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Brown adipose tissue thermogenesis in the resistance to and reversal of obesity

A potential new mechanism contributing to the metabolic benefits of proglucagon-derived peptides

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The capacity for increased thermogenesis through brown adipose tissue (BAT) activation is important for body weight homeostasis. Differences in BAT thermogenesis can underlie significant differences in body weight and body composition, as we demonstrate in a rat model of obesity. This mini-review focuses on our current understanding of physiological BAT regulation, with a view to how it may be exploited therapeutically. BAT activation is under central nervous system control, with the most potent activator of BAT being the sympathetic nervous system, although other humoral and hormonal factors also contribute to BAT regulation. The peptide products of the proglucagon gene are important in energy homeostasis, with well-described effects on feeding and body weight. We recently demonstrated that the peptides glucagon-like peptide 1, glucagon, and oxyntomodulin are also able to induce BAT thermogenesis by a central, sympathetic mechanism. Given the wide spread use of GLP-1 receptor based therapies for type 2 diabetes, drugs targeting this system may be useful in a wider energy balance context.

Until 2009 the question of whether adult humans had brown adipose tissue (BAT) and whether it could conceivably contribute to whole body energy usage in a meaningful way was a matter of vigorous debate. The publication of three papers in the *New England Journal of Medicine*[1-3] that demonstrated adult humans do have BAT, that it can be activated, and that this activation appears to be defective in obesity reframed the debate, and revived interest in BAT physiology. The thermoregulatory role of BAT in small rodents has been known for a very long time and its role in body weight regulation postulated almost as long.[4] A number of studies have demonstrated that disruption of the thermogenic capacity of BAT leads to deficits in both thermoregulation and body weight control. Since heat production from BAT is an energetically inefficient process, activated BAT can account for a significant proportion of energy expenditure in small rodents. In humans, it has been estimated that activated BAT could contribute as much as 15% of energy expenditure.[5] One potent inducer of BAT thermogenesis is excessive dietary calories[6] and inability to utilize this process to dispose of excess caloric content of food results in obesity.[7]

The brain is the master regulator of thermogenesis, with intact sympathetic innervation of BAT being critical for appropriate functional activation.[8] While much work has been done on the neurocircuitry underlying BAT function[9-11] the physiological regulation of BAT in intact animals has been less well studied. Our recent publication examining the role of the proglucagon-derived peptides GLP-1, oxyntomodulin (OXM), and glucagon (GCG) in modulating BAT thermogenesis uses intracerebroventricular administration of these peptides[12] aimed to take a step toward addressing this question.

The sympathetic nervous system (SNS) is best known as the mediator of the "flight or fight" response; however, it is also extremely important in the maintenance of homeostasis of all major physiological functions including metabolic homeostasis. The relationship between SNS activity and body weight maintenance and/or its dysregulation in obesity is complex and unresolved. Obese individuals are generally found to have increased release of catecholamines, but downregulated adrenoceptor expression,[13] although it is likely that interactions between SNS dysfunction and obesity occur in a tissue-specific manner. Activation of sympathetic outflows can selectively increase heart rate, arterial pressure, thermogenesis, and adrenal catecholamine release. These responses have been shown to arise from specific neuronal populations within the DMH, with selective modulation of the response occurring in downstream medullary nuclei.[14]

These neuronal pathways directed to sympathetic outflows can be modulated by circulating factors, with leptin and insulin both able to increase sympathetic activity by acting through neuropeptide intermediaries in the hypothalamus.[15] Activation via these pathways resulting in problematically high blood pressure can occur over a relatively short time and secondary to only mild weight gain.[16] Sympathetic activation of BAT thermogenesis

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following the intake of energy dense foods occurs presumably as a defense against excessive weight gain.[17] The neural pathways subserving the sympathetic innervation of BAT have been defined, and the neurochemical content of the hypothalamic neurons from which they originate has been characterized.[18] These neurons contain neuropeptides which are regulators of energy metabolism and are under the influence of peripheral factors such as leptin and insulin—allowing the possibility that key neuronal populations are master regulators of both energy intake and energy expenditure.[9,19] Thus, BAT as a therapeutic target for weight loss by increased energy expenditure is both an attractive and plausible option.

The SNS mediates a number of metabolic processes that are able to effect net weight loss. It is critically important for adaptive thermogenesis and combating weight gain associated with high fat feeding,[7,20] it plays a key role in lipolysis, and in the absence of sympathetic innervation fat cell number and fat mass increase.[21] In terms of energy balance, the SNS is able to induce energy expenditure in target tissues such as BAT and muscle[22] in an effort to counteract body weight gain in response to overfeeding. One mechanism for this is via increased thermogenesis. Thermogenesis is commonly thought of in terms of heat production—in order for endotherms to maintain a stable core temperature they must be capable of de novo heat production; however this processes can also be exploited as a method of "wasting" excess ingested energy. This is done by uncoupling the process of oxidative phosphorylation from adenosine triphosphate (ATP) production via specialized proteins called uncoupling proteins (UCPs) in the mitochondria: it essentially redirects chemical energy that could be used for kinetic work into heat production. In the usual state of oxidative phosphorylation, energy production is driven by the proton gradient across the inner mitochondrial membrane, and proton passage is mediated by ATP synthase, resulting in ATP production. In BAT, UCP1 provides an alternative route into the mitochondrial matrix, allowing the energy of the proton gradient to be released as heat without ATP production.[23] This means that energy is "burned" in preference to storing it as fat, and is termed "diet-induced thermogenesis" (DIT).[17] The teleology of DIT is somewhat obtuse, but it may be important in defending a body weight set point by allowing organisms to take in as much nutritional value from food as possible without the impediment of increased body weight.[24] This view has been challenged[25] but the case in favor of an essential role for DIT in body weight control is considerably strengthened by observations made in mice in thermo-neutral conditions, further discussed below.[7]

In rats and mice the major thermogenic organ is BAT, which is largely situated in discreet depots between the scapulae, known as the interscapular BAT (iBAT). Rats, mice, and newborn humans have appreciable BAT depots but until recently it was contentious as to whether the tissue existed in adult humans. As mentioned above, it is now well accepted that adult humans have discrete BAT depots. The major stimulus for iBAT thermogenesis comes from the sympathetic nervous system in response to either changes in temperature[26] or overfeeding.[27] Specific activity of BAT can underlie quite significant differences in body weight in rats, with increased thermogenesis being protective against obesity on a high fat diet. In an experiment repeated several times we placed a cohort of outbred Sprague Dawley rats and placed them on a high energy "cafeteria" diet consisting of a range of foods for human consumption including shortbread, chips, peanuts, sausage, and pies, similar to diets used previously.[28] Over the period of exposure to the diet, the rats developed obesity, but to differing extents (**Fig. 1A**). This is a well-described phenomenon where some rats, called obesity prone, gain a large amount of weight in response to the diet while others, called obesity resistant, gain weight at the same rate as chow fed rats.[29] In addition, some rats show an intermediate weight-gain phenotype, which are typically removed from studies to produce pure cohorts of OR and OP rats. These differences in body weight in OR and OP rats are reflected in body composition, with the OR rats having significantly lighter intraperitoneal fat depot weights than the OP rats (**Fig. 1B and C**). The OR rats do not escape the effects of the diet entirely, as the epididimal fat pad weights of the OR rats were significantly heavier than those of low-fat fed controls (**Fig. 1C**). After 16 weeks on the diet a cohort of rats were implanted with temperature sensitive radio-telemetry devices to constantly record iBAT temperature, as described previously.[30] Recordings of iBAT temperature showed a significant elevation in OR compared with OP rats across the 24-h recording period (**Fig. 1D**), with no significant alteration in locomotor activity (**Fig. 1E**). This significantly different thermogenic output between the two groups of rats provides a likely physiological substrate for the very large differences in body weight observed. There is data to suggest a similar relationship may exist in humans. A correlative relationship between body weight and BAT activity has been described, where lower levels of BAT activation determined by PET imaging correlate with increased adiposity.[3] The BAT of obese individuals is also less responsive to stimulation by ephedrine, indicating that the observed deficits in thermogenesis in obese individuals may result from dysregulated sympathetic control of the tissue.[31]

The importance of functional thermogenic capacity of BAT in both temperature and body weight regulation is observable in mice lacking the UCP1 gene. At regular ambient temperatures (~23 °C) UCP1 knockout mice have no phenotype; however, they are both hypersensitive to cold when exposed to lower temperatures[32] and susceptible to obesity when housed in a thermoneutral environment.[7] The concept of thermoneutrality contributing to the obesogenic environment is pertinent to the human situation where very few people experience sustained exposure to lower than optimal temperatures for any extended time. Heat production requires significant amounts of chemical energy and it may be that removing situations where we are required to produce heat has shifted us as a species toward weight gain.

The neurons which project to the BAT pads are synaptically connected to neurons in the brainstem and hypothalamus that contain feeding-related peptides, including elements of the melanocortin pathway.[18] Activation of central melanocortin receptors, known master controllers of metabolism, increases sympathetic nerve activity (SNA) activity to BAT[33] and functional thermogenic output.[34] Leptin's ability to induce BAT thermogenesis is dependent on this pathway in the dosomedial hypothalamus.[35]

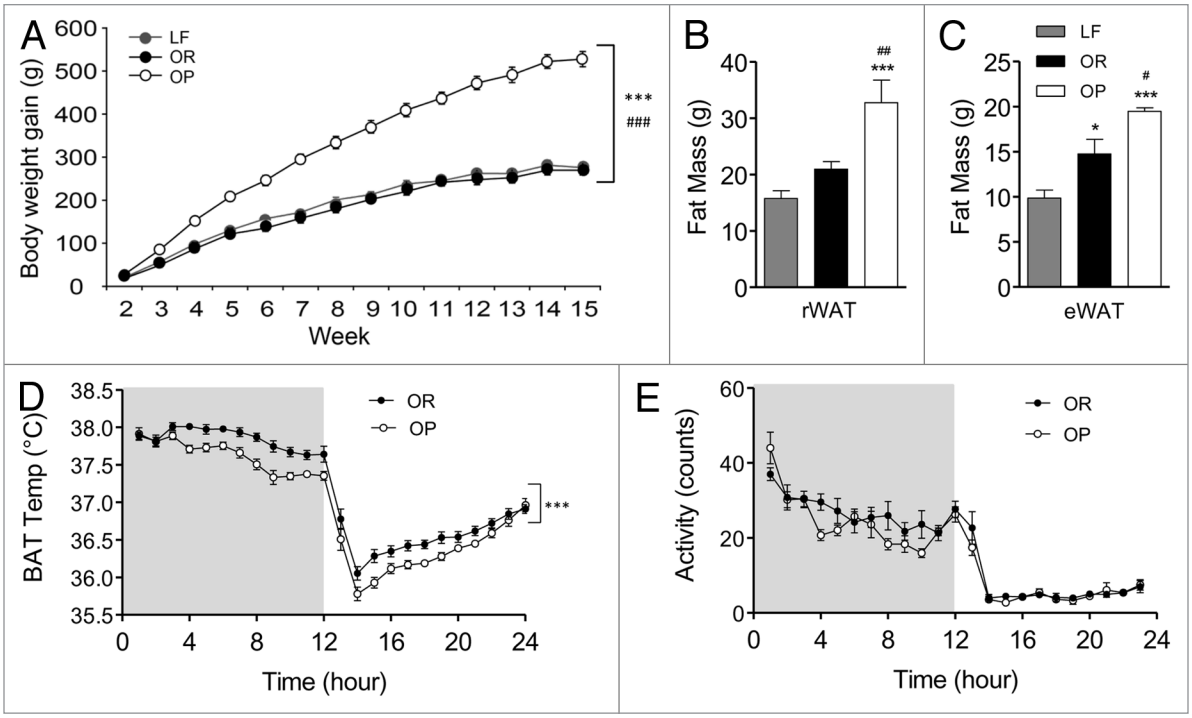

Figure 1. Outbred Sprague–Dawley rats placed on a high-fat cafeteria diet split into two distinct phenotypic groups, those that are obesity-prone (OP) and gain weight and fat mass and those that are obesity-resistant (OR), which maintain a similar weight and fat mass to rats on a control low-fat diet (LF). These differences in body size and composition are accompanied by alterations in BAT thermogenesis, where the OR animals show significantly increased BAT temperature compared with the OP rats. (**A**) Body weight change over 15 weeks on high-fat diet, two-way RM ANOVA, ***$P < 0.001$ comparing OP and OR, ###$P < 0.001$ comparing OP and LF. Dissected (**B**) retroperitoneal and (**C**) epididymal fat pad mass at death, one way ANOVA with the Tukey post test *$P < 0.05$, ***$P < 0.001$ compared with low fat, #$P < 0.05$ ##$P < 0.01$ compared with OR, $n = 5$–10. Hourly average (**D**) BAT temperature and (**E**) activity level of OP ($n = 7$) and OR ($n = 7$) rats across 9 recording days. A two-way RM ANOVA showed a significant main effect of obesity status (***$P < 0.001$), as well as a significant interaction (*$P < 0.05$) for BAT temperature, but not for activity.

Increased catecholamines due to increased SNA regulate downstream molecular alterations in the tissue that ultimately modulate BAT thermogenesis. Increased adrenergic stimulation of BAT leads to increases in a number of factors, including peroxisome proliferator-activated receptors (PPARs), PPAR-coactivator 1α (PGC1α), UCP1, and fibroblast growth factor 21 (FGF21). UCP1 is the ultimate mediator of BAT thermogenesis, however it is not constituently active, and its functional induction is regulated at multiple levels. Transcriptionally, UCP1 is regulated by both PPARs and PCG1a, with PPARα and γ activation resulting in upregulation of transcription, which is further augmented by PGC1α.[36] Both PGC1α and UPC1 levels are upregulated by FGF21.[37] FGF21 is synthesized in BAT and levels are increased with both increased thermogenesis, an effect which is driven by the sympathetic nervous system,[38,39] and increased free fatty acids,[40] indicating that this protein may play a role in translating the adrenergic drive from the SNS into functional thermogenesis. It has recently been demonstrated that mild cold exposure in humans is enough to significantly raise circulating FGF21 levels, which correlates with the extent to which subjects increased their energy expenditure in response to cold.[41] Over-feeding and insulin infusion (a signal of over-nutrition) also increase circulating FGF21 in humans, indicating a role for this hormone in diet-induced, as well as cold-induced, thermogenesis. Our recent observation that activation of the GLP-1R in the brain is able to increase *fgf21* gene expression in BAT provides additional evidence that FGF21 induction is responsive to nutritional regulation and may play a role in diet induced thermogenesis.

UCP1 is also acutely regulated by ATP and fatty acids. Fatty acids activate UCP1 uncoupling as a function of availability, with removal of fatty acid availability resulting in an immediate repolarization of the mitochondrial membrane and cessation of uncoupling.[42] ATP, which is always present in vivo, inhibits UCP1, and thus provides constitutive inhibition of uncoupling.[43] The ability of fatty acids to induce uncoupling is possibly independent of nucleotide inhibition;[44] however, this is yet to be fully described.

Although an appropriate thyroid function is essential for the maintenance of overall energy balance, it is especially critical for the regulation of BAT metabolism. Hypothyroidism is associated with increased body weight and lethargy while hyperthyroidism results in leanness. The activity of type II iodothyronine deiodinase (DIO2), the enzyme which converts thyroxine to 3,3',5-triiodothyronine (T4 to T3), in BAT is crucial to its ability to sustain thermogenic output in response to cold,[45] and whole body loss of this enzyme may increase susceptibility to diet-induced obesity.[46] In addition to the impact at the adipocyte level, thyroid hormones regulate the activity of the sympathetic fibers innervating BAT by regulating energy metabolism in hypothalamic neurons.[47]

BAT thermogenesis uses fatty acids liberated by the lipolytic actions of the SNS; however for sustained thermogenesis to occur de novo, lipogenesis must be able to fuel the process. In response to cold there is an upregulation of lipogenic enzymes in BAT,[48,49] and when this process is blocked and mice are challenged with cold they exhibit hypothermia.[45] Overall, thermogenesis is a process that requires shifts in both lipolysis and lipogenesis, in both BAT and white fat pads, to fuel and sustain increased uncoupling in the BAT for heat generation. This is a process regulated by the brain via the SNS, but is additionally controlled in BAT by a number of peripheral factors which have considerable influence over the ultimate thermogenic output.

We recently demonstrated that BAT in mice can be activated by intracerebroventricular administration of several peptides derived from the proglucagon gene. GLP-1, oxyntomodulin (OXM), and glucagon all induce both SNS activity and increased BAT temperature in vivo. OXM binds to both the GLP-1 and glucagon receptors (GLP-1R and GCGR, respectively), and it appears to exert its thermogenic actions through the GLP-1R as it was unable to affect BAT temperature or molecular markers of altered BAT metabolism in GLP-1R knockout mice.[12] This is in agreement with other reports suggesting that central GLP-1Rs mediate adipocyte metabolism and inhibit triglyceride storage in white fat depots,[50] indicating that central GLP-1R may promote a catabolic state in adipose tissue via the SNS. Importantly, GLP-1R knockout mice are not sensitive to cold exposure, so this pathway is not critical for temperature regulation.[12] Whether both circulating and centrally produced GLP-1 contribute to the control of BAT activity remains unknown. GLP-1 levels rise postprandially, so it is possible that this pathway may be involved in adaptive or diet induced thermogenesis as a defense against excessive weight gain. Interestingly, a rodent model with increased circulating levels of active GLP-1, namely the *Dpp4*$^{-/-}$ mouse, has increased energy expenditure and higher UCP-1 expression in BAT compared with their wild-type counterparts.[51] On the other hand, preproglucagon gene expression in the brainstem positively correlates with the degree of obesity induced by high fat feeding in rats,[52] which opens the possibility of a role of centrally produced GLP-1 in the control of diet-induced thermogenesis. The specific neuronal pathways that subserve proglucagon-derived peptide induction of thermogenesis remain to be elucidated. GLP-1R is expressed in POMC neurons within the Arcuate nucleus of the hypothalamus,[53] which suggests that the melanocortin pathway may be involved in the control of BAT by GLP-1. Additionally, GLP-1R is expressed in hypothalamic nuclei that play a critical role in the control of thermoregulation, such as the dorsomedial nucleus (DMN) and the medial preoptic area (MPOA).[54] Given that these areas receive projections from brainstem proglucagon neurons,[55] it is possible that neurally derived GLP-1 plays a direct role in the control of BAT activity by the brain.

Conclusion

BAT thermogenesis vitally important for small rodents for thermoregulation and its importance in body weight regulation in these animals has been demonstrated in a laboratory setting. The possibility that it may also be important in human body weight control, and that it may be amenable to pharmacological manipulation for weight management, is attractive, but as yet undemonstrated. Drugs targeting the GLP-1 system, either in the form of long acting agonists or agents which inhibit the degrading enzyme DPP-IV, are already widely prescribed for their incretin properties to treat type 2 diabetes. In particular, the long acting agonists are able to induce weight loss separate from their effects on glycemic control,[56] and it would be most interesting to know if these patients had increased BAT activation.

The first step in realizing the possibility of obesity therapeutics which utilize increased BAT thermogenesis to effect weight loss is a firm physiological understanding of BAT function and regulation. There is much exciting work being done to this end, and although there is much still to be done both in basic physiology and in translation to the human situation, it is a possibility which burns brightly.

Disclosure of Potential Conflicts of Interest

DPT has a collaborative association with Roche Research Laboratories pertaining to peptide-based therapeutics in metabolism; SHL, AS, and BJO have no conflicts to declare.

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