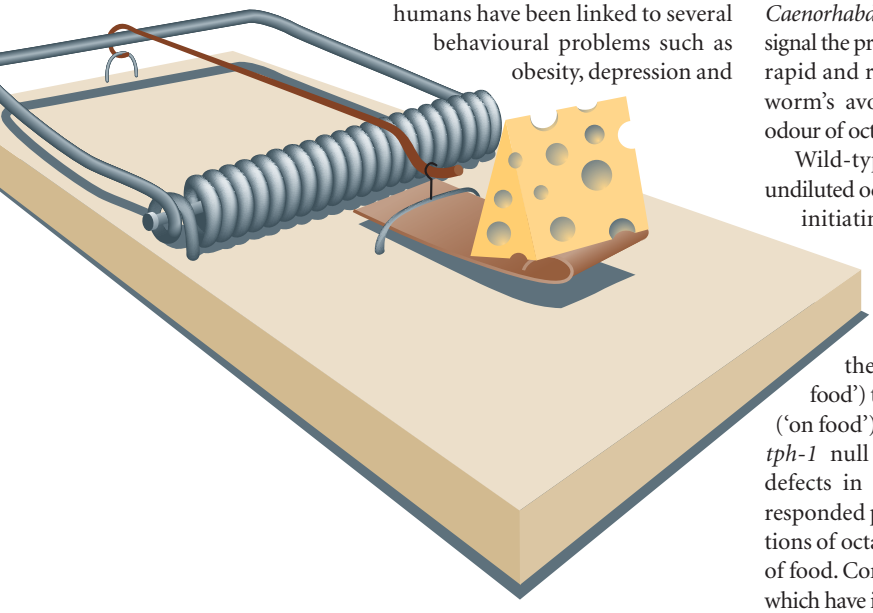
BEHAVIOURAL NEUROSCIENCE

Of food and danger



Defects in serotonin regulation in humans have been linked to several behavioural problems such as obesity, depression and addiction. How serotonin affects human behaviours is unclear, but studies on animals might shed some light on this. Reporting in the *Proceedings of the National Academy of Sciences*, Chao and colleagues show that, in the nervous system of *Caenorhabditis elegans*, serotonin can signal the presence of food and lead to rapid and reversible changes in the worm's avoidance of the noxious odour of octanol.

Wild-type *C. elegans* respond to undiluted octanol in three seconds by initiating backward movement regardless of feeding status. When diluted octanol is used, they respond more slowly in the absence of food ('off food') than when food is present ('on food'). The authors found that *tph-1* null mutants, which show defects in serotonin biosynthesis, responded poorly to low concentrations of octanol even in the presence of food. Conversely, *mod-5* mutants, which have increased serotonin levels, were hypersensitive to diluted octanol off food. Chao *et al.* then removed subpopulations of sensory neurons by laser microsurgery and found that ASH, but not ADL or AWB, neurons are responsible for detecting diluted octanol both on and off food. Serotonin signalling was mediated by a Gα protein encoded by *gpa-11*, as *gpa-11* null mutants responded poorly to diluted octanol on and off food.

Detecting undiluted octanol, however, is more complicated. Although worms can normally sense undiluted octanol equally well on and off food, mutant worms with ASH neurons removed by laser microsurgery fail to respond to undiluted octanol on food. By contrast, the avoidance of undiluted octanol off food can only be abolished when ADL and AWB neurons are also ablated. These data indicate that ASH neurons are mainly responsible for sensing undiluted octanol on food, and that all three types of neurons are involved when

SYNAPTIC FUNCTION

Adapting to epilepsy

AP-3 is a member of the adaptor protein (AP) complex family, which regulates formation of clathrin-coated vesicles and intracellular trafficking of membrane proteins. Although the function of the ubiquitously expressed AP-3A has been elucidated, that of the neuron-specific AP-3B remains unknown. Reporting in *Journal of Cell Biology*, Nakatsu and colleagues show that AP-3B is important in the regulation of GABA (γ-aminobutyric acid) release and might underlie the pathogenesis of epilepsy.

The authors found that mice that lack μ3B, a subunit of AP-3B, have no abnormalities in their overall brain structure. However, these animals showed spontaneous epileptic seizures when presented with a stimulus such as positional change. When intravenous infusion of pentylenetetrazole (a $GABA_A$ receptor antagonist) and electrical kindling were used to trigger seizures, a much lower level of stimulus was required to induce seizures in μ3B-knockout mice compared to their wild-type counterparts, indicating that the mutant animals have higher susceptibility to seizures.

Although the brain morphology of μ3B-knockout mice is basically normal, the number of synaptic vesicles per unit area is lower in the hippocampus, and the diameter of the synaptic vesicles in inhibitory synaptic terminals is also smaller. These observations prompted the authors to test synaptic function and neurotransmitter release in mutant mice. They found that the basal release of glutamate and GABA in hippocampal mini-slices was normal in the mutant mice, but that the K^+-evoked release of GABA, but not of glutamate, was significantly reduced.

As the amounts of these neurotransmitters in the hippocampus are comparable between wild-type and mutant mice, the authors suspected that it might be the trafficking rather than metabolism of GABA that was responsible. As expected, the amount of vesicular GABA transporter (VGAT) was lower than normal in synaptosomal lysates from the hippocampus of μ3B-knockout mice, whereas the concentrations of vesicle glutamate transporters and other synaptic vesicle proteins were normal.

If the inhibitory pathway is weaker due to reduced amounts of VGAT and GABA release on stimulation, are neurons more excitable in μ3B-knockout mice? The authors found that long-term potentiation (LTP) induced by standard conditioning was intact in the mutant mice. When weak conditioning was applied, LTP was induced in the mutant but not wild-type mice. This difference disappeared when the $GABA_A$ antagonist picrotoxin was present, indicating that weaker stimulation can induce LTP in μ3B-knockout mice, because the inhibition is weaker.

This is an interesting finding that assigns a new function to AP-3B and adds another aspect to the pathogenesis of epilepsy. μ3B-knockout mice might serve as a novel animal model of this disorder, which affects millions of people worldwide.

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References and links

ORIGINAL RESEARCH PAPER Nakatsu, F. *et al.* Defective function of GABA-containing synaptic vesicles in mice lacking the AP-3B clathrin adaptor. *J. Cell Biol.* **167**, 293–302 (2004)