Brain Insulin and Leptin Signaling in Metabolic Control

From Animal Research to Clinical Application

Thomas Scherer, MD[a,*], Hendrik Lehnert, MD[b], Manfred Hallschmid, PhD[c,d]

KEYWORDS

• Leptin • Insulin • Brain • Metabolism • Energy homeostasis
• Intranasal administration

KEY POINTS

- Brain insulin and leptin signaling are implicated in regulating key processes of metabolic function, such as food intake, appetite, energy expenditure, and nutrient partitioning.
- Both hormones act as negative feedback signals to the brain to maintain energy balance.
- Behavioral and functional neuroimaging studies support the notion that both peptide hormones affect human brain function, including memory formation and emotional state.
- Brain insulin signaling may be implicated in the pathophysiology of neurodegenerative diseases, such as Alzheimer disease.
- In the obese state, the brain's sensitivity for insulin and leptin is reduced, which hampers the efficacy of both signals to reduce food intake, lose weight, and improve glycemic control.
- In humans and rodents, peptide hormones, such as insulin and leptin, can easily be targeted to the brain along the olfactory system via the intranasal (IN) route of administration.
- Modulating brain insulin and leptin signaling may represent a future therapeutic option in the treatment of diabetes and obesity and also cognitive impairments.

INTRODUCTION

Paleontologic evidence indicates that changes in dietary composition benefited brain growth and the associated development of higher cognitive capacity during human evolution.[1,2] Moreover, hormones secreted from the digestive system are potent

Disclosure Statement: The authors have no conflict of interest.
[a] Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, Vienna 1090, Austria; [b] Department of Internal Medicine I, University of Luebeck, Ratzeburger Allee 160, Luebeck 23538, Germany; [c] Department of Medical Psychology and Behavioral Neurobiology, University of Tuebingen, Otfried-Mueller-Strasse 25, Tuebingen 72076, Germany; [d] Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Centre Munich, University of Tuebingen (Paul Langerhans Institute Tuebingen), Otfried-Mueller-Strasse 10, Tuebingen D-72076, Germany
* Corresponding author.
E-mail address: thomas.scherer@meduniwien.ac.at

Endocrinol Metab Clin N Am 42 (2013) 109–125
http://dx.doi.org/10.1016/j.ecl.2012.11.002 **endo.theclinics.com**
0889-8529/13/$ – see front matter

modulators of central nervous functions, affecting not only ingestive behavior but also mood and memory formation.[1,3] The notion that, vice versa, the central nervous system (CNS) could be involved in the regulation of energy metabolism dates back as far as the nineteenth century. Claude Bernard reported that a "piqûre" at the base of the fourth ventricle in rabbits led to glucosuria and, in his words, "artificial diabetes."[4] In the 1940s, hypothalamic lesion studies in rodents suggested that the hypothalamus represents the key brain region where control of satiety and energy homeostasis are anatomically integrated.[5] In recent years, the concept of brain control of energy metabolism has progressed considerably and received a particular boost by the discovery of leptin.[6] Leptin is an adipocyte-derived hormone that crosses the blood-brain barrier (BBB) via a saturable transport.[7,8] It functions as an adiposity signal that communicates energy storage levels to the brain, which in turn regulates food intake and energy homeostasis.[9] Leptin administration in leptin-deficient humans and rodents reduces food intake and adiposity.[10,11] In addition, brain leptin signaling has functions that go beyond its ability to alter food intake. It is implicated in the regulation of glucose homeostasis,[12] lipid metabolism,[13] reward-related behavior,[14] and the processing of the reward value of nutrients.[15] Leptin also positively controls reproductive function,[16,17] acting as a pivotal hormonal energy signal that links nutritional status and reproduction.[18] Furthermore, the hormone modulates synaptic plasticity in the hippocampus[19] and has been shown to improve depression-like behavior in animals,[20] suggesting that impaired central nervous leptin signaling might contribute to the association between obesity and depression.[21]

Similar to leptin, insulin, despite being secreted by pancreatic β cells, also circulates approximately in proportion to body fat,[22] particularly in the prediabetic state, and is considered an adiposity signal that suppresses food intake. This was first demonstrated by intracerebroventricular (ICV) application of insulin in baboons more than 3 decades ago.[23] Although there is some evidence for local insulin production in the CNS,[24] it is generally believed that peripheral insulin, like leptin, enters the brain by crossing the BBB via a saturable transport system.[25,26] Brain insulin signaling has also been implicated in the regulation of glucose and lipid homeostasis[27,28] and the nonhomeostatic control of food intake by reward processing[14,29,30] as well as in learning,[31] synaptic plasticity,[32] and a variety of other functions, such as reproductive control[33] and growth,[34] and might likewise play a pathophysiologic role in neurodegenerative diseases.[35]

The above-mentioned studies that shaped the concept of leptin and insulin brain signaling were mainly performed in rodents. Neuronal insulin and leptin signaling can be manipulated locally by stereotaxic infusion of the respective hormone via a preimplanted cannula, which targets either the ventricular system or the mediobasal hypothalamus (MBH). Both neuronal insulin and leptin receptor signaling are able to affect peripheral hormone concentrations by, for example, modulating insulin secretion from the pancreas.[36,37] Thus, in order to isolate the brain effects of insulin and leptin, it is key to control for circulating glucose and insulin levels by using euglycemic pancreatic clamp studies. Targeted peptide delivery to the human CNS without changing peripheral insulin and glucose concentrations is particularly difficult, because a direct route of delivery seems to be missing. Although it is possible to use an intravenous approach for peptides that are selectively transported across the BBB to induce CNS effects,[38] these peptides inevitably activate their peripheral receptors, if present. In the case of insulin, this leads to hypoglycemia, which itself triggers a strong sympathetic nervous system (SNS) response. Even if this is prevented by a continuous glucose infusion, the systemic application of insulin does not allow differentiation between peripherally and centrally mediated effects of the infused hormone.