

Human Brown Adipose Tissue—A Decade Later

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The recognition of the presence of metabolically active brown adipose tissue (BAT) in adult humans has boosted a tremendous number of studies in the past 12 years. In brief, BAT is characterized by, among other things, its large thermogenic capacity, cells with high mitochondrial density, and the presence of uncoupling protein 1 (UCP1) in the mitochondrial inner membrane. When activated by cold exposure, it generates heat by the process of mitochondrial uncoupling. It was with the onset of new scanning techniques in nuclear medicine (^{18}F -deoxyglucose positron emission tomography/X-ray computed tomography [^{18}F -FDG-PET/CT]) that the functional activation of BAT (i.e., cold-induced glucose uptake) in human adults could be visualized *in vivo* (1). The first dedicated studies, all in 2009 (2–4), revealed that in adult humans, BAT can be activated by cold, shows a positive relation with cold-induced nonshivering thermogenesis, has a high prevalence without sexual dimorphism, is related to seasonal variation in outdoor temperatures, is negatively related to percentage body fat, declines in amount with age, and may have a potentially significant contribution to glucose disposal. These findings, combined with animal and epidemiological studies showing that the presence and activity of BAT are linked to a healthier (cardio)metabolic profile, triggered scientists' and journalists' hope (and fantasy) to use BAT to beat human obesity and diabetes.

So what happened next? What did we learn, and what about the next decade?

A Flexile Tissue

Major breakthroughs were made in the cellular mechanisms and origin of brown adipocytes. These revealed the distinction between so-called “classical brown” and inducible beige adipocytes. Lineage tracing studies revealed that the classical brown adipocytes share precursors with skeletal muscle cells. The beige cells, also characterized by the presence of brown fat characteristic protein UCP1, can be induced in white adipose tissue (WAT) and they share their origin. Interesting findings with respect to browning, *de novo* recruitment from preadipocytes, and transdifferentiation between white and beige adipocytes were described, e.g., by Rosenwald et al. (5). Both brown and beige cells were shown in adult humans, and many findings in humans paralleled those of the mouse models. Although brown and beige adipocytes in human adults and mice show common molecular markers, distinctive molecular profiles also exist between mice and men (6). The field is still progressing, and the last word about origins of beige cells and their potential have not yet been spoken. Despite the many unknowns, these

studies confirm that human brown and beige adipocytes in classical and in WAT depots are characterized by high plasticity and responsiveness to environmental conditions.

This flexibility of the tissue is in line with the effects of pharmacological treatment (such as treatment with the β 3-adrenergic receptor agonist mirabegron) (7) and repeated cold exposure. Following classical studies on cold acclimation and the related increase of nonshivering thermogenesis (8), studies revealed that BAT amounts can be significantly increased upon a cold acclimation period of only 10 days to 6 weeks (9–12). Although BAT amount increased in abundance, skeletal muscle metabolism, more specifically the translocation of glucose transporter GLUT4 in the muscle fibers, seem to be involved (13). This intriguing question pops up: What is the actual contribution of BAT during acute cold and after cold acclimation?

Quantifying BAT Amount and Activity

The first studies made estimations of BAT amounts in adults, based on ^{18}F -FDG uptake combined with a CT scan (^{18}F -FDG-PET/CT), i.e., measuring an approximation of glucose uptake or uptake rate in the cells. Rough estimates of cold-induced amounts of BAT, based on this technique, ranged from 50 to 150 g. Taking these amounts and calculations based on dynamic PET scanning, the contribution of active BAT would be 2.5% to 5% of the basal metabolic rate (3,14). Next, several studies used other dynamic scanning techniques with isotopes linked to actual metabolic rate, such as ^{15}O - O_2 . Two independent studies using ^{15}O - O_2 isotope measuring oxygen consumption revealed a contribution of only ~1% of whole-body energy expenditure (15,16). All in all, it should be noted that the contributions of BAT in humans are still approximations because of limitations of the techniques used. Several alternative tracers for PET and other techniques, such as magnetic resonance imaging, are used and under development, with the potential of better quantification of BAT metabolism and substrate utilization (for a recent overview, see Richard et al. (17)).

In conclusion, the amount of BAT does not seem to be more than 1% to 5% of basal metabolic rate during cold exposure (even after cold acclimation), after meal ingestion (18), or with pharmacological treatment. During normal life conditions under thermoneutral or close to thermoneutral conditions, BAT will not be continuously activated, and the contribution to whole-body energy expenditure or substrate utilization will therefore be less.

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BAT, Substrate Metabolism, and Insulin Sensitivity

Rodent studies revealed that BAT plays a significant role in lipid and glucose metabolism, in which the presence of BAT is linked to increased triglyceride uptake and improved glucose handling and insulin sensitivity. An issue in human studies is that BAT does not respond functionally upon repeated cold exposure, but that most studies only show correlations with metabolic parameters and substrates. Several authors stated that BAT, although not playing a significant role in whole-body energy metabolism, still may serve as a glucose and/or fatty acid sink. However, as stated earlier, in adults BAT occurs in relatively small amounts, and the clearance capacity of BAT is reported to be less than 1% of systemic whole-body glucose turnover (17). Therefore, it is unlikely that BAT in humans will be an important glucose or fatty acid sink as it is in rodents.

In humans it was also shown that cold acclimation improved insulin sensitivity significantly (12,13) in type 2 diabetes. However, the increase in BAT was only marginal (though determining BAT activity in type 2 diabetes is hampered by methodological issues). These studies pointed toward a significant contribution of skeletal muscle, i.e., the increase of translocation of glucose transporter GLUT4 to the skeletal muscle membrane. It can be concluded, based on the current evidence, that the actual contribution of BAT to energy and substrate metabolism is not large. On the other hand, it is unlikely that a tissue that shows such a clear functional response to cold and cold acclimation is just a rudimentary organ. BAT may be crucial in the interaction with other, more abundant tissues.

Cross Talk

A fascinating field is the BAT cellular and tissue cross talk. BAT factors (“batokines”) have been described that target different cell types within BAT but also serve in cross talk with other tissues and organs, such as liver, skeletal muscle, gut, and even the central nervous system (CNS), and can influence systemic metabolism (among others, see Scheele and Wolfrum (19)). In addition, BAT can be activated by other tissues via hormones (such as the gut hormone secretin) and may in turn affect the CNS, thus potentially mediating whole-body metabolism and food consumption (among others, see Li et al. (20)). Among the first described batokines are neuregulin (21), interleukin 6, fibroblast growth factor 21, and lipokines (12,13-diHOME) (22); for a review, see Villarroja et al. (23). For example, there are indications that neuregulin, which is low in obesity, elevates BAT activity, affects expression of lipogenic genes, increases WAT browning, promotes hepatic fat oxidation, and improves glucose homeostasis (21). Another example of cross talk is from gut microbiota that may impact BAT physiology (24). What is interesting is that most BAT depots in adult humans are closely connected to the CNS. A functional relation might be that BAT serves to keep those sites warm for optimal nerve action potentially regulating nerve conduction velocity, since this is temperature dependent. This, however, cannot be the only function because it does not explain browning of more peripheral fat depots. Another intriguing possibility is that afferent neural signaling from BAT to CNS is important, and, in addition, it may be possible that there is the potential of peptide exchange between BAT and neighboring neurons (19). Alternatively, BAT–brain cross talk has been described by gut hormone secretin-activated BAT, mediating the induction of satiation (20). It is interesting to explore the aforementioned options and also whether additional signaling peptides from metabolic tissues such as gut, liver, pancreas, and muscle target BAT with a forwarding effect to the CNS.

Pitfalls

Discussion sections of quite a few papers suggested the importance of restoring BAT in adults to childhood levels or, as others stated, the potential of WAT stores that can be turned into beige adipocytes. In some cases, the potential of all WAT in so-called “brownable” depots was calculated to come to its full metabolic capacity, moving to speculative (and spectacular) theoretical contributions of BAT to human energy expenditure. Such ideas also reached the media and create high expectations among laypeople as well. However, the assumption that such high levels of BAT are healthy has never, as far as I know, been discussed. Yes, indeed in mice, high amounts of BAT are linked to a healthy metabolic profile with improved body composition and insulin sensitivity. But the amount of BAT in relation to body mass between mice and men is different by at least one order of magnitude. Moreover, the mistake is often made that human tissues can be as metabolically active as that in rodents, neglecting allometric relationships. We have to deal with functional, though (relative to rodents and babies) low, levels of BAT in adults. Yes, we can increase the amount of BAT by cold acclimation and in potential by a safe pharmacological intervention. In the past, before industrialization, we were used to living in cooler (indoor) environments, and probably our levels of BAT were maximized in winter. But we have to realize that the maximal amount of BAT will still be low compared with rodents, as well as the corresponding contribution to energy metabolism. Moreover, as soon as the cue (regular cold exposure or drug intervention) stops, the amount of BAT will decrease again, owing to its functional flexibility. Such information should also be communicated within the scientific community and to the general public in order not to arouse overly high expectations.

The Future

BAT is likely not the magic thermogenic bullet to combat metabolic disorders. The fact that it correlates with cold-induced thermogenesis does not necessarily mean that it is the tissue (on its own) responsible for the improvements in energy, glucose, and lipid metabolism observed after cold acclimation. It can still play a significant role, but in concert with other tissues. The study of BAT metabolism together with other tissues, such as skeletal muscle, liver, the cardiovascular system, and the CNS, as well as the cross talk between these tissues, shows interesting (potential) mechanisms and targeted approaches to combat the metabolic syndrome where main lifestyle factors such as nutrition and physical activity alone fail. If we have more insight into those processes, then we will be better able to unravel to which healthy levels BAT should be increased and maintained. Finally, further development of imaging techniques and related quantification of metabolic processes with a focus on the interplay between BAT and other tissues is warranted. **O**

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References

1. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 2007;293:E444-E452.
2. van Marken Lichtenbelt WD, Vanhommel JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy adult men. *N Engl J Med* 2009;360:1500-1508.
3. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med* 2009;360:1518-1525.
4. Saito M, Okamatsu-Ogura Y, Matsushita M, et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. *Diabetes* 2009;58:1526-1531.

5. Rosenwald M, Perdikari A, Rulicke T, Wolfrum C. Bi-directional interconversion of brite and white adipocytes. *Nat Cell Biol* 2013;15:659-667.
6. Ikeda K, Maretich P, Kajimura S. The common and distinct features of brown and beige adipocytes. *Trends Endocrinol Metab* 2018;29:191-200.
7. O'Mara AE, Johnson JW, Linderman JD, et al. Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity. *J Clin Invest* 2020;130:2209-2219.
8. Davis TRA. Chamber cold acclimatization in man. *J Appl Physiol* 1961;16:1011-1015.
9. van der Lans AAJJ, Hoeks J, Brans B, et al. Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. *J Clin Invest* 2013;123:3395-3403.
10. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *J Clin Invest* 2013;123:3404-3408.
11. Blondin DP, Labbe SM, Tingelstad HC, et al. Increased brown adipose tissue oxidative capacity in cold-acclimated humans. *J Clin Endocrinol Metab* 2014;99:E438-E446.
12. Lee P, Smith S, Linderman J, et al. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. *Diabetes* 2014;63:3686-3698.
13. Hanssen MJ, Hoeks J, Brans B, et al. Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. *Nat Med* 2015;21:863-865.
14. van Marken Lichtenbelt WD, Schrauwen P. Implications of non-shivering thermogenesis for energy balance regulation in humans. *Am J Physiol Regul Integr Comp Physiol* 2011;301:R285-E296.
15. Muzik O, Mangner TJ, Granneman JG. Assessment of oxidative metabolism in brown fat using PET imaging. *Front Endocrinol* 2012;3:15. doi:10.3389/fendo.2012.00015
16. Din MU, Raiko J, Saari T, et al. Human brown adipose tissue [O-15]O-2 PET imaging in the presence and absence of cold stimulus. *Eur J Nucl Med Mol Imaging* 2016;43:1878-1886.
17. Richard MA, Pallubinsky H, Blondin DP. Functional characterization of human brown adipose tissue metabolism. *Biochem J* 2020;477:1261-1286.
18. Din MU, Saari T, Raiko J, et al. Postprandial oxidative metabolism of human brown fat indicates thermogenesis. *Cell Metab* 2018;28:207-216.e203.
19. Scheele C, Wolfrum C. Brown adipose crosstalk in tissue plasticity and human metabolism. *Endocr Rev* 2020;41:53-65.
20. Li Y, Schnabl K, Gabler SM, et al. Secretin-activated brown fat mediates prandial thermogenesis to induce satiation. *Cell* 2018;175:1561-1574.e12.
21. Tutunchi H, Ostadrahimi A, Hosseinzadeh-Attar MJ, Miryan M, Mobasser M, Ebrahimi-Mameghani M. A systematic review of the association of neuregulin 4, a brown fat-enriched secreted factor, with obesity and related metabolic disturbances. *Obes Rev* 2020;21:e12952. doi:10.1111/obr.12952
22. Lynes MD, Leiria LO, Lundh M, et al. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. *Nat Med* 2017;23:631-637.
23. Villarroya F, Cereijo R, Villarroya J, Giralt M. Brown adipose tissue as a secretory organ. *Nat Rev Endocrinol* 2017;13:26-35.
24. Moreno-Navarrete JM, Fernandez-Real JM. The gut microbiota modulates both browning of white adipose tissue and the activity of brown adipose tissue. *Rev Endocr Metab Disord* 2019;20:387-397.