

Brown fat: the biological furnace that could burn away obesity

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It is believed that brown adipose tissue (BAT) arose in mammals about 100 million years ago. This thermogenic (also known as heat-producing) organ likely provided a selective advantage that allowed our placental ancestors to leave the dark underground and enter surface habitats which used to be merely dominated by large predators up until the last mass extinction 65 million years ago [1]. For modern humans, harnessing the thermogenic, calorie-burning power of brown fat may now hold the key to battling metabolic disease.

Perfect timing: why is brown fat research all of a sudden so hot?

Although the gross anatomy of BAT was first described as early as 1551 and more detailed morphological depictions were published in the early 1900s, our understanding of BAT physiology did not really evolve until the latter half of the 20th century. Intense research efforts in the 1960s-1980s revealed that this organ mediates both non-shivering and diet-induced thermogenesis [1, 2]. In fact, its potent ability to generate heat is not just utilized in the febrile response to pathogen infections, it also allows for periodic arousal during hibernation, ensures survival of neonates, and makes it possible for larger mammals to thrive in cold conditions [2].

While these revelations represent landmark discoveries to our field, it should be pointed out that the more classical biochemical and molecular biological tools available at that time were quite restrictive factors in early brown fat investigation. In light of novel multi-omic approaches and other modern methodologies, one could view these scientific endeavors as an exploration of the darkness guided only by the dim light of an oil lantern. Nevertheless, the seminal work of these pioneering BAT researchers still revealed some of the most significant features of brown fat. These include 1) multiple lipid droplets and enormous amounts of uncoupling protein 1 (UCP1)-containing mitochondria in brown adipocytes, 2) extensive vasculature and sympathetic innervation of this organ and, impor-

tantly, 3) the ability of brown fat to attenuate adiposity in rodents.

Despite of these findings, the initial enlightening era of BAT research eventually waned. This stagnation was a result of the prevailing public view that human brown fat was only present in appreciable amounts in infants. Fortunately, this changed with the new millennium. Using a common cancer diagnostic tool called the PET-scan, radiologists noticed symmetrical regions in the upper-body areas of patients that consumed significant amounts of glucose. Prominent BAT biologists speculated that these observed phenomena could mark the existence of brown fat in human adults.

However, it was not until 2009, when several simultaneous investigations combined imaging technology with histological staining to confirm that the previously detected patches of these glucose-consuming regions were indeed UCP1-positive brown adipocytes. The fact that three out of the five key papers were published in the same issue of *The New England Journal of Medicine* galvanized the re-ignited interest in brown fat research, as clearly evidenced by the subsequent explosion in publications (Figure 1).

Given that the period between 1960 and 1980 can be seen as the brown adipose 'Age of Enlightenment', one could infer that the last decade marks a renaissance in brown fat research. However, we would like to emphasize that this renaissance, in contrast to the one in European history, will not take another three centuries. The field of

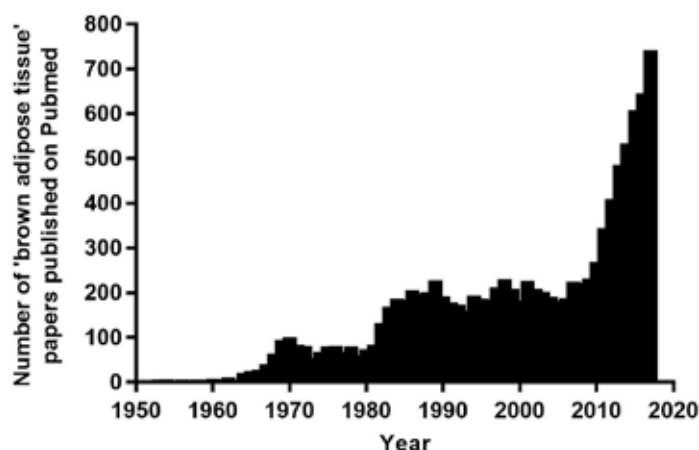


Figure 1. The emergence of research on brown adipose tissue.

adipose research is virtually exploding as a result of technological advances that are continuously generating major leaps forward. We are able to increasingly delve deeper into the metabolic machinery and unravel the innermost cellular complexities of this fascinating organ that clearly does much more than just keeping us warm.

Fueling the engine: what does brown fat burn to create heat?

One of the central tenets of brown fat biology is that when mammals are exposed to cold temperature, activated brown adipocytes liberate fatty acids from intracellular lipid droplets to fuel UCP1-dependent thermogenesis [2]. Yet several recent studies have overturned this long-held dogma using newly developed lipidomic techniques and tissue-specific genetic knockout mouse models. Contrary to previous belief, we now know that brown fat is capable of consuming enormous amounts of circulating lipids (Figure 2) derived from both the intestines (in the fed state) and white adipose depots (in the fasted state) and this appears to bypass the need for lipid reserves within the brown adipocyte itself.

Moreover, white fat-derived lipids can apparently travel towards brown fat via several routes in the form of both triglycerides and acylcarnitines. Another characteristic feature of brown fat is its capacity to consume glucose from the blood. In fact, this is the trait for which the presence of brown fat in adult humans was definitively shown

in 2009. While some of it is converted into lactate (Figure 2), the role of this increased glucose uptake in thermogenic function still largely remains a mystery.

Although intracellular and extracellular sugar and lipid substrates likely supply the majority of combustibles required for brown fat metabolism, alternative sources of energy could be utilized under certain conditions. Skeletal muscle shivering is differentially fueled by amino acids when glycogen stores are depleted. Could a similar transition in substrate utilization occur in BAT over the course of long-term cold exposure? Moreover, what helped sustain brown fat when our mammalian ancestors had to survive times of both

prolonged cold exposure and shortage of food? A deeper understanding of how brown fat metabolism is driven will be indispensable in designing strategies to exploit its function therapeutically.

Running the engine: how is brown fat activity controlled?

We have known for decades now that the "fight or flight" sympathetic nervous system is a predominant regulator of brown fat function. It induces non-shivering thermogenesis by activating β 3-adrenergic receptors and hampers heat production via α 2-adrenoceptor agonism [2]. These basic adrenergic mechanisms are crucial for rapidly

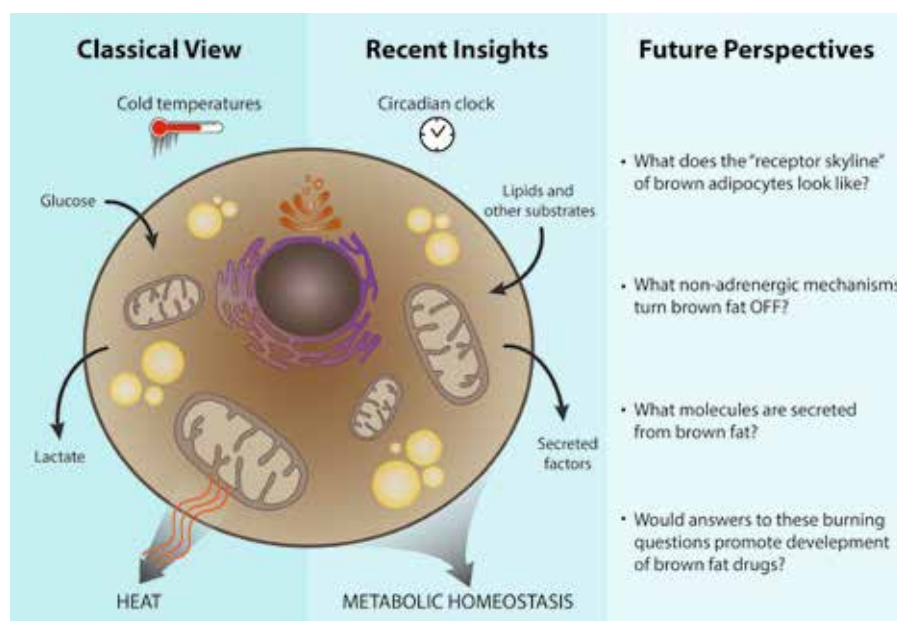


Figure 2. The evolving understanding of brown adipose regulation and its biological impact.

switching thermogenesis ON or OFF in response to acute changes in ambient temperature. However, other cellular systems refine brown fat responses according to more predictable environmental changes that occur on a seasonal and daily basis. These programs are responsible for the expansion of brown fat depots that takes place during winter and its subsequent shrinkage during summer as well as oscillation of brown fat activity throughout the day and night (Figure 2).

The 24-hour rotation of our planet has shaped evolution and provided mammals with sophisticated cellular clockworks that are fine-tuned according to the length of day. Like a molecular metronome, an internal system of interlocked transcription-translation feedback loops generates rhythms for regulating physiological tempos of various tissues in order to match environmental cues and hence favor survival. In brown fat, these pendulum swings also dictate diurnal fluctuations in metabolic activity, as evidenced by reduced

fuel intake and thermogenesis prior to the onset of sleep [3]. It is unknown why the system is set like this, but one feasible explanation could be that it served to spare calories when most ancient mammals clustered together in a warm and safe nest. Furthermore, the fact that brown fat activity peaks just before dawn highly suggests that it is involved in arousal. Pushing the thermogenic throttle at this critical time of the day may have helped our ancestors to, so to say, gather both attention and muscle strength before entering harsh and cold environments for hunting prey.

The holy grail: can brown fat be exploited for biomedical gain?

Besides its role as a defender of mammalian core body temperature, brown fat is also an important regulator of human metabolic homeostasis (Figure 2). The beneficial effects of activated BAT can be attributed to its direct ability to consume circulating glucose and lipids

in addition to indirect effects such as its secretion of cytokines, also known as batokines [4]. Various techniques examining molecules secreted from fat cells have recently been employed to identify several cold-induced factors. The way these substances affect whole-body metabolism is currently still under investigation. Another potentially fruitful area of research aims at identifying non-adrenergic receptors able to trigger brown fat thermogenesis. This is of special importance because stimulation of such receptors could circumvent the adverse cardiovascular effects associated with systemic administration of β -adrenergic receptor agonists. Several cell-surface receptors have already been identified [5], but the entire brown adipocyte 'receptor skyline' has yet to be constructed (Figure 2).

Despite all that has been explored, we believe that the vast body of knowledge, collectively acquired over decades of research, combined with the newest technological developments have uniquely poised brown fat biologists to make unprecedented leaps over the next decade. We hope that these insights will reveal how scientists can take what was once an evolutionary advantage to ancestral mammals and exploit it as a powerful pharmacological weapon in the battle against metabolic disorders that critically threaten the health of our species.

References

- [1] Jastroch M, Oelkrug R, Keipert S. Insights into brown adipose tissue evolution and function from non-model organisms. *Journal of Experimental Biology* 2018;221:March 7.
- [2] Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance 2004; 84:277–359.
- [3] Ninel Hansen S, Peics J, Gerhart-Hines Z. Keeping fat on time: circadian control of adipose tissue. *Experimental Cell Research* 2017;360:31–34.
- [4] Villarroya F, Gavalda-Navarro A, Peyrou M, Villarroya J, Giralt M. The lives and times of brown adipokines. *Trends in Endocrinology and Metabolism* 2017;28:855–867.
- [5] Braun K, Oeckl J, Westermeier J, Li Y, Klingenspor M. Non-adrenergic control of lipolysis and thermogenesis in adipose tissues. *Journal of Experimental Biology* 2018;221:March 7.

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