Brown adipose tissue at the intersection of sleep and temperature regulation

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The article demonstrates the importance of brown fat in creating and maintaining a metabolic environment which is permissive for optimal restorative sleep after sleep loss. The authors propose that impaired brown fat function could be a common underlying cause of poor sleep and metabolic disorders.

The tight relationship between sleep, metabolism and thermoregulation was already recognized in the early decades of sleep research. During this time, fundamental observations were made describing the correlation between body size and sleep, changes in energy expenditure across sleep cycles, and the effects of feeding-related signals as well as inflammatory and thermoregulatory challenges on vigilance. More recent findings on the correlation between poor sleep and unhealthy metabolic profiles in humans underline the need for understanding sleep in the context of the physiology of the entire organism. In their recent paper,1 Szentirmai and Kapás have made significant strides toward this goal by presenting evidence that the activated brown adipose tissue (BAT) generates sleep-promoting signals which are required for restorative sleep after extended periods of wakefulness.

Many consider brown fat the “good fat” with fundamentally different functions from the white adipose tissue. White fat cells are responsible for storing excess energy in the form of triglycerides, while brown adipocytes dissipate energy as heat. Brown fat plays a critical role in maintaining metabolic homeostasis by regulating energy expenditure and glucose disposal. The long-held belief that BAT exists only in infants but not in human adults has tempered interest in BAT physiology for decades. Global research interest got reinvigorated in 2009, when a series of five independent studies using positron emission tomography imaging demonstrated the presence of metabolically highly active BAT in adult humans (reviewed in ref. 2).

In their featured paper, Szentirmai and Kapás provide evidence that intact BAT thermogenesis is required for restorative sleep responses after sleep loss. The thermogenic property of BAT is conferred by the tissue-specific presence of uncoupling protein 1 (UCP-1), a hydrogen ion transporter on the inner mitochondrial membrane of brown adipocytes. In their studies, the Authors showed that sleep deprivation by gentle handling activates BAT thermogenesis manifested as increased UCP-1 mRNA expression and elevated temperature of the interscapular brown fat pad. Sleep loss is followed by rebound, compensatory, increases in sleep due to the activation of homeostatic sleep-promoting mechanisms. This response is greatly attenuated UCP-1-KO mice.3 It is attenuated in UCP-1 KO mice, which suggests that the thermogenic activity of brown fat is required for recovery sleep responses. In preliminary studies, the Authors also showed that pharmacological stimulation of brown adipocytes by using a selective β3 adrenergic receptor agonist elicits robust sleep increases; this response is absent in UCP-1 KO mice.3 While activation of BAT leads to increased body temperature, the significant time lag between the sleep-promoting and temperature effects suggests that increased sleep in response to brown fat activation is not due to elevated body temperature.3

The interscapular brown fat pads are innervated by sympathetic efferents as well as small-diameter sensory fibers. The role of sensory innervation in sleep signaling from BAT was determined in mice subjected to BAT-specific sensory denervation. In response to sleep deprivation, sensory-denervated mice showed a phenotype almost identical to UCP-1 deficiency (i.e., attenuated sleep rebound). This suggests that a neuronal link from the BAT plays a key role in mediating somnogenic signals. Some of the sensory fibers are temperature sensitive, therefore it is possible that the sleep-promoting signal is elevated BAT temperature itself. Alternatively, heat production-related metabolic activity of BAT may elicit local metabolic changes (e.g., in osmolarity, PCO2, etc.) or the production of tissue hormones which may activate metaboreceptors in a paracrine fashion.

Spontaneous sleep of UCP-1 KO mice also showed ambient temperature-dependent deficiencies. In prior studies it was demonstrated that sleep is suppressed in UCP-1 KO mice when they are exposed to subthermoneutral temperatures.4 This featured article reports that UCP-1 deficient mice have sleep deficiency even at thermoneutral temperature (30 °C) and during the course of 5 d of exposure to 35 °C. While warm exposure elicited significant decreases in respiratory exchange ratio in WT animals, the response was greatly attenuated in the UCP-1 KO mice. This suggests that UCP-1 KO mice have impaired ability and/or a decreased need to metabolize fat in warm environment.

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Abbreviations: BAT, brown adipose tissue; UCP-1, uncoupling protein-1; KO, knockout; WT, wild-type

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Since increased lipolysis is a significant sleep-promoting signal, the attenuated lipolytic response by the transgenic animals may explain their sleep deficiency in the warm environment.

There is significant correlation between chronic poor/short sleep and obesity in humans. The correlation is based on observational research where the causality between chronic sleep loss and weight gain is difficult to establish. One possibility is that obesity impairs sleep in humans due to the high incidence of obstructive sleep apnea episodes and other factors. Another possibility is that sleep loss impairs metabolic homeostasis which eventually leads to obesity. While the latter idea has gained significant popularity, animal experiments fail to support it. Szentirmai and Kapás suggest a new, hitherto unexplored, third possibility. The findings that BAT activation enhances sleep, together with the well-established role of BAT in stimulating energy expenditure suggest that impaired BAT function could be a common cause of obesity and poor sleep in humans.

Multiple factors affect the amount and timing of sleep. The most widely accepted model ascribes sleep regulation to the interaction between two basic processes, prior sleep loss and the circadian phase of the day. By applying this two-process model, we have gained important insight into basic mechanisms of sleep regulation. It is clear, however, that the model works only under limited conditions when multiple physiological parameters, e.g., feeding, immune status, and metabolism, are tightly controlled. Sleep, however, does not occur under such controlled conditions in nature. To understand sleep fully, we need to extend our existing models of sleep regulation by including multiple physiological signals arising from the brain and from peripheral organs. The Authors posit that sleep can occur in optimal amounts and quality when the organism does not need to invoke functions that require the animal to be awake. Several functions that are linked to wakefulness are related to metabolism, e.g., feeding/foraging, behavioral thermoregulation and muscle activity. The Authors hypothesize that there is a complex signaling system that monitors the metabolic status of the organism and adjusts the sleep–wake activity according to the current metabolic need of the body. When the metabolic status permits, this regulatory system allows the suspension of wakefulness; this is manifested as increased sleep propensity. Signals arising from BAT are part of this signaling system (Fig. 1).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Submission Note

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References

1. Szentirmai É, et al. Eur J Neurosci 2014; 39:984-98; PMID:24372950; http://dx.doi.org/10.1111/ejn.12463
2. Lee P, et al. Endocr Rev 2013; 34:413-38; PMID:23550082; http://dx.doi.org/10.1210/er.2012-1081
3. Ames C, et al. Sleep 2013; 36(Suppl):A42
4. Kapás L, et al. Sleep-wake activity of UCP-1 KO mice at various ambient temperatures. 2012 Neuroscience Meeting Planner. New Orleans, LA: Society for Neuroscience.
5. Vetrivelan R, et al. Sleep 2012; 35:1511-20; PMID:23115400
6. Borbély AA. Arch Ital Biol 2001; 139:53-61; PMID:11256187