Obesity is a global problem and effective drug therapy treatment is still unavailable. Obesity develops due to an imbalance between energy intake and energy expenditure (EE). Understanding what happens to EE in obesity may be the key to developing new treatments for obesity. If EE in obesity can be elevated, it could be a potential therapeutic target. We recently discovered that in baseline conditions obese mice have increased EE, in terms of thermogenesis. However, this increase in EE is not great enough to offset the elevated calorie intake that leads to the development of obesity. In obesity, the adipose derived hormone leptin is significantly elevated. This elevated leptin concentration appears to cause an increase in thermogenesis through increased sympathetic nerve activity (SNA) to brown adipose tissue deposits. The brain region of the dorsomedial hypothalamus (DMH) appears to be a key region that leptin activates in obesity to cause this increased thermogenesis. One unsettling finding is that the sympathetic nervous system (SNS) in obesity is elevated via leptin and it seems unlikely that SNA would be selectivity increased to only brown adipose tissue. Previously, it has been observed that leptin can increase SNA to numerous organs including the kidney. Furthermore, in obesity, SNA is increased in numerous organs. This leads to the critical question: is the leptin-mediated elevation of SNA and thermogenesis also chronically activating the kidney and contributing to the development of hypertension in obesity?
resistance through changes in the activity of the SNS. Thermogenesis is increased in obese animals as well as when animals are exposed to cold. In both situations, thermogenesis is increased by increased SNS input to brown adipose tissue (BAT). Pioneer works, by either surgical or chemical denervation, have demonstrated the crucial importance of the SNS for the activation of BAT. Also, mice that lack the ability to produce catecholamines (the products of increased SNA) lack the ability to elevate thermogenesis in response to cold, highlighting the importance of this system in mediating messages from the brain to initiate thermogenesis. BAT cells are also crucially important to enable thermogenesis to take place as these cells contain uncoupling protein 1 (UCP1) and this protein has the capacity to convert the energy dense substrates into heat rather than being converted into ATP energy. For animals to effectively expend energy through thermogenesis, the central nervous system increases SNA causing increased catecholamines (noradrenaline) release, this leads to increased activation of β-3 adrenergic receptors (β-3R) on BAT cells. Activation of β-3R causes activation of G-coupled cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). This results in increased lipolysis of triglyceride droplets, thereby increasing the levels of intracellular free fatty acids. The elevated levels of free fatty acids in turn activate UCP1 and initiate heat production. UCP1 enables the proton produced by the mitochondrial reaction to be released as heat rather than using the proton gradient to produce ATP. With therapeutic intervention, the hope in obesity research is that if more stored energy can be converted into heat a new therapy to help combat excess body fat may be developed.

Since 2007, it is acknowledged that humans, like rodents, express BAT deposits/cells in adulthood. Via positron emission tomography (PET) scanning, brown adipose tissue depots were identified in humans and appear to be particularly concentrated in the neck, supraclavicular area, para-aortic, paravertebral and suprarenal areas. The protein UCP1 is increased at baseline conditions in obese animals as well as when animals, including humans, are exposed to cold conditions, suggesting protein activity and increased thermogenesis in these conditions. Interestingly, UCP1 expression and thermogenesis are only elevated in obese mice that are hyperleptinemic, but not in adipose tissue mass matched obese mice that are genetically leptin-deficient (ob/ob mice) or leptin receptor-deficient (db/db mice), suggesting a role of leptin in increasing thermogenesis in obesity.

Selective Leptin Resistance could be the Link between Adiposity and Elevated Sympathetic Outflow

Leptin, a cytokine discovered in 1994, is secreted from adipocytes in proportion to the mass of adipose tissue an animal accumulates. Since its discovery, and the recognition that leptin is the inhibitory signal from fat informing the brain of the body’s stocks of stored energy, leptin has been extensively studied regarding its ability to produce anorexigenic actions. Leptin decreases food intake and this is particularly dependent on the depolarization and hyperpolarization of neurons in the arcuate nucleus of the hypothalamus (ARH). Leptin resistance develops in obesity, a condition in which the ARH neurons expressing leptin receptors do not become further activated from baseline in response to exogenous leptin, and therefore the elevated leptin levels do not decrease food intake or increase energy expenditure. How leptin resistance develops in obesity and how it could be corrected is now under substantial research. Recently, we directly measured thermogenesis from tissue expressing BAT cells in obese leptin-resistant mice (diet induced obese mice, DIO) and discovered that despite the leptin resistance, these mice still experience increased thermogenesis in response to leptin. DIO mice have an elevated baseline BAT temperature compared with lean mice, and ob/ob mice have an even lower BAT temperature at baseline compared with lean mice, confirming previous research that leptin appears to have a role at baseline in controlling sympathetic outflow to BAT and regulating the body’s levels of thermogenesis.

We discovered that leptin elevated thermogenesis by actions in the brain because intracerebroventricular injection, like peripheral injections of leptin, elevated thermogenesis. The DMH has been recognized for a number of years to influence sympathetic activity to organs, including BAT. The role of leptin in this region, however, has not been thoroughly studied. The DMH region appears to be at least one region in which leptin mediates its ability to increase thermogenesis, even in obesity and despite leptin resistance developing in ARH. A large concentration of leptin receptors is present in the DMH, although the exact chemical characteristics of these neurons expressing leptin receptors are still not clearly understood. Leptin acts via the DMH, increasing SNA, and we have demonstrated that blocking β-3 receptors abolishes the increased thermogenic response in DIO mice. The DMH contains no direct projections to the premotor sympathetic neurons and therefore the DMH neurons that respond to leptin must be innervating premotor neurons in other areas of the brain. These areas potentially include the paraventricular nucleus (PVN), an area previously demonstrated to receive direct innervations from leptin receptor-expressing neurons in the DMH.

Our data suggests that the elevated leptin levels in obesity activate the leptin receptors in the DMH, increasing sympathetic outflow to BAT, increasing the activity of UCP1 and increasing thermogenesis. Physiologically this could be a potential way that the body tries to balance energy homeostasis in obesity, but obviously this fails and energy intake still exceeds energy expenditure.

Recently, a paper by Chao et al. identified a key role for neuropeptide Y (NPY) neurons in the DMH for mediating thermogenic actions. The expression of NPY neurons in the DMH is elevated in models of obesity, so these neurons may...
indeed play a role in mediating the increased thermogenic response in obesity. However, very low concentrations of leptin receptors have been reported in NPY neurons of the DMH in young animals, whether this level changes in obesity deserves to be examined.

For the leptin-mediated increase in thermogenesis to be targeted and manipulated in obesity, an understanding of the leptin receptor-expressing neurons in the DMH is needed in order to exacerbate thermogenesis and rebalance energy homeostasis. An understanding of the neuronal circuitry leading from the DMH to the increased sympathetic nerve outflow to BAT cells would also have to be established. This is critical as the leptin-mediated increase in SNA and thermogenesis in BAT, is unlikely to be selectively elevating SNA solely to BAT in obesity.

In obesity (Fig. 1), SNA is increased. Controversy remains as to whether this elevation leads to innervation of all organs throughout the body or whether SNA elevation in obesity is organ specific. Leptin has previously been demonstrated to have the ability to increase SNA in anaesthetised rats in a dose-dependent manner not only to BAT, but also to the adrenal, hind limb and kidney regions. Overall, it is generally recognized that SNA is increased in obesity and, as we recently demonstrated, in BAT. A concerning finding, as it is now readily hypothesized, is that increasing SNA chronically to the kidney contributes to the development of hypertension. Hypertension is one of the metabolic diseases that often develops in obesity and it significantly contributes to the development of cardiovascular diseases, the number one cause of death globally. Therefore, future research in this area is warranted. Studies have established that leptin can acutely elevate SNA. Nevertheless, no conclusive results demonstrating that leptin chronically elevates SNA, leading to hypertension, have yet been shown.

Overactivity of SNS is a common feature of obesity in humans. The increased SNA in obesity also appears to cause organ damage, which exacerbates the risk of cardiovascular disease and metabolic syndrome. Research has already established that acute microinjection of leptin into the DMH of anesthetized rats elevates heart rate and blood pressure. Determining if hyperleptinemia is the cause of chronically elevated SNA in obesity, via activation of leptin receptors in higher brain regions, will potentially generate new therapeutics and improves the care of patients with metabolic syndrome. Moreover, it may even provide a new alternative treatment for obesity itself.
Our study shows that leptin retains the ability through actions in the DMH to increase thermogenesis via the SNS, and in obesity, provides an exciting prospect for new therapies. Indeed, thermogenesis could be therapeutically manipulated to counteract increased caloric intake and restore energy homeostasis. Nevertheless, it should be viewed with caution as the same system and pathways mediating a leptin-evoked increase in thermogenesis in obesity may also be adversely elevating the risk of hypertension and the ultimate development of cardiovascular diseases.

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