An endocrine role for brown adipose tissue?

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Submitted 3 May 2013; accepted in final form 8 July 2013


An endocrine role for brown adipose tissue?—White adipose tissue is recognized as both a site of energy storage and an endocrine organ that produces a myriad of endocrine factors called adipokines. Brown adipose tissue (BAT) is the main site of nonshivering thermogenesis in mammals. The amount and activity of brown adipocytes are associated with protection against obesity and associated metabolic alterations. These effects of BAT are traditionally attributed to its capacity for the oxidation of fatty acids and glucose to sustain thermogenesis. However, recent data suggest that the beneficial effects of BAT could involve a previously unrecognized endocrine role through the release of endocrine factors. Several signaling molecules with endocrine properties have been found to be released by brown fat, especially under conditions of thermogenic activation. Moreover, experimental BAT transplantation has been shown to improve glucose tolerance and insulin sensitivity mainly by influencing hepatic and cardiac function. It has been proposed that these effects are due to the release of endocrine factors by brown fat, such as insulin-like growth factor I, interleukin-6, or fibroblast growth factor-21. Further research is needed to determine whether brown fat plays an endocrine role and, if so, to comprehensively identify which endocrine factors are released by BAT. Such research may reveal novel clues for the observed association between brown adipocyte activity and a healthy metabolic profile, and it could also enlarge a current view of potential therapeutic tools for obesity and associated metabolic diseases.

Brown adipose tissue; adipokine; batokine; fibroblast growth factor-21; endocrine

TWO TYPES OF ADIPOSE TISSUE exist in mammals: white adipose tissue (WAT) and brown adipose tissue (BAT). They play opposing roles, with WAT acting as the main site of metabolic energy storage in the form of lipids, whereas BAT is a main site of energy expenditure. Rodent studies have shown that BAT plays a major role in protecting against obesity and obesity-associated metabolic alterations through the capacity of brown adipocytes to dissipate energy via uncoupling protein 1 (UCP1)-mediated uncoupling of mitochondrial oxidative processes and subsequent heat production. BAT activity has been associated with a healthy systemic metabolic profile, which is at least partly due to the ability of BAT to act as a sink of circulating glucose and lipids, thereby preventing excessive metabolic fuel deposition, diabetes, and dyslipidemia. Although researchers have long doubted the relevance of BAT in adult humans, the recent use of positron emission scanning techniques has revealed BAT activity in adult humans and decreased BAT activity in obese patients (8, 57).

Cells exhibiting a brown adipocyte thermogenic phenotype (including UCP1 expression) and appearing in WAT depots after thermogenic activation have been identified and characterized. Some authors claim that these cells, usually termed “beige” or “brite” cells, arise from a cell lineage different from that leading to brown adipocytes in anatomically defined BAT depots (37, 45), but there is still ongoing research to clarify the precise origin of distinct cells showing a brown adipocyte phenotype. There is genetic evidence that the capacity to induce these cells in WAT depots is highly relevant for protection against obesity in rodents (18).

In this Perspectives article, we will refer to BAT as the anatomically defined, developmentally programmed BAT depots; cells present in these depots are referred as brown adipocytes. “Beige/brite” will be used to refer to the cells noted above that share thermogenic properties with brown adipocytes and appear in WAT depots under conditions of long-term adaptation to thermogenic challenges.

We Know That WAT is an Endocrine Organ, But What About BAT?

The traditional concept of WAT as a mere site of storage of fat to be used under conditions of shortage of energy supply has been modified dramatically in recent decades, especially after the discovery of leptin as a hormone produced by white adipocytes in 1994, following earlier predictions in the studies of Coleman (7). Multiple bioactive molecules released by white adipocytes have been identified to date as the so-called adipokines. With some parallelism with white adipocytes years ago, practically until present times, the brown adipocyte has been considered just a site of metabolic energy consumption to produce heat. Recent direct and indirect evidence suggests the need to change this concept to incorporate the recognition of a potential specific endocrine role of brown adipocytes (see below). Although still a matter of speculation, the physiological role of BAT and its association with healthy metabolism may extend beyond its capacity for metabolite oxidation to include the release of endocrine signals that act on other organs. When BAT is activated to respond to thermogenic requirements (e.g., in a cold environment), the body undergoes a set of systemic metabolic adaptations, including decreased glycemia and systemic insulin sensitization (3). Enhanced sensitivity to insulin and subsequent glucose uptake by BAT contributes to this systemic effect (17). Other tissues such as WAT and skeletal muscle do not show such insulin sensitization, and catabolic processes are increased (e.g., WAT lipolysis) (17, 52) in association with enhanced BAT activity, channeling fuel substrates to BAT for thermogenesis. Are BAT-
A role for BAT beyond its capacity of metabolite oxidation for thermogenesis was first proposed based on observations that genetically mediated ablation of BAT (21, 30) had a much more profound impact on metabolism than specific blockade of BAT thermogenic activity via UCP1 gene invalidation (13). Whether the association of active BAT detected in positron emission tomography scan assays with a lean and metabolically healthy phenotype in adult humans solely reflected intrinsic energy expenditure or indicates another facet of the physiological role of BAT is currently unknown.

The main adipokines released by WAT (e.g., leptin and adiponectin) are poorly expressed in BAT, especially when it is thermogenically active (5). Indeed, the expression levels of leptin and/or adiponectin are even used as WAT vs. BAT markers in situations of adipose tissue plasticity. If endocrine factors are released by BAT in response to thermogenic induction, we might assume that these factors, termed “batakines” by some authors (49, 51, 1) may have different (and perhaps opposite) actions from those of the WAT adipokines, 2 will act on other tissues (and possibly the central nervous system) to favor systemic adaptations for high energy expenditure, such as overall catabolic processes and the channeling of metabolic supplies to BAT for oxidation, and 3) will be actively released under conditions in which BAT is thermogenically activated. These endocrine factors released by BAT would also be expected to interact with the sympathetic nervous system activity, which is classically believed to coordinate the systemic response to thermogenic activation.

BAT as a Secretory Organ of Autocrine and Paracrine Factors

Although the endocrine role of BAT remains a largely unsolved mystery at this point, accumulating evidence indicates that BAT releases factors that act either on the secreting brown adipocytes (autocrine action) or on other cells types nearby (paracrine action). A summary of the paracrine/autocrine factors released by BAT is shown in Table 1; this information, based on currently available literature in this field, is derived almost exclusively from rat and mouse studies. Some are released by brown adipocytes under conditions of BAT recruitment in development or in response to thermogenic activation. These include vascular endothelial growth factor-A, which possibly favors angiogenesis in response to sympathetic activation/vascularization, and insulin-like growth factor I (IGF-1) and fibroblast growth factor-2 (FGF2), which may increase the density of brown adipocyte precursor cells. Moreover, indirect evidence based on targeted disruption of the cyclooxygenase gene has stressed the importance of local prostaglandin generation in development of the “beige/brite” adipocytes in WAT depots (the so-called “browning” process) (53).

In general, expression of proinflammatory cytokine genes is lower in BAT than in WAT, possibly owing to the less proinflammatory phenotype of locally infiltrating immune cells (33, 35). However, interleukin (IL)-10 and especially IL-6 are expressed and released by brown adipocytes in response to thermogenic stimuli (4). Although IL-6 is commonly considered a proinflammatory cytokine that has local paracrine and autocrine effects, it can also act as a myokine (a skeletal muscle-released hormonal factor) that has metabolic effects at a distance from its site of release (36). Furthermore, a major BAT-released factor, bone morphogenetic protein-8b (BMP8b), was recently identified and shown to have a unique capacity to sensitize brown adipocytes to noradrenergic action (56). Lipocalin prostaglandin D synthase, in addition to its role in the synthesis of D-series prostaglandins, is secreted to the extracellular milieu and can act as a carrier of lipophilic molecules such as thyroid hormones and retinoic acid (2, 50), all of which are hormonal factors relevant to brown adipocyte activity (5). Loss-of-function approaches have revealed a relevant role of lipocalin prostaglandin D synthase in BAT activity (54), thus suggesting a putative autocrine role. In summary, although an endocrine role cannot be excluded for some of these factors (e.g., IGF-I, IL-6, BMP8b), these bona fide BAT-released factors collectively appear to function primarily at the autocrine and/or paracrine levels.

**Triiodothyronine, the Only Known Classical Endocrine Product of BAT**

To date, the only known recognized endocrine role of BAT is its capacity to release the active thyroid hormone triiodothyronine (T3). The enzyme type II thyroxine 5'-deiodinase,

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**Table 1. Summary of bioactive factors secreted by BAT preferentially expressed in brown vs. white adipocytes and/or activated in BAT under thermogenic stimuli (cold, norepinephrine)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Main Role</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triiodothyronine (due to 5'-deiodinase local activity)</td>
<td>A/E</td>
<td>14, 48&lt;sup&gt;<strong>&lt;/sup&gt;, 53&lt;sup&gt;</strong>&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prostaglandins (due to local prostaglandin synthesis enzyme activity)</td>
<td>A/P</td>
<td>31, 39, 53&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Angiotsinogen</td>
<td>A</td>
<td>6&lt;sup&gt;′&lt;/sup&gt;</td>
</tr>
<tr>
<td>Interleukin-1α</td>
<td>P/A</td>
<td>4&lt;sup&gt;′&lt;/sup&gt;</td>
</tr>
<tr>
<td>Insulin-like growth factor I</td>
<td>A</td>
<td>20, 62&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>A/P/E</td>
<td>4, 49&lt;sup&gt;<strong>&lt;/sup&gt;, 53&lt;sup&gt;</strong>&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vascular endothelial growth factor-A</td>
<td>P</td>
<td>1, 60&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nitric oxide (due to local eNOS expression)</td>
<td>A/P</td>
<td>25, 34&lt;sup&gt;′&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibroblast growth factor-2</td>
<td>A/E</td>
<td>9, 22&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Retinol-binding protein-4</td>
<td>A/P/E (?)</td>
<td>41&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bone morphogenetic protein-8b</td>
<td>A/P/E (?)</td>
<td>56&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lipocalin prostaglandin D synthase</td>
<td>A/E</td>
<td>54&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

BAT, brown adipose tissue; A, autocrine; P, paracrine; E, endocrine; eNOS, endothelial nitric oxide synthase. *Studies performed in BAT or brown adipocytes from rats; **studies performed in BAT or brown adipocytes from mice; (?)role of these factors not fully established.
present specifically in BAT, converts thyroxine into T3 and is strongly activated upon the induction of BAT thermogenic activity (47). Locally generated T3 contributes to the intracellular pathways of thermogenic activation of brown adipocytes (10). In 1985, tracer-based kinetic studies demonstrated that, under conditions of high BAT activity, BAT is an important site for the generation of systemic T3 (48). This was further confirmed using independent experimental approaches (14).

Conversely, the observation that mice with targeted ablation of type II 5'-deiodinase gene maintain normal T3 levels (10) weakened the argument that BAT is an important source of T3. However, we might expect compensatory processes in a highly homeostatic system, such as the maintenance of thyroid status. Considering the role of thyroid hormones in the promotion of catabolic energy-expending processes, it would seem logical that BAT could send peripheral signals that contribute to energy expenditure and thermogenesis.

**Is Retinol-Binding Protein-4 a BAT-Released Endocrine Factor?**

Retinol-binding protein-4 (RBP4) is a blood protein that transports retinol. In 1995, RBP4 was reported to behave as a WAT adipokine, transmitting signals to the liver and other tissues (63). Since then, there has been some controversy on the actual role of RBP4 as an inducer of insulin resistance. A recent study showed that thermogenic activation of BAT is associated with a strong induction of RBP4 expression in BAT, and brown adipocytes release high amounts of RBP4 when activated by norepinephrine (41). The action of putative BAT-released RBP4 on systemic metabolism is not yet known, but it is unlikely to reduce systemic insulin sensitivity, as proposed for WAT-released RBP4 (63), since BAT activation is associated with enhanced systemic insulin sensitivity (3). Perhaps the function may be related to the retinol-transporting role of RBP4 and the cold-induced hydrolysis of retinyl esters under conditions of enhanced BAT lipolysis associated with thermogenic activation.

**FGF21: Recent Evidence for the Existence of BAT-Derived Endocrine Factors**

Possibly the most substantive evidence that BAT may release endocrine factors is the recent recognition of BAT as a site of FGF21 production (22). FGF21, which is an endocrine member of the FGF family, powerfully promotes glucose oxidation in multiple tissues (liver, WAT, pancreas, and possibly the central nervous system) and can protect against obesity and type 2 diabetes in rodent models (40, 43). Under basal conditions, the liver appears to be the main site of FGF21 production. However, thermogenic activation induces FGF21 gene expression in BAT and triggers the release of FGF21 by brown adipocytes (9, 16, 22). An autocrine role of FGF21 in BAT cannot be excluded (16, 23); however, it has been demonstrated directly in vivo that BAT actively releases FGF21 to circulation upon activation of thermogenesis (22). Recent studies showing that transplantation of BAT can benefit metabolism and enhance FGF21 levels (see below) are consistent with the notion that BAT-released FGF21 transmits signals from BAT to other organs and tissues. Like RBP4, FGF21 is also expressed in WAT, but there is no induction associated with thermogenic activation; in fact, it has been proposed that FGF21 plays mainly an autocrine role in WAT (11). Moreover, FGF21 appears to be able to cross the blood-brain barrier (24), and there are data showing that FGF21 may act on the brain to increase hepatic insulin sensitivity and metabolic rate in obese rats with diet-induced obesity (43). This would confirm the possibility that BAT-derived endocrine factors may be able to act on the central nervous system, like conventional adipokines, and by these means influence overall energy metabolism. Finally, it is worth noting that studies evaluating the expression of genes capable of distinguishing between “classical” brown adipocytes (present in anatomically defined BAT depots) and “beige/brite” cells have identified FGF21 as more intensely expressed in “beige/brite” cells (46, 58). This suggests that FGF21 may be especially relevant in the autocrine and/or endocrine role of this particular type of inducible brown adipocyte. Recently, FGF21 has been reported to be expressed and released by “beige/brite” adipocytes in adult humans (26).

**BAT Transplantation, the Ultimate Approach Showing Evidence of the Existence of BAT-Derived Endocrine Factors**

Very recent reports examining the consequences of experimental BAT transplantation offer the most compelling evidence that BAT releases endocrine signals. For example, Gunawardana and Piston (20) showed that subcutaneous BAT transplants normalized glucose levels and reversed diabetes symptoms in rodent models of type 1 diabetes. The authors proposed that BAT-released IGF-I acts as an endocrine factor mimicking the actions of insulin in ameliorating diabetes. A similar approach yielded a second breakthrough when Stanford et al. (49) reported that BAT transplantation to mice improved glucose tolerance, enhanced insulin sensitivity, decreased fat mass, and reversed high-fat diet-induced insulin resistance. Furthermore, they found that WAT and the heart were the major tissue targets of improved glucose uptake. BAT transplantation was associated with a strong enhancement in blood FGF21 levels, consistent with the idea that FGF21 could be the endocrine factor responsible for mediating the systemic effects of BAT transplantation. BAT-derived IL-6 was also found to be required for the effects of BAT transplantation, as transplantation of BAT from IL-6-null mice neither improves metabolic status of mice nor induces FGF21 increase. We do not yet know whether IL-6 acts directly or whether it induces FGF21 to mediate systemic effects.

**Further Directions for the Establishment of the Endocrine Role of BAT and the Identification of Endocrine Factors Released by BAT**

Although all of the evidence mentioned above points to the existence of a specific system of release of endocrine signals by BAT, definitive proof should await further research. The above findings should be considered the tip of the iceberg when it comes to proving the existence of BAT-derived endocrine factors and examining their ability to explain the endocrine role of BAT (Fig. 1). In the future, systematic research approaches will be needed to comprehensively test the endocrine actions of BAT and the molecules involved. This could include detailed studies of the systemic alterations in BAT ablation models. Unfortunately, classical approaches in endocrine research based on surgical ablation of the suspected endocrine organ are
hardly feasible in BAT. Surgical ablation of major BAT anatomic sites in rats results only in the removal of 40% of total BAT, and moreover, this manipulation leads to rapid compensatory proliferation at other BAT depots (42). Furthermore, genetic manipulation leading to atrophy of BAT at major anatomic sites also leads to compensation through “browning” of WAT, i.e., the induction of “beige/brite” cells in WAT depots (44). Perhaps other models of BAT ablation, such as the UCP1-DTA mice, in which brown adipocytes are genetically ablated through UCP1 promoter-driven diphtheria toxin, would be useful (30).

Research on the endocrine role of BAT could employ high-throughput screening approaches. The use of updated proteomic technologies to identify the proteins released to the medium by brown adipocytes in cell culture (i.e., the establishment of the brown adipocyte secretome) could be an important step. Bioinformatic scanning of BAT gene expression databases for predicted secretable proteins could also help to identify candidate endocrine factors for further experimental exploration. The strict cell specificity of UCP1 gene transcription in brown adipocytes suggests that BAT-specific gene-invalidated (“knockout”) models using previously reported systems in which UCP1 promoter-driven recombinase is used to invalidate genes in brown adipocytes (19, 32) may also be exploited in future studies of endocrine factors released by BAT.

Finally, as seen for the endocrine role of WAT, it is possible that BAT-infiltrating cells other than brown adipocytes may contribute to the release of bioactive molecules. The recent recognition that the immune cell subpopulations infiltrating BAT differ from those in WAT (33, 35, 59) may suggest that BAT vs. WAT differences in secretory activity could also involve the activities of nonadipocyte cells.

Anatomists of old named BAT as the hibernating “gland” due to its relevant presence in hibernating mammals. Their intuition may be proven correct in the near future thanks to the ongoing research efforts to resolve questions surrounding the physiological implications of putative endocrine functions of BAT. The identification of endocrine factors released by BAT would be of utmost relevance as tools in future clinical applications focused toward improving metabolic health in highly relevant diseases such as obesity, diabetes, and dyslipidemia.

**GRANTS**

This work was supported by MINECO (SAF2011-23636). Instituto de Salud Carlos III (Grant PI11/00376), Generalitat de Catalunya, Spain, and the European Commission (BetaBat project). J. Villarroya is the recipient of a
REFERENCES


