose metabolism and ameliorated hepatic steatosis in diet-induced obese mice.[42] Another peptide with potent co-agonism at both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) was efficient in several models of obesity and diabetes, including rodents, monkeys and humans.[43] Although these peptides were not tested at central level, it seems plausible to hypothesize that part of their metabolic actions may be mediated by the CNS, but again, further studies are needed to confirm at what extent the stimulation of brain GLP-1 receptors is necessary for the efficacy of these new promising therapeutic

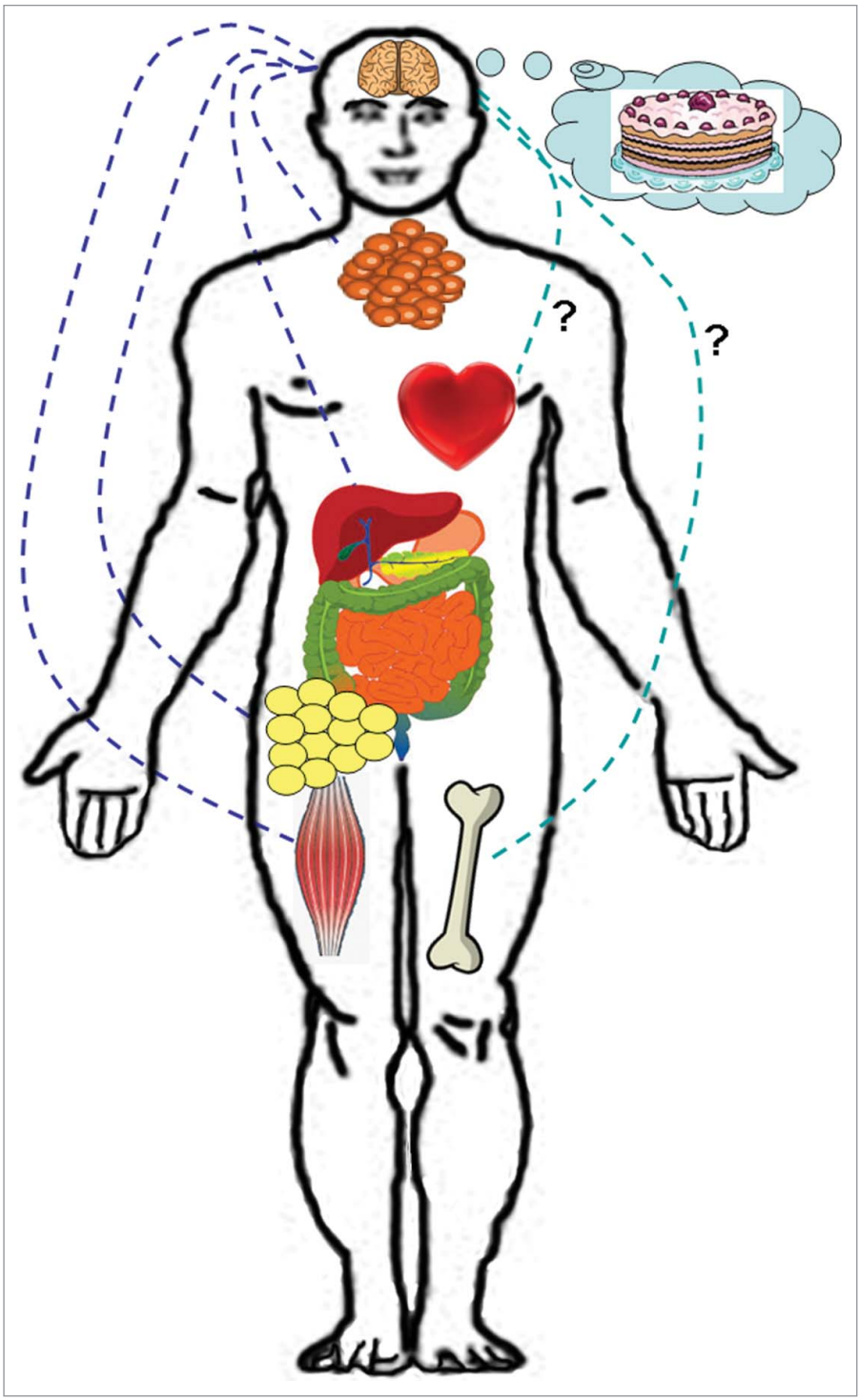

Figure 1. Schematic representation of the biological action of the brain GLP-1 system. Brain GLP-1 reduces food intake through both homeostatic and hedonic mechanisms; increases thermogenesis in brown adipose tissue; and stimulates lipid mobilization in white adipose tissue. Under hyperglycemic and hyperinsulinemic conditions, brain GLP-1 increases insulin secretion in pancreatic islets; reduces glucose utilization in muscle and suppresses hepatic glucose production. Whether other important actions of GLP-1 such as cardiovascular or bone metabolism are also regulated by brain GLP-1 remain to be elucidated.

strategies. In addition, these findings raise the possibility that other well documented effects of GLP-1 receptor activation such as gastrointestinal motility, gastrointestinal secretion, blood pressure, modulation of innate immune-mediated inflammation or bone metabolism could also be exerted to some extent at central level (**Fig. 1**). In summary, based on their incretin effects, potent GLP-1 agonists were developed and are at present at the forefront in the management of type 2 diabetic patients. Clinical experience indicated that these compounds could also suitable for the treatment of obesity, which has now been well documented. In parallel, studies carried out in experimental animals demonstrate the likelihood that many of the beneficial actions of GLP-1 agonists on energy homeostasis are exerted at central level. Noteworthy, the findings that hypothalamic GLP-1 receptors, leading to AMPK inhibition and subsequent activation of BAT thermogenesis and WAT browning open up a new paradigm regarding the mechanisms by which GLP-1 exert a beneficial effect in obesity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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