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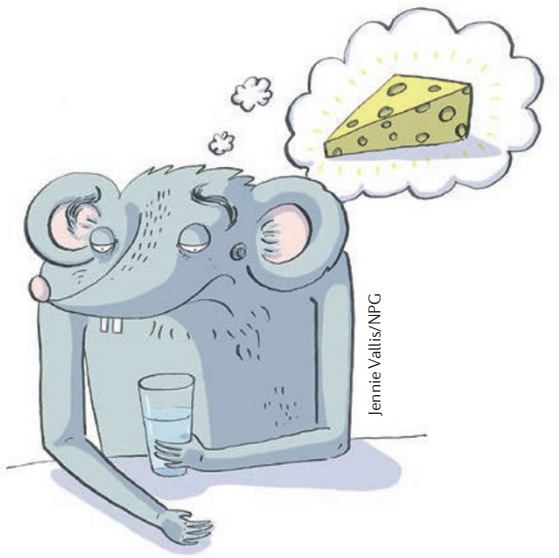
SYNAPTIC PLASTICITY

Feast or famine



Jennie Vallis/NPG

In the hypothalamus, neurons expressing agouti-related peptide (AgRP neurons) respond to the fasted state by generating more dendritic spines and show increased spiking. The cellular mechanisms underlying these changes are not well understood, but here, Kong *et al.* show that AMP-activated protein kinase (AMPK), which is expressed in AgRP neurons, has a crucial role.

In the hypothalamus, AMPK is inhibited by leptin and stimulated by fasting, and manipulation of hypothalamic AMPK activity influences energy balance. The authors first measured AMPK activity specifically in AgRP neurons and found that it more than doubled in fasted animals compared with fed controls. Furthermore, in ad libitum fed mice, expression of a constitutively active form of AMPK selectively in AgRP neurons of the hypothalamic arcuate nucleus (ARC) resulted in increases in the number of dendritic spines, and in the frequency and firing rate of mini excitatory post-synaptic currents (mEPSCs), indicating that excitatory neurotransmission was increased. Fasting produced similar effects, which were largely absent in mice expressing a dominant negative form of AMPK selectively in ARC AgRP neurons. Together, these results suggest that activation of AMPK in ARC AgRP neurons is necessary and sufficient for fasting-induced increases in excitatory neurotransmission in these neurons.

The authors next turned their attention to downstream targets of AMPK activation, which include p21-activated kinases (PAKs). ARC AgRP neurons express group I PAKs, which are known drivers of excitatory post-synaptic plasticity and spinogenesis, and have been identified recently as substrates of AMPK. The authors found that under fasted conditions, an increase in AMPK activity in AgRP neurons was accompanied by increases in the phosphorylation of PAK2 and LIM kinase 2 (LIMK2), a PAK2 target. The increase in mEPSC frequency and spinogenesis were reduced by dominant negative expression of the PAK auto-inhibitory domain, which inhibits all group I PAK isoforms. Moreover, in fed mice, increased mEPSC frequency resulting from expression of constitutively active AMPK was also prevented by inhibition of PAK. These findings suggest that the increased AMPK activation that occurs in ARC AgRP neurons following fasting drives a PAK-mediated signalling pathway and results in increased dendritic spines and increased excitatory synaptic activity in these neurons. This mechanism might play an important part in the regulation of energy balance.

Sian Lewis

ORIGINAL ARTICLE Kong, D. *et al.* A postsynaptic AMPK→p21-activated kinase pathway drives fasting-Induced synaptic plasticity in AgRP neurons. *Neuron* http://dx.doi.org/10.1016/j.neuron.2016.05.025 (2016)

> “activation of AMPK in ARC AgRP neurons is necessary and sufficient for fasting-induced increases in excitatory neuro-transmission in these neurons”