More News About NUCB2/Nesfatin-1: A New Factor in the Hypothalamic Control of Glucose Homeostasis?

Andrew A. Butler

Insulin resistance and declining insulin production define a spectrum of metabolic diseases afflicting a growing portion of the population (1). Current estimates suggest that 26 million Americans have diabetes, with the incidence of type 2 diabetes involving insulin resistance and β-cell decompensation far exceeding that of type 1 diabetes. Treatment of type 2 diabetes involves secretagogues that increase insulin secretion and insulin sensitizers to improve insulin receptor (INSR) action (and likely include other effects on glucose production) (1). These drugs exhibit a short duration of efficacy in many patients and often require a multidrug approach as the disease progresses and insulin injections when other treatment options fail. A clear need exists for continued research aimed at developing more effective strategies for maintaining glycemic control.

In this issue, Yang et al. (2) report that intracerebroventricular (ICV) infusion of nesfatin-1 improves glucose homeostasis in diet-induced obese rats by inhibiting hepatic glucose production. Improved insulin action is one mechanism for the reduction in hepatic glucose production. Increased phosphorylation of the INSR and insulin receptor substrate-1 was observed in lean and obese rats following ICV administration of nesfatin-1. Tyrosine phosphorylation of multiple residues in the insulin receptor substrate-1 coding sequence is an important early event following INSR activation. This leads to an intracellular signaling cascade that facilitates changes in energy metabolism by regulating gene transcription and enzymatic activity (3). The changes in phosphorylation of AKT, AMP-dependent protein kinase, mammalian target of rapamycin, and mammalian target of rapamycin complex 2 that were also observed were consistent with improved actions of these important downstream effectors in the INSR signaling cascade. Activity of phosphoenolpyruvate carboxykinase, the rate-limiting enzyme in gluconeogenesis, was also reduced in livers of lean and diet-induced obese rats administered nesfatin-1 ICV. Finally, a modest effect to stimulate whole-body glucose disposal and increased glucose uptake in skeletal muscle was also observed.

Nesfatin-1 is an 82–amino acid peptide derived from the posttranslational processing of nucleobindin-2 (NUCB2), and was originally reported by Oh-I et al. (4) in 2006 to function as a “satiety” factor (Fig. 1). Daily ICV injections of nesfatin-1 reduced food intake and attenuated weight gain in rats (4). Importantly, antibodies that inhibit nesfatin-1 action or antisense oligonucleotides that target Nucb2 expression had the opposite effect: increasing food intake and weight gain. Other laboratories reported similar inhibitory effects of nesfatin-1 on food intake in rats and mice (5). Subsequent studies reported that the functions of nesfatin-1 are consistent with a role in metabolic homeostasis including inhibiting gastric motility, stimulating the adrenal axis and autonomic function, and stimulating of glucose-induced insulin secretion from β-cells (5). Oh-I et al. reported that Nucb2 mRNA is expressed in the arcuate and paraventricular (PVN) nuclei of the hypothalamus and in the lateral hypothalamus (4). Subsequent analysis indicated that Nucb2 mRNA is widely expressed in the central nervous system, where it exhibits associations with neuropeptides involved in regulating ingestive behaviors, gonadal function, and the stress response (5).

To appreciate the results presented in this issue of Diabetes, it is important to be aware that, at least in rodents, actions involving hypothalamic neurons are essential for glucose homeostasis. Most hypothalamic neuropeptides and neurotransmitters regulating appetite also affect peripheral glucose metabolism (6–8). Well-studied examples include the regulation of insulin sensitivity in peripheral tissues through modulation of autonomic activity by leptin and melanocortin receptors expressed by hypothalamic (and extrahypothalamic) neurons (9). Indeed, the effective control of glucose homeostasis by insulin requires the actions of INSRs expressed in the hypothalamus (7). The attenuated response of hypothalamic neurons to signals of metabolic status such as insulin, glucose and leptin has been hypothesized to be a contributing factor in deteriorating control of metabolic homeostasis in obesity (6,7).

Experimental data suggesting a link between nesfatin-1 and the melanocortin system provide further rationale for the experiments described by Yang et al. and suggest future research. For example, it is not clear whether melanocortin neurons in the PVN implicated in the effects of nesfatin-1 on feeding are involved in mediating these actions, whereas actions of nesfatin-1 in other regions of the brain that regulate autonomic functions may also be involved (Fig. 1). Nucb2 expression in the PVN is stimulated by central injection of α-melanocyte-stimulating hormone whereas the anorectic response to nesfatin-1 is inhibited by SHU9119, an antagonist for the melanocortin-4 receptor (10). Melanocortin-4 receptors regulate satiety and also modulate autonomic outputs that affect insulin action in the liver (11–13). Although Yang et al. report increased Fos immunoreactivity in the arcuate and PVN with nesfatin-1 treatment (2), they did not investigate the identity of neurons involved. Future studies could therefore investigate these neural pathway(s) and whether central antagonism of melanocortin signaling inhibits the effects of nesfatin-1 on glucose homeostasis (4). Sophisticated genetic tools have been developed that could be used to

See accompanying original article, p. 1959.
further investigate the interaction between nesfatin-1 and melanocortins (11,14–16).

Another important question is whether attenuated nesfatin-1 activity in the hypothalamus contributes to insulin resistance in obesity. A conditional targeting strategy to target nesfatin-1 production in various brain regions might be informative. This would be a technically challenging experiment as nesfatin-2 and -3 produced from the processing of NUCB2 may also have important functions. One approach would be to define and then target critical residues needed for nesfatin-1 function. The problem with this strategy is structure-activity relationship studies require knowledge about the identity of the receptor(s) involved. Lack of knowledge about the receptor limits our ability to determine where the peptide is working in the brain and periphery. Identification of this receptor(s) and the intracellular signaling pathways involved are critical end points in future studies investigating mechanism of action.

Finally, while the result reported by Yang et al. is important progress, it is also important to acknowledge some of the limitations to their work. Although nesfatin-1 is present in rat cerebrospinal fluid and human plasma samples, an important question is whether (and where) full-length NUCB2 protein is processed into nesfatin-1 in the brain (4,17). Whether the hypothalamus regulates peripheral glucose metabolism in larger mammals such as humans is also unclear (18). Finally, history has also shown that the link between neuropeptides controlling appetite and the autonomic control of insulin action can be problematic when compounds targeting these systems reach the clinic (19). Answers to these questions can only come from further research that investigates whether this poorly understood protein will have potential for developing new therapies to improve glycemic control in type 2 diabetes.

ACKNOWLEDGMENTS

A.A.B. is supported by the National Institutes of Health (R01-DK073189) and the Novo Nordisk Diabetes Innovation Award Program. No other potential conflicts of interest relevant to this article were reported.
REFERENCES

1. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011;378:182–197
2. Yang M, Zhang Z, Wang C, et al. Nesfatin-1 action in the brain increases insulin sensitivity through Akt/AMPK/TORC2 pathway in diet-induced insulin resistance. Diabetes 2012;61:1959–1968
3. Cheng Z, Tseng Y, White MF. Insulin signaling meets mitochondria in metabolism. Trends Endocrinol Metab 2010;21:589–598
4. Oh-I S, Shimizu H, Satoh T, et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature 2006;443:709–712
5. Stengel A, Taché Y. Mini-review: nesfatin-1—an emerging new player in the brain-gut, endocrine, and metabolic axis. Endocrinology 2011;152:4033–4038
6. Xu Y, Elmquist JK, Fukuda M. Central nervous control of energy and glucose balance: focus on the central melanocortin system. Ann N Y Acad Sci 2011;1243:1–14
7. Belgardt BF, Brüning JC. CNS leptin and insulin action in the control of energy homeostasis. Ann N Y Acad Sci 2010;1212:97–113
8. Obici S. Mini-review: Molecular targets for obesity therapy in the brain. Endocrinology 2009;150:2512–2517
9. Gautron L, Elmquist JK. Sixteen years and counting: an update on leptin in energy balance. J Clin Invest 2011;121:2087–2093
10. Cone RD. Studies on the physiological functions of the melanocortin system. Endocr Rev 2006;27:736–749
11. Rossi J, Dalgaard LT, Lee CE, et al. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell Metab 2011;13:195–204
12. Kumar KG, Sutton GM, Dong JZ, et al. Analysis of the therapeutic functions of novel melanocortin receptor agonists in MC3R- and MC4R-deficient C57BL/6J mice. Peptides 2009;30:1892–1900
13. Liu H, Kishi T, Roseberry AG, et al. Transgenic mice expressing green fluorescent protein under the control of the melanocortin-4 receptor promoter. J Neurosci 2003;23:7143–7154
14. Tsuchiya T, Shimizu H, Yamada M, et al. Fasting concentrations of nesfatin-1 are negatively correlated with body mass index in non-obese males. Clin Endocrinol (Oxf) 2010;73:484–490
15. Levin BE, Sherwin RS. Peripheral glucose homeostasis: does brain insulin matter? J Clin Invest 2011;121:3392–3395
16. Greenfield JR, Miller JW, Koehn JM, et al. Modulation of blood pressure by central melanocortinergic pathways. N Engl J Med 2000;360:44–52