



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 results¹ 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 organelle⁶. 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 status⁷.

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.

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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.

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