The Brain–Liver Connection Between BDNF and Glucose Control

Young-Hwan Jo and Streamson C. Chua, Jr.

Growing knowledge of the control of glucose metabolism permits the testing of alternative treatments to insulin to maintain euglycemia. Diminishing glucagon action on the liver (1) and increasing leptin (2) are prime examples of promising peptide hormone treatments that could be useful in glucose regulation. A report from Morton and colleagues (3) in this issue provides data that a systems biology model could integrate these two points of view of glucose regulation.

Brain-derived neurotrophic factor (BDNF) and its cognate receptor TrkB are involved in the regulation of energy balance and glucose homeostasis via its effects in the central nervous system. Perturbed BDNF signaling in the brain triggers hyperphagia and obesity in mice, suggesting that BDNF acts as an anorexigenic signaling molecule (4–6). However, the cellular mechanisms underlying the anorexigenic effects of BDNF have not been clearly defined. As a neurotrophic factor, BDNF promotes survival, induces differentiation of neurons in the developing and adult central nervous system (7), and forms appropriate synaptic connections at central synapses (8). Thus, the obesity phenotype observed in BDNF- and TrkB-mutant animals can be, in part, due to neurodevelopmental anomalies (6,9–11).

In addition to neurotrophic functions of BDNF, BDNF has acute and nonneurotrophic effects on body weight and food intake. Hypothalamic infusions of BDNF alter eating behavior and attenuate obesity in BDNF heterozygous mutant mice (9). Central administration of a TrkB agonist reduces food intake and body weight in mice (12). Furthermore, systemic BDNF administration improves glucose tolerance in diet-induced obesity and diabetic mice (13), as well as in *db/db* animals (14). Thus, it is likely that BDNF alters feeding-related neuronal activity, which in turn regulates energy homeostasis.

The ventromedial nucleus of the hypothalamus (VMH) attracted major attention as early lesion studies of the VMH induced hyperphagia and obesity in a variety of species, including humans (rev. in 15). BDNF is expressed at high levels in this nucleus, and its expression in the VMH is regulated by nutrients and nutrient-related signal molecules, including glucose, leptin, and melanocortins (5,6,16). Moreover, a recent study (17) demonstrated that a subset of steroidogenic factor-1 (SF-1) neurons in the VMH synthesize and release BDNF in an activity-dependent manner. Endogenous and exogenous BDNF attenuates gamma-aminobutyric acid (GABAergic) inhibitory tone onto SF-1 neurons, suggesting that the electrophysiological action of BDNF on synaptic activity in the VMH may play a role in regulating overall energy homeostasis. In this issue, Morton and colleagues provide direct physiological evidence that the VMH is the target for BDNF action on blood glucose levels in an animal model of uncontrolled insulin-deficient diabetes. In this study, the authors demonstrate that central injection of BDNF lowers blood glucose levels and that this effect is independent of insulin since streptozotocin-diabetic animals show severe insulin deficiency. Alternatively, BDNF reduces hepatic glucose production through inhibition of the key gluconeogenic enzymes, including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, which are elevated in streptozotocin-diabetic animals. The authors further show that microinjection of BDNF into the VMH lowers fasting blood glucose levels without changing energy intake. This is in contrast with the fact that lowering glucose levels induced by intracerebroventricular administration of BDNF is associated with reduced food intake, suggesting that BDNF also acts outside the VMH. Interestingly, intracerebroventricular injection of BDNF does not improve glucose uptake in skeletal muscle and brown adipose tissue in streptozotocin-diabetic animals.

In fact, the identity of TrkB-expressing hypothalamic and/or extrahypothalamic neurons remains to be determined. BDNF induced Finkel-Biskis-Jinkins osteogenic sarcoma (FOS) expression in the paraventricular nucleus (PVN), dorsomedial nucleus (DMH), and VMH (5). Moreover, the VMH sends projections to the PVN and DMH (18). It is plausible that disinhibition of VMH SF-1 neurons by BDNF (17) increases the excitability of PVN and DMH neurons and then subsequently alters glucagon secretion and liver glucose production. Interestingly, although TrkB-expressing neurons are found in the arcuate and lateral hypothalamus, it appears that few neurons in these nuclei, including orexin, melanin-concentrating hormone, cocaine- and amphetamine-regulated transcript, and neuropeptide Y neurons, express TrkB (6). It should also be noted that not only VMH neurons respond to BDNF but also a subset of VMH neurons synthesize and release BDNF (17). Thus, the regulation of BDNF-expressing neurons in the VMH will be critical in maintaining blood glucose levels in normal and diabetic conditions.

The current report by Morton and colleagues (3) builds upon the group's previous work with leptin's effect on diabetic rats (19) with the clear anticipation that BDNF is a mediator of leptin. With a clear glucose lowering effect in insulin-deficient rats, leptin caused an increase in peripheral glucose uptake as well as a decrease in hepatic glucose production. This is the major difference between leptin and BDNF, which only reduced liver glucose output, indicating that leptin has other significant mediators that act independently of BDNF.

From the Division of Endocrinology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York.
Corresponding author: Streamson C. Chua, Jr., streamson@gmail.com.
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Although previous studies, including the present work of Morton and colleagues, suggest that the nonneurotrophic actions of BDNF regulate blood glucose levels, the neurotrophic role of BDNF may also play a role in maintaining overall energy balance, including glucose homeostasis (20,21). In summary, one would predict that the ability of leptin to control glucose is dependent upon decreasing hepatic glucose output, mediated by BDNF and partially dependent upon decreasing glucagon secretion as well by increasing peripheral glucose uptake that is independent of BDNF.

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