News & views

Metabolism

Light-activated neurons can alter body heat

Gary J. Schwartz

A light-sensitive receptor protein expressed in neurons deep in the mouse brain has been shown to be stimulated by violet light, and to activate a pathway that reduces heat production in brown fat. **See p.420**

Light has profound effects on human behaviour and physiology, from synchronizing sleep–wake cycles to inducing daily fluctuations in body temperature and energy metabolism. Our ability to see is mediated by a family of opsin proteins in the retina. When exposed to light, opsins modulate the flow of ions across neuronal membranes, ultimately activating the optic nerves[1]. In mammals, an opsin called opsin 5 (OPN5) is expressed in an unusual place — in neurons deep in the brain's preoptic area[2] (POA), which has a role in metabolism. On page 420, Zhang *et al.*[3] report a pathway by which OPN5 in the POA regulates heat production in mice. The authors' findings open up the possibility of modulating metabolism by manipulating environmental light.

Zhang and colleagues first asked which neurons activate OPN5-containing POA cells in mice. They injected the POA with a tracer virus that selectively labels OPN5-containing neurons. The tracer is taken up by the nerves that send impulses to these cells, by the nerves that feed into them, and so on up the neuronal circuit. The authors found that OPN5-containing neurons receive input from multiple pools of neurons in the forebrain and brain stem.

These upstream neurons are all part of a circuit that senses changes in skin temperature and controls regulatory responses in a type of fat called brown adipose tissue (BAT). The main role of BAT is to generate heat, raising body temperature as it burns fuel. Heat production is stimulated by the neurotransmitter noradrenaline, which is released from neurons of the sympathetic nervous system in response to cold temperatures. Noradrenaline binds to β_3-adrenergic-receptor proteins on the brown-fat cells, rapidly triggering fuel burning and robust heat production.

Zhang *et al.* next injected a tracer virus into the BAT. The tracer labelled the entire circuit of neurons upstream of the BAT, and confirmed that the OPN5-expressing neurons are part of the circuit that projects into BAT. The group found that these neurons express three neurochemicals: glutamate, pituitary adenylate cyclase-activating peptide and brain-derived neurotrophic factor. This combination has previously been shown to be characteristic of heat-sensitive neurons[4].

The authors modulated the activity of the OPN5 neurons by engineering them to express synthetic excitatory or inhibitory ion-channel proteins, which, respectively, activate or inhibit neurons in response to an injected chemical. Stimulation of the excitatory channels rapidly and robustly reduced heat production by BAT, and so reduced core body temperature. These data indicate that the OPN5 neurons inhibit BAT activity (Fig. 1). By contrast, stimulation of the inhibitory channels increased core temperature.

In line with these results, mice engineered to lack the *Opn5* gene showed higher BAT activity and body temperature than did controls. They also exhibited a raft of other metabolic changes: increased energy expenditure, smaller fat cells, lower fat-pad weights, lower levels of circulating cholesterol and better resistance to environmental cold.

OPN5 responds to violet light, and Zhang and colleagues found that the mutant mice were insensitive to violet light. By contrast, violet light induced a decrease in BAT activity and core temperature in control animals. The authors also raised control animals in the absence of violet light throughout embryonic and postnatal development. Under such lighting, these mice were resistant to environmental cold, similar to animals lacking OPN5.

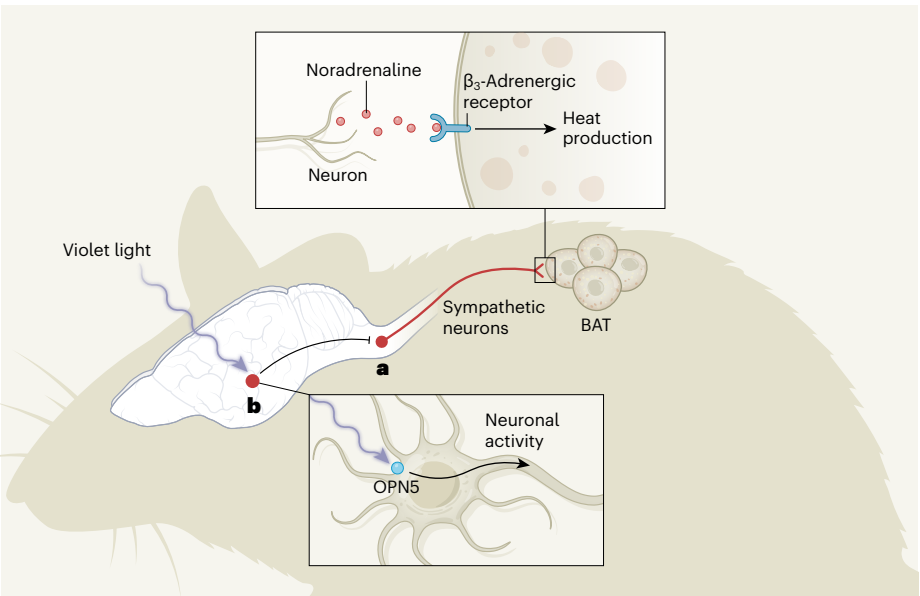

Figure 1 | Shining a light on heat production in mice. a, Neurons of the sympathetic nervous system project from the brain to the cells of brown adipose tissue (BAT). These neurons release the neurotransmitter molecule noradrenaline, which binds to β_3-adrenergic-receptor proteins on the BAT cells, triggering the cells to break down glucose and so produce heat. **b**, Zhang *et al.*[3] report that violet light activates a light-sensitive protein called opsin 5 (OPN5) on neurons in the preoptic area of mouse brains. When activated, these neurons inhibit the pathway outlined above, and so prevent heat production.

It is important to note that the *Opn5*-mutant animals did not express the gene at any point in their lives – including during crucial developmental periods when the neural circuitry and identities of neurons are established. It is not yet known whether this led to unexpected developmental changes that might underlie the animals' insensitivity to violet light. Going forward, the same analysis should be performed in animals in which *Opn5* is deleted only during adulthood, after normal neurological development has finished.

To prove that violet light could penetrate the skull and reach the POA neurons, Zhang *et al.* implanted a miniature, wavelength-sensitive radiometer probe into the brain. They found that violet light could indeed penetrate deep enough to activate OPN5-expressing POA neurons. Finally, they compared the response to cold of animals exposed to a full spectrum of light and of animals exposed to light that lacked violet wavelengths. The 'full-spectrum' animals showed greater reductions in BAT and body temperature in response to cold than did the 'minus-violet' animals. This experiment indicates a physiologically relevant role for OPN5-expressing POA neurons – repressing heat production in BAT in response to violet light.

Whether violet light directly stimulates OPN5 neurons remains to be proved. Zhang *et al.* used neuroimaging techniques to show that light activates the neurons in tissue slices, but proof will involve applying these techniques *in vivo*.

OPN5 has been identified in the hypothalamus (the brain region in which the POA is located) in monkeys[2]. However, we do not yet know whether ambient light will reach this deep brain region. Such a demonstration would be a key step in determining the applicability of these results to humans.

As with many exciting and unanticipated findings, Zhang and colleagues' study opens the door to larger questions of biological relevance. Humans today have unprecedented control over ambient light, temperature and nutrient supply, and are consequently much less susceptible to natural environmental metabolic challenges than were our ancestors. Eating only during daylight hours has been shown to markedly improve insulin sensitivity in people with prediabetes[5] – a change that might lower the risk of developing full-blown diabetes. It is tempting to speculate that limiting violet light might activate BAT, and thereby augment the metabolic benefits of daytime-restricted eating. Similarly, drugs called β-agonists activate BAT, lower blood glucose levels and increase resting metabolic rate and insulin sensitivity in people[6–9], and Zhang and co-workers demonstrated that animals reared without violet light show increased responses to these drugs. Limiting violet light might therefore extend the beneficial metabolic effects of β-agonists.

Remarkably, mouse and human BAT expresses a red-light-sensitive protein, OPN3 (ref. 9). Red-light stimulation of OPN3 increases glucose uptake and heat production in BAT, both *in vitro* and in mice. Thus, different spectra of environmental light might act both in the brain and in brown-fat cells to alter BAT heat production in ways that can help the body to control glucose levels.

Finally, a population of neurons has recently been found in the mouse POA that controls torpor – a state characterized by low body temperature and a markedly reduced metabolic rate, typically induced by harsh environmental challenges such as cold and lack of food[10]. It remains an open question whether this neuronal circuit is also sensitive to violet light. But Zhang and colleagues' findings raise the possibility that environmental light might orchestrate a host of coordinated brain responses that together determine the highs and lows of metabolism.

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This article was published online on 2 September 2020.

Developmental biology

Keratin as an aide-memoire

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Filaments of keratin – stable protein polymers best known for their function in hair and nails – provide a memory of cell polarity at a crucial stage in early mouse development. **See p.404**

The processes by which a single cell – the fertilized egg – gives rise to all the different cell types that make up an adult organism remain some of life's great mysteries. We know that it takes time for cells in an embryo to settle on a fate, because a single embryo that splits during early development can give rise to twins, triplets and more. But how are cell-fate decisions made, and how do cells coordinate their choices with their peers? Researchers have suggested numerous mechanisms that influence the paths taken by cells in early mammalian embryos. On page 404, Lim *et al.*[1] describe a surprising role for a protein polymer, keratin, in the first of these decision-making processes.

"Keratins provide a physical memory of polarity that is relatively independent of cell-division events."

Two of the main challenges of early development are to increase the number of cells through repeated rounds of cell division, and to ensure that these cells assume distinct forms and functions at the right time and place to generate functional tissues and organs. The two processes can be coupled through 'asymmetric' cell divisions. These are divisions that give rise to two sibling cells with distinct identities, either as a result of the asymmetric segregation of material, or in response to local differences in the extracellular environment that the cells encounter after division.

It is during the 8- to 16-cell transition that cells in early mammalian embryos first become asymmetrically organized – with subsets of proteins becoming concentrated at opposite cell poles, a feature called apical–basal polarity. Cell identity remains plastic at this stage, but daughter cells that end up at the periphery (termed the trophectoderm) of the 16-cell embryo give rise to the placenta, whereas daughter cells that end up inside the embryo contribute to the fetus.

The observation of apical–basal polarity at the 8- to 16-cell transition led to the proposal that the future identity of these cells is determined by the asymmetric inheritance of the outward-facing apical domain[2], which is rich in