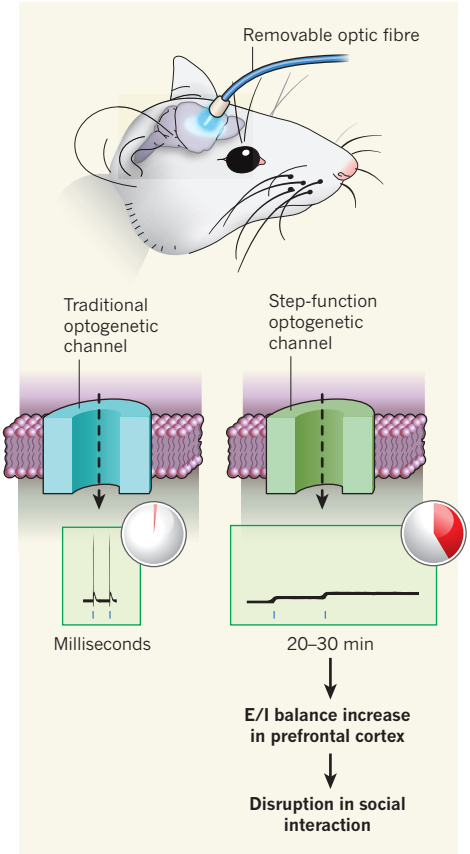

Figure 1 | Optogenetics and analysis of social dysfunction. Yizhar *et al.*[1] used step-function optogenetic channels to analyse the excitation–inhibition (E/I) balance in specific neural circuits within the prefrontal cortex of the mouse brain. Like traditional optogenetic channels, this latest tool is activated in response to light delivered by optic fibres through the animal's skull; this in turn allows ions to enter the neuron (dashed arrows). Step-function optogenetic channels, however, do not necessarily induce immediate firing by their host neuron. Instead, they cause a gradual increase in neuronal depolarization, increasing the probability of the neuron firing in response to endogenous stimuli over 20–30 minutes. This gave the authors sufficient time to perform behavioural analysis on the animals without the optic fibre being attached. They found that increasing the E/I balance in the prefrontal cortex disrupts social interaction between mice.

synaptic development and function[6]. Moreover, introduction of a mutation seen in patients with autism (the R451C mutation in the protein neuroligin-3) into the equivalent mouse protein increases inhibitory synaptic transmission[7]. So to clarify the significance of E/I ratios in disease states, future studies should traverse the added level of complexity arising from relevant human mutations in relation to regional and cell-type-specific gene expression. Such studies should also consider whether the broader circuits affected have an inhibitory or an excitatory effect on their downstream neuronal targets.

Yizhar and colleagues' paper[1] highlights a notable point — to unravel the complexity of the mammalian brain, it is essential to understand the functioning of circuits in both healthy and diseased brains. Combining information arising from observation, and control, of neuronal circuits will also be crucial in such efforts[8]. Together, these approaches should not only magnify our ability to predict how changes in circuit function may lead to abnormal behaviours, but also give a glimpse of how circuit-level manipulations might ultimately be used for the treatment of neuropsychiatric disorders. ■

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METABOLISM

Let them eat fat

A specialist neuron uses an intriguing process to help control the body's response to hunger. A lipid pathway involving the breakdown of cellular components regulates the expression of a neuropeptide that affects feeding and body weight.

SCOTT M. STERNSON

When resources become scarce, we tighten our belts and make do with what we have. This is also true for our bodies, which in the absence of food intake start to consume themselves. In a paper published in *Cell Metabolism*, Kaushik *et al.*[1] describe how, when mice are deprived of food, a specialized starvation-sensitive neuron dines on fat released from body stores. Strikingly, the authors find that disrupting this process in these neurons results in leaner, lighter mice, even when food is freely available.

Hunger results from food deprivation and leads to food seeking and consumption. An internal sensory system detects signals of energy deficit circulating in the blood and modulates neural circuits that regulate these behaviours. A neuron that is crucially involved in this system is defined by its expression of the gene Agouti-related protein (*Agrp*), which encodes the AgRP neuropeptide.

The AgRP neuropeptide increases feeding and body weight when injected into the brain. Furthermore, AgRP-expressing neurons have properties expected of a starvation-sensing system: they alter their firing rate and gene expression in response to signals from hormones and metabolites such as ghrelin, leptin, glucose and fatty acids. Without these neurons, mice stop eating[2]. Conversely, voracious eating can be induced in well-fed mice by increasing the electrical activity of these neurons[3,4]. It is therefore clear that the regulation of AgRP-neuron function is important for controlling hunger-related behaviour.

During food deprivation, changes occur in the body to conserve energy and to signal the need to replenish energy levels by eating. The body switches to using stored fat as a fuel, releasing free fatty acids into the blood that can be sensed by the brain. Kaushik *et al.*[1] examine the influence of this process on AgRP neurons in cell culture and in mice.

The authors explore an unusual mechanism for modulating *Agrp* gene expression by investigating the role of macroautophagy (here termed autophagy) in fatty-acid utilization. Autophagy is a regulated, cannibalistic process in which cells consume and recycle their components (such as damaged organelles) and use their internal structures as a fuel source during starvation. In autophagy, cellular components are enveloped in a membrane-bounded vesicle called an autophagosome for transport to an organelle known as the lysosome for degradation. Some of the authors of the current study previously discovered an intriguing mechanism in liver cells whereby the autophagy pathway can mobilize stored fat as a fuel source[5].

Kaushik *et al.*[1] report that a similar pathway operates in AgRP neurons, with consequences that seem to extend beyond fuel utilization. They propose that AgRP neurons accumulate free fatty acids from the blood during food deprivation and that these fatty acids are then quickly converted into triglyceride fats and stored in lipid droplets (Fig. 1). These lipids are rapidly remobilized through autophagy of the lipid droplet, and free fatty acids are re-formed for use as fuel. The authors suggest that this circuitous pathway provides a mechanism for regulatory control over the accumulation of free fatty acids in the cell, so that they can be used in an orderly fashion. It remains to be seen

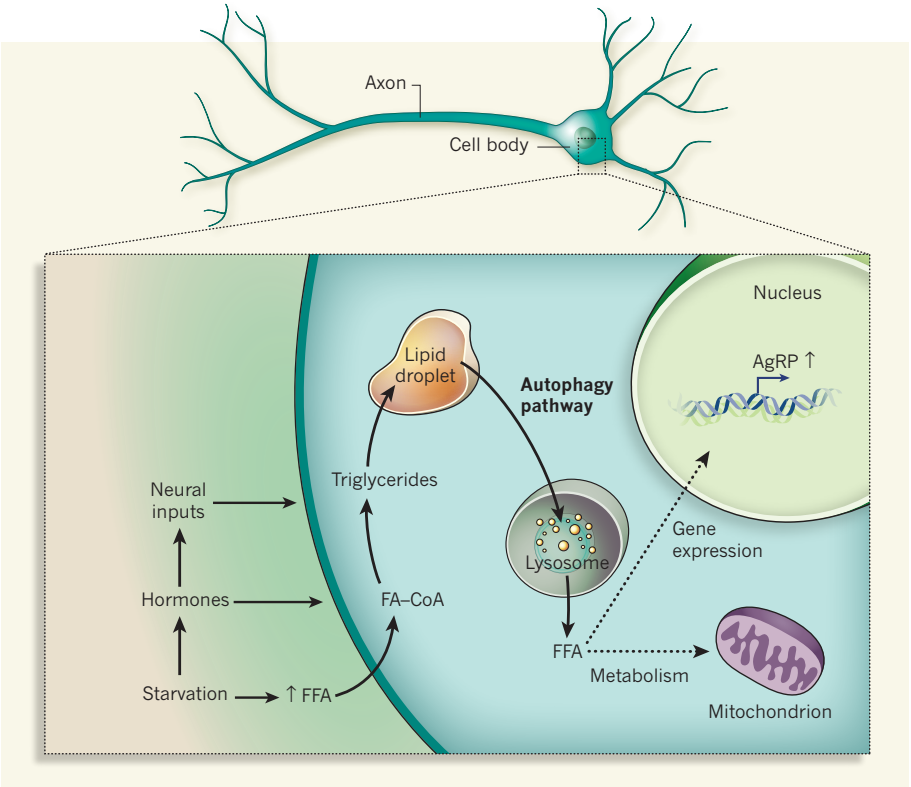

Figure 1 | Fatty-acid regulation of starvation-sensitive neurons. Neurons expressing the neuropeptide AgRP respond to raised concentrations of circulating free fatty acids (FFA) released from fat stores, as well as to other hunger signals such as hormones and neural inputs. Kaushik *et al.*[1] show how these fatty acids are taken up and processed into triglycerides via fatty acid–coenzyme A thioesters (FA–CoA) for storage in lipid droplets. The fatty acids can be released again through the autophagy pathway, in which lysosomes degrade the lipid droplets. These fatty acids increase *Agrp* gene expression in the nucleus and are also available for metabolism in the mitochondria.

whether this process operates in other neurons.

A key finding from these experiments is that *Agrp* expression, which promotes eating, is increased by free fatty acids. In addition, this effect on gene expression requires lysosomal processing, as would be expected of the autophagy pathway.

There is a clear consequence of disrupting this lipid-utilization scheme in mice. Using genetic elimination of a crucial component of the autophagy pathway in AgRP neurons, the authors find that, relative to controls, mice eat less when re-fed after food deprivation and their body weight decreases. They go on to show that expression of the AgRP neuropeptide is reduced in these mice, which they suggest is why the mice eat less and weigh less.

These results[1] should be considered in the light of other studies demonstrating a role for fatty-acid metabolism in the regulation of *Agrp* expression. For example, *Agrp* expression is reduced when fatty-acid utilization is inhibited by eliminating an uncoupling protein involved in the activity of the mitochondrion, the cell's energy-producing organelle[6]. One implication is that the autophagy pathway could be linked to the transport of fatty acids for mitochondrial metabolism. Then there is the question of how cellular fatty acids regulate *Agrp*. One possibility for future investigation is the involvement of the transcription factor FoxO1, which regulates *Agrp* expression according to hunger status[7].

It is not yet clear whether disruption of the autophagy pathway in AgRP neurons regulates feeding and body weight solely through the lipid-processing mechanisms described here. It will therefore be essential to explore the effect of this pathway on the electrical activity of AgRP neurons, on their development, and on their interaction with other mediators of AgRP-neuron function, such as synaptic input and hormonal regulation.

Could blocking this cannibalistic process be used to reduce body weight? Possibly, but the autophagy pathway is ubiquitous in cells throughout the body, so extensive investigation will be needed to find selective points of entry for therapeutic interference in obesity and eating disorders. ■

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50 Years Ago

The normal method of concentrating a substance in solution is by distillation. In the course of certain experiments it was found that it is possible to do so to a certain extent by refrigeration. A column of skim milk in a 250-ml. cylinder was frozen between −5° and −10° C. The frozen column was taken out and allowed to thaw at room temperature … The melted column showed a graded separation, ranging from solid concentration at the bottom to a thin, watery layer at the top … Solutions of copper sulphate, potassium permanganate and potassium ferrocyanide, similarly frozen and thawed, yield a higher concentration of the salts at the bottom of the column, at once evident by the greater intensity of colour … It is perhaps typical of cryoscopic concentration of solutes.

From *Nature* 9 September 1961

100 Years Ago

Just about three o'clock this afternoon (I had a few minutes previously asked the time at the village post office) I witnessed a remarkable and very beautiful phenomenon. Coming through a woodland walk, I was caught by a heavy downpour of rain. As it was passing away, the sun shone down from a suddenly clear sky over the tops of the trees behind and to the right. Instantly … not more than three yards from where I stood, a perfect miniature rainbow was formed, its highest part being just about level with my eyes. It appeared broader than an ordinary rainbow, and much the greater portion was of one deep violet colour, the remaining colours forming merely a narrow border above. Very vivid at first, it quickly faded away, as the shower came to an end.

From *Nature* 7 September 1911