Commentary

MOLECULAR METABOLISM

Why leptin keeps you warm[a]

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If a good layer of insulating fat would be sufficient to stay warm, leptin deficient ob/ob mice should do fine in a cold environment since they are massively obese. But once exposed to low temperatures, ob/ob mice rapidly die of hypothermia. Even at ambient temperatures ob/ob mice have a core body temperature that is 2 °C lower than that of wild type littermates [1]. This hypothermia can be normalized through the administration of leptin [2] demonstrating that leptin action controls thermogenesis. Since the thermogenic effects of leptin are an important contributor to its anti-obesity properties, it is important to understand this basic biology from a clinical standpoint. How and where does leptin regulate thermogenesis?

Brown adipose tissue (BAT) is the designate tissue for thermogenesis in mammals, including humans, as it has the unique ability to uncouple respiration from ATP production. BAT activity is centrally regulated through the sympathetic nervous system. Key areas in the central nervous system that regulate BAT activity appear to be the median preoptic subnucleus (MnPO) of the preoptic area (POA). Both cool and warm cutaneous thermosensory signals are transmitted from the spinal dorsal horn to the POA via neurons in the lateral parabrachial nucleus (LPB) [3]. Neurons in the MnPO project to sympathetic premotor neurons in the rostral raphe pallidus (rRPa) to regulate sympathetic BAT inputs. In addition to this MnPO-rRPa pathway regulating BAT thermogenesis, prior studies have reported that neurons in the dorsomedial hypothalamus/dorsal hypothalamic area (DMH/DHA) also participate in the regulation of BAT activity [4]. Moreover, it has been described that leptin receptor-expressing neurons in the DMH increase sympathetic outflow to BAT and vice versa and that the injection of leptin into the DMH/DHA normalized body temperature in ob/ob [5], suggesting that leptin normalizes energy expenditure by inducing BAT activation and thermogenesis via neurons in the DMH/DHA.

In the last issue of Molecular Metabolism, Rezai-Zadeh and colleagues report that the injection of leptin into the DMH/DHA restores core body temperature and increases locomotor activity in leptin deficient ob/ob mice [6], providing a striking example of the role of leptin signaling within the DMH/DHA in regulating energy expenditure. To define the role of leptin receptor expressing (LepRb) neurons in the DMH/DHA, the authors selectively activated these neurons via DREADDs, which are mutated muscarinic receptors that lack responsiveness for acetylcholine but respond to an otherwise inert drug, *clozapine-N-oxide*. This technique allows one to probe the role of LepRb neurons within the DMH/DHA in the regulation of biological pathways, which is distinct from asking what leptin signaling does in these neurons. After only three days of activation of DMH/DHA LepRb neurons via DREADDs, mice lost body weight, which was only partially reduced after β3-adrenergic blockade. Conversely, deletion of the leptin receptor from DMH/DHA neurons promoted body weight gain by reducing energy expenditure, illustrating the physiological importance of DMH/DHA LepRb neurons and leptin signaling in these neurons in the regulation of whole body energy homeostasis.

Of particular interest is the finding that DMH/DHA LepRb neurons directly project to the raphe pallidus that contains sympathetic premotor neurons [7]. The activation of DMH/DHA LepRb neurons increased BAT thermogenesis, which suggests that LepRb neurons in the DMH/DHA provide excitatory synaptic inputs to rostral raphe pallidus neurons. Indeed, a recent study by Nakamura's group clearly demonstrates that neurons in the rRPa directly receive glutamatergic excitatory synaptic inputs from neurons in the DMH [7]. Given that NPY-expressing neurons in these areas are activated by leptin [8] and the deletion of NPY alters energy expenditure [9], it is plausible that DMH NPY-expressing neurons interact with sympathetic premotor neurons in the rRPa. There are cocaine- and amphetamine-regulated transcript (CART)-expressing neurons in the DMH/DHA that appear to co-express LepRb and thyrotropin-releasing hormone (TRH) [10]. Thus, the identification of the phenotypes of the DMH/DHA LepRb neurons will be very useful to understand how leptin regulates BAT activity and may furthermore allow the identification of other signaling pathways besides leptin that are amenable to therapeutic manipulation with the aim to increase BAT thermogenesis.

Another important finding is that the activation of LepRb neurons not only stimulates sympathetic outflow but also locomotion, which was not prevented through beta3 blockade. This is consistent with the more general role of the DMH in regulating wakefulness, arousal, feeding and locomotor activity and is likely mediated via different projections of lepRb-expressing neurons in the DMH/DHA. For instance, the DMH also project to the lateral hypothalamus that contains orexin neurons that are well known to play a critical role in locomotor activity. Enhanced locomotion following activation of LepRB neurons in the DMH/DHA could be mediated through these orexin neurons. Recent work by Kataoka and colleagues clearly shows that optogenetic stimulation of the DMH-PVN pathway did not increase BAT temperature, heart rate and arterial pressure, although stimulation of the DMH-rMR pathway strongly alters these parameters [11]. Hence, the

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detailed cellular and neuroanatomical analysis of LepRb neurons in these areas will be beneficial to understand how leptin fine-tunes the balance between energy intake and expenditure in physiology.

Leptin regulates many other organ systems and bodily functions ranging from food intake, glucose and lipid metabolism in organs such as liver and adipose tissue to inflammation and blood pressure. It is unlikely that leptin signaling in DMH neurons only regulates BAT thermogenesis, but rather initiates a coordinate response that involves fatty acid release from adipose tissue which is the major substrate for thermogenesis in BAT. Future work should carefully examine a potential role of leptin action in the DMH in regulating nutrient partitioning such as hepatic glucose production and/or adipose tissue lipolysis, both critical pathways that warrant the main energy sources for BAT, glucose and fatty acids.

REFERENCES

[1] Trayhurn, P., Thurlby, P.L., James, W.P., 1977. Thermogenic defect in pre-obese ob/ob mice. Nature 266(5597):60—62.

[2] Harris, R.B., Zhou, J., Redmann Jr., S.M., Smagin, G.N., Smith, S.R., Rodgers, E., et al., 1998. A leptin dose-response study in obese (ob/ob) and lean (+/?) mice. Endocrinology 139(1):8—19.

[3] Morrison, S.F., Madden, C.J., Tupone, D., 2014. Central neural regulation of brown adipose tissue thermogenesis and energy expenditure. Cell Metabolism 19(5):741—756.

[4] Nakamura, K., Morrison, S.F., 2011. Central efferent pathways for cold-defensive and febrile shivering. The Journal of Physiology 589(Pt 14): 3641—3658.

[5] Enriori, P.J., Sinnayah, P., Simonds, S.E., Garcia Rudaz, C., Cowley, M.A., 2011. Leptin action in the dorsomedial hypothalamus increases sympathetic tone to brown adipose tissue in spite of systemic leptin resistance. The Journal of Neuroscience 31(34):12189—12197.

[6] Rezai-Zedah, K., Yu, S., Jiang, Y., Laque, A., Schwartzenburg, C., Morrison, C.D., et al., 2014. Leptin receptor neurons in the dorsomedial hypothalamsu are key regulators of energy expenditure and body weight, but not food intake. Molecular Metabolism 3(7):681—693.

[7] Zhang, Y., Kerman, I.A., Laque, A., Nguyen, P., Faouzi, M., Louis, G.W., et al., 2011. Leptin-receptor-expressing neurons in the dorsomedial hypothalamus and median preoptic area regulate sympathetic brown adipose tissue circuits. The Journal of Neuroscience 31(5):1873—1884.

[8] Lee, S.J., Verma, S., Simonds, S.E., Kirigiti, M.A., Kievit, P., Lindsley, S.R., et al., 2013. Leptin stimulates neuropeptide Y and cocaine amphetamine-regulated transcript coexpressing neuronal activity in the dorsomedial hypothalamus in diet-induced obese mice. The Journal of Neuroscience 33(38): 15306—15317.

[9] Chao, P.T., Yang, L., Aja, S., Moran, T.H., Bi, S., 2011. Knockdown of NPY expression in the dorsomedial hypothalamus promotes development of brown adipocytes and prevents diet-induced obesity. Cell Metabolism 13(5): 573—583.

[10] Elias, C.F., Lee, C.E., Kelly, J.F., Ahima, R.S., Kuhar, M., Saper, C.B., et al., 2001. Characterization of CART neurons in the rat and human hypothalamus. Journal of Comparative Neurology 432(1):1—19.

[11] Kataoka, N., Hioki, H., Kaneko, T., Nakamura, K., 2014. Psychological stress activates a dorsomedial hypothalamus-medullary raphe circuit driving brown adipose tissue thermogenesis and hyperthermia. Cell Metabolism 20(2):346—358.

