Neurotrophism and energy homeostasis: perfect together

Barry E. Levin
Neurology Service, Veterans Administration Medical Center, East Orange, and Department of Neurology and Neurosciences, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey

ENERGY HOMEOSTASIS DEPENDS upon the balance between anabolic and catabolic drives. Generally, anabolic neuropeptides such as neuropeptide Y (NPY) increase food intake and decrease thermogenesis (5), while catabolic ones such as α-melanocyte stimulating hormone (α-MSH), which is released from proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus (Arc), reduce intake and increase energy expenditure (32). The companion papers published in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology by Wang et al. (62, 63) demonstrate that brain-derived neurotrophic factor (BDNF) acts as a prototypic catabolic factor when injected into the hypothalamic paraventricular nucleus (PVN). Food intake is decreased without provoking an aversive reaction, and resting energy expenditure is increased without affecting overall motor activity. These papers are important because they add to the growing body of data that demonstrate unequivocally that BDNF can act at a specific site as a relatively pure catabolic agent (4, 61). They also demonstrate that PVN BDNF injections act with different temporal patterns on energy expenditure and feeding. These findings support others (2) that demonstrate a divergence of neural pathways originating in the PVN by which energy intake and expenditure are regulated. On the other hand, these studies raise several questions about the regulation of energy homeostasis and the role of BDNF and other neurotrophic factors in this process.

Why Does a Neurotrophic Factor Affect Energy Homeostasis?

There is no factual answer to this question currently available, only observations and speculation. First, are the multiple observations that BDNF, along with many other factors that affect neuronal development, differentiation, survival, and process outgrowth also affect energy homeostasis. All of these are catabolic in their actions and include insulin (48, 49, 64), leptin (7, 20), insulin-like growth factor-1 (60), and ciliary neurotrophic factor (17, 26). Aside from insulin, the other acts through JAK/STAT signaling pathways, and all, including insulin, engage MAP kinase, mammalian target of rapamycin, and phosphoinositol-3 kinase as overlapping downstream pathways that converge on a variety of physiologic functions (15, 34, 40, 52, 58). Of particular interest, all share a common effect on activation of the transcription factor, STAT3 (6, 11, 15, 27, 40, 46). Insulin appears to exert a particularly important influence on the development of pathways involved in energy homeostasis during the prenatal period (23). However, in rodents, much of the development of these pathways in the hypothalamus occurs during the first 2–3 wk of postnatal life (8) during which both insulin and leptin play a dual role. They influence both the development of these pathways (7, 47) and contribute to the regulation of energy homeostasis (21, 55).

BDNF is a member of a family of neurotrophins that are functionally separate from leptin and insulin but play similar roles in the regulation of energy homeostasis and in neuronal development, survival, and plasticity. All act through the tyrosine kinase (Trk) family of receptors and BDNF acts specifically at TrkB receptors (3). BDNF is highly localized in the ventromedial hypothalamic nucleus (VMN), but is also found in the lateral hypothalamic area, dorsomedial nucleus (DMN), and PVN (54). Its TrkB receptors are found throughout the nervous system in neuronal cell bodies, axons, and dendrites in the cerebral cortex, hippocampus, dentate gyrus, amygdala, striatum, septal nuclei, substantia nigra, cerebellum, motor neurons, brain stem sensory nuclei, and ependymal cells lining the ventricular walls. In the hypothalamus, TrkB is expressed in the PVN, medial preoptic area, supraoptic nucleus, and the mammillary body (35, 66). Its diffuse localization undoubtedly reflects its prominent role as a neurotrophic factor.

On the other hand, a regulatory role for BDNF in energy homeostasis was first demonstrated by reduced food intake and body weight gain, which follow chronic systemic and intraventricular BDNF administration to rats (30, 45). Also, BDNF expression in the VMN is increased by intake of a palatable diet (1) and is decreased by caloric restriction (65). Although complete deletion of BDNF or TrkB is fatal, partial reductions produce obesity-prone animals that are particularly susceptible to high fat diets (24). However, these knockout animals are also hyperactive (24), as are mice infused intraventricularly with BDNF (38). This reflects the fact that BDNF and its receptors mediate a number of functions, not all of which are directly related to the regulation of energy homeostasis. It also emphasizes the importance of the findings of the studies of Wang et al. (62, 63) demonstrating that the localized injections into the PVN alter energy homeostasis without affecting motor activity. Also, in common with insulin and leptin, BDNF is affected by exercise (31, 42), learning and memory (36) (25, 44) and stress (16, 54, 59). While such observations do not answer the question of why neurotrophic factors might double as regulators of both neuronal development and energy expenditure, they do demonstrate that the regulation of both of these critical physiological functions appears to be a common feature of several families of trophic factors, peptides, and hormones.

What Are the Downstream Mediators and Pathways of the Thermogenic and Feeding Effects of BDNF?

Although Wang et al. (29, 61–63) have proposed an antagonistic relationship between the anabolic effects of NPY and the catabolic actions of BDNF in the PVN, several lines of evidence suggest that BDNF is more likely downstream of leptin and melanocortin signaling. BDNF reduces food intake and body weight and improves glucose tolerance in db/db
mice, which have defective leptin signaling (39, 43), whereas leptin increases BDNF mRNA in VMN neurons, which also express leptin-induced phosphorylation of STAT3 (27). BDNF reduces food intake and body weight in A^2 mice, which have impaired melanocortin signaling (39, 65), and melanocortin-4-receptor-deficient and A^2 mice have reduced VMN BDNF mRNA. Finally, Ac-Nle^4-c[Asp^5, d-Phe^7, Lys^10]α-MSH-(4-10)-NH2 (MTII), a melanocortin receptor agonist, increases VMN BDNF mRNA expression (65). To date, there are no comparable data supporting such critical interactions between NPY and BDNF. This, of course, does not mean that such interactions do occur.

Aside from the issue of its interactions with NPY, melanocortin, and leptin pathways, BDNF alters GABA, glutamate, and serotonin transmission. It acts postsynaptically on GABA_A receptors in both the PVN (22) and hippocampus (9) by effecting rapid alterations in functional synaptic contacts, possibly by reducing the surface expression of postsynaptic GABA_A receptors. It also enhances gluta-matergic synaptic transmission at a presynaptic locus in hippocampal cultured neurons (33) and increases hypotalamic 5-HT turnover (45). In the PVN, thyrotropin releasing hormone (TRH) neurons are excellent candidates for the actions of BDNF since TRH has both thermogenic (53) and anorectic (28, 57) properties (Fig. 1). TRH neurons in the PVN express BDNF and TrkB receptors (18), as well as leptin and melanocortin-4 receptors (19, 51). BDNF, leptin, and α-MSH increase and NPY decreases TRH mRNA in hypothalamic cultures (18, 41). Similarly, α-MSH and NPY have opposing actions on downstream signaling in PVN TRH neurons (50). Figure 1 provides a hypothetical framework for integration of BDNF’s effects with the several of the other neural systems that affect both feeding and energy expenditure.

Why Do the Effects of PVN BDNF on Feeding and Energy Expenditure Have Different Temporal Patterns?

There are several potential reasons for this important observation. First, there are multiple pathways and systems that regulate food intake and energy expenditure (Fig. 1). Food intake is a multifaceted behavioral response that is modulated by both homeostatic and nonhomeostatic systems. Reductions in leptin and insulin that occur during starvation stimulate anabolic and inhibit catabolic homeostatic systems, such as Arc NPY and POMC neurons, respectively. The resultant net anabolic balance drives the starving animal to seek and ingest food. In addition, palatable food and pleasurable associations act on nonhomeostatic reward and motivational pathways, such as those in the amygdala to enhance food-seeking behavior. Some of the factors driving ingestive behavior are acute and mediated by neuroendocrine and hard-wired neural systems. Others are more long-term and require gene transcription and synaptic plasticity. On the catabolic side, energy expenditure occurs through resting metabolic rate or diet-induced, exercise-induced, or nonexercise-induced thermogenesis. Each of these has a defined temporal pattern and depends on overlapping control systems. Depending upon the physiologic state of the animal, BDNF appears capable of modifying several of these responses either directly or indirectly through its actions on neurons localized within the PVN. Relatively acute inhibition of feeding can occur by the BDNF-mediated release of TRH which acts on as-yet-undefined targets. BDNF’s anorectic actions in the VMN (61) might occur via efferents to anabolic NPY and catabolic POMC neurons in the Arc (56), which then alter their release of their respective peptides onto PVN TRH neurons to alter feeding. Finally, a potential BNDF pathway from the PVN to the amygdala might engage TrkB receptors in that structure (12, 35) to inhibit nonhomeostatic pathways involved in promoting feeding. The presumptive final common pathway of all of these feeding circuits is to motor areas in the midbrain and brain stem.

Similarly, the pathways through which BDNF acts in the PVN to stimulate thermogenesis are open to speculation. Potentially, BDNF acting on TRH neuron TrkB receptors could increase energy expenditure through downstream projections from the PVN to sympathetic effector areas in the brain stem (rostroventrolateral medulla) and raphe pallidus (RPa), and
the intermediolateral cell column of the thoracic spinal cord to activate thermogenesis in muscle and brown adipose tissue (BAT) (53) (Fig. 1). Through both direct actions on TrkB receptors and indirect projections from BDNF neurons in the VMN, BDNF might also engage downstream pathways mediating thermogenesis from the DMN to RPa (10, 37). A more sustained elevation of energy expenditure could result from TRH stimulation of pituitary thyroid stimulating hormone release, which increases thyroid production of triiodothyronine (T3). T3 can increase thermogenesis by acting directly on muscle (14) and synergistically acting with norepinephrine in BAT (13).

Summary and Conclusions

The important studies of Wang et al. (62, 63) establish that BDNF acting in the PVN plays a physiological role in the regulation of both energy intake and expenditure by acting as a catabolic factor. It can now be added to a number of other trophic factors, peptides, and hormones that share the dual role of regulating both energy homeostasis and neural plasticity. BDNF appears to be downstream of both leptin and melanocortin signaling but clearly interacts with other mediators of energy homeostasis, such as NPY. The PVN TRH neurons provide a reasonable final common pathway upon which these various inputs converge to mediate energy intake and expenditure.

REFERENCES

neurotrophic factor. Exercise reverses the harmful effects of consumption of a high-fat diet on 


37. Molteni R, Wu A, Vaynman S, Ying Z, Barnard RJ, Gomez-Pinilla F. Exercise reverses the harmful effects of consumption of a high-fat diet on 
synaptic and behavioral plasticity associated to the action of brain-derived 

38. Morrison SF, Sved AF, Passerin AM. GABA-mediated inhibition of 
rhapha pallidus neurons regulates sympathetic outflow to brown adipose 

infusion of brain-derived neurotrophic factor modifies hypothalamic–
pituitary-adrenal axis activity, locomotor activity and body temperature 

40. Nakagawa T, Tsuchida A, Itakura Y, Nonomura T, Ono M, Hirota F, 
Inoue T, Nakayama C, Taigi M, Noguchi H. Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in 

41. Ng YP, Cheung ZH, Ip NY. STAT3 as a downstream mediator of Trk 

Insulin-mediated regulation of neuronal maturation.

43. Ono M, Ichihara J, Nonomura T, Itakura Y, Taiji M, Nakayama C, 
Noguchi H. Brain-derived neurotrophic factor regulates blood glucose level in 
obese diabetic mice but not in normal mice. Biochem Biophys Res 

44. Paulus K, Schulz C, Lehner H. Central nervous effects of leptin and 
insulin on hippocampal leptin and insulin receptor expression following a 

45. Pellegmouther MA, Cullen MJ, Wellman CL. Characteristics of BDNF-

46. Peterson WM, Wang Q, Tzekova R, Wieand SG. Ciliary neurotrophic factor 
and stress stimuli activate the Jak-STAT pathway in retinal neurons 

47. Plagemann A, Harder T, Rake A, Janert U, Melchior K, Rohde W, 
Dorner G. Neurotrophic function and stress stimuli activate the Jak-STAT pathway in retinal neurons 


49. Rezio-Pinto E, Lang FF, Ishii DN. Insulin and insulin-like growth factor 
II permit nerve growth factor binding and the neurite formation response 
in cultured human neuroblastoma cells. Proc Natl Acad Sci USA 81: 

50. Sarkar S, Lechan RM. Central administration of neuropeptide Y reduces 
α-melanocyte-stimulating hormone-induced cyclic adenosine 5’-mono-
phosphate response element binding protein (CREB) phosphorylation in 
pro-thyrotropin-releasing hormone neurons and increases CREB phos-
phorylation in corticotropin-releasing hormone neurons in the hypotha-