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RESEARCH HIGHLIGHT

Cool(ing) brain stem GABA neurons

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The preoptic area of the hypothalamus has received much attention for its role in the control of body temperature and energy expenditure. Using an unbiased approach, Schneeberger et al. have identified neuronal populations in the dorsal raphe nucleus of the brainstem as another major region regulating these processes and brown adipose tissue.

Control of energy expenditure and intake is essential for an organism's survival. In vertebrates, these processes are regulated by the brain, which integrates information from within the body (e.g., fuel levels, current and anticipated metabolic need) with that from the environment (e.g., food availability, food desirability, sights, smells, ambient temperature, predation risk, etc.).[1] The neural circuitry regulating food intake has received considerably more attention than the pathways that regulate energy expenditure.

Homeothermic, "warm blooded" species, maintain a core body temperature that is tightly regulated, including a diurnal rhythm. In small mammals a large fraction of total energy expenditure is devoted to heat generation for maintaining body temperature.[2] This heat is produced principally by brown adipose tissue (BAT). This contrasts with adult humans, where thermal physiology is oriented towards heat dissipation, with a small, possibly negligible role for BAT.

In a recent paper published in *Cell*, Schneeberger et al.[3] screened the mouse brain for regions activated by a hot environment. They identified multiple areas within the hypothalamus, a region already known for contributing to body temperature regulation. Additional hot-activated neurons were found in the brainstem's dorsal raphe nucleus (DRN), a region possessing a wide variety of functions and implicated in several neuropsychiatric diseases (including mood disorders and neurodegenerative diseases), harboring serotonin and other neuron populations. The DRN temperature-responding neurons use the inhibitory neurotransmitter GABA, as identified by the vesicular GABA transporter (*Vgat*), and are denoted DRN^{Vgat}. Artificial stimulation of the DRN^{Vgat} neuron populations produced two types of responses. One effect was to reduce BAT activity, energy expenditure, BAT temperature, and core body temperature. This is due to reduced sympathetic stimulation of BAT. Retrograde tracing from BAT was consistent with a DRN^{Vgat} → raphe pallidus (RPa) → spinal cord intermediolateral column → sympathetic ganglion → BAT circuit. This links the DRN^{Vgat} neurons to a previously described pathway (Fig. 1).

The other effect of DRN^{Vgat} stimulation was to reduce physical activity, which may also contribute to the reduced metabolic rate. Conversely, inhibition of DRN^{Vgat} neurons increased physical activity, metabolic rate, and core body temperature, but did not cause BAT activation. In this effect of DRN^{Vgat} neuronal stimulation, the body temperature changes may be a consequence of changes in physical activity. Thus, it is likely that the reduction in metabolic rate is contributed by both decreased physical activity and decreased BAT activation.

The DRN^{Vgat} neurons also have ascending projections to the hypothalamus (dorsomedial hypothalamus (DMH) and medial preoptic area (MPOA)) and the bed nucleus of the stria terminalis (BNST), part of the extended amygdala. Selective activation of DRN^{Vgat} neurons projecting to each of these three regions likewise reduced body temperature, although the mechanism(s) were not investigated in detail.

Recent single-cell RNA profiling of the DRN has identified 18 neuron types, four of which are GABAergic (https://doi.org/10.1101/573923). It is not known which subset(s) of DRN^{Vgat} neurons regulate BAT; which neurons regulate physical activity; whether there is overlap; or even if there are only four types of DRN^{Vgat} neurons. Undoubtedly, future studies will be aimed at defining the functions of subsets of hot-sensing DRN^{Vgat} neurons, such as by RNA expression patterns, by the subsets' upstream inputs and projection pathways, and by selective neuronal inactivation or ablation.

Due to the importance of maintaining body temperature in energy homeostasis, homeotherms likely have distributed circuits for thermoregulation. Previously, neuronal populations that are responsive to high ambient temperatures and/or that cool the body when activated, have been identified in the preoptic area (POA) and parabrachial nucleus.[4–8] Some POA populations regulate BAT via descending GABAergic projections to the DMH, but BAT-regulating DMH neurons also receive glutamatergic input from the POA.[4–6,9] The DMH then uses descending projections to the RPa to regulate BAT activity.[8–10] Just as DRN^{Vgat} neurons are a new addition to the list of contributors to the neural control of BAT, it is likely that other novel neuronal populations will be identified.

BAT, in addition to being triggered by cold exposure, is also activated by feeding rodents a high fat diet, producing diet-induced thermogenesis. This BAT activation is hypothesized to protect against obesity (although why the biology would evolve to burn extra calories, rather than to reduce food intake, is food for thought). The new understanding of neural control of BAT should assist in elucidation of the non-thermal neural circuits that control BAT activity.

Given the different thermal biology of mice and humans, does knowledge of rodent thermoregulatory neural circuits apply to humans? Three lines of evidence suggest yes. First, human babies rely on BAT for thermogenesis, thus neural control circuits are required. Second, it is now accepted that most adult humans have BAT that can be activated by cold exposure or pharmacologic β-adrenergic stimulation.[11] Finally, while circuit tracing is difficult in humans, pharmacologic and genetic results suggest conservation of hormones, neuropeptides, and circuits that control energy

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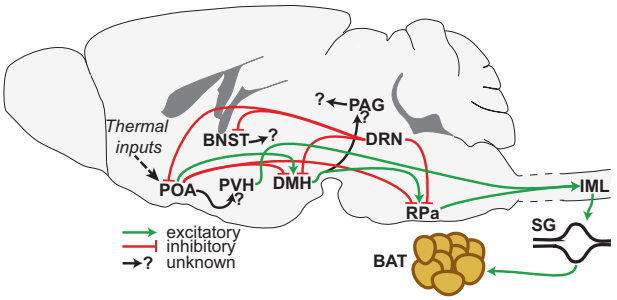

Fig. 1 Neuronal regulation of BAT. Schematic depiction of pathways regulating BAT, as discussed in the text. Schneeberger et al.[3] have added the DRN to this map. Thermal inputs include those from warm- and cold-sensing neurons in the brain and from peripheral sensation of environmental temperature. BAT brown adipose tissue, BNST bed nucleus of the stria terminalis, DMH dorsomedial hypothalamus, DRN dorsal raphe nucleus, IML intermediolateral column of the spinal cord, PAG periaqueductal grey, POA preoptic area, PVH paraventricular nucleus of the hypothalamus, RPa raphe pallidus, SG sympathetic ganglion

homeostasis (although this is better demonstrated for food intake than for energy expenditure).

The mouse has advantages for studying regulation of thermal biology.[12] Its small size causes exaggerated thermal responses, which are more amenable to study. Mice also exhibit physiology that is not seen in adult humans, including mild reduction of body temperature in a cold environment and torpor, a hibernation-like state with a profound reduction in body temperature and metabolic rate. The plethora of thermal physiology in mice also means that sorting out mechanisms can be complex. For example, a mouse exposed to 38 °C[3] may perceive the environment as dangerous, in addition to hot.

One of the exciting results of this work[3] is the identification of the DRN as contributor to control of BAT and energy homeostasis. The more we understand the circuits that regulate energy expenditure and food intake, the more we discover additional inputs, nuclei, and connections that contribute to these processes. We have come a long way from the era of the 'preoptic area' as the brain controller of body temperature.

ADDITIONAL INFORMATION

Supplementary information accompanies this paper at https://doi.org/10.1038/s41422-019-0223-y.

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