electron microscopy revealed that otoferlin specifically localizes to IHC synaptic vesicles.

The IHC synaptic structure of mice that lack otoferlin forms normally. However, otoferlin-deficient mice were deaf and did not show auditory brain stem activity in response to sound stimulation. Given the localization of otoferlin, failure at the IHC synapse seemed most likely to blame.

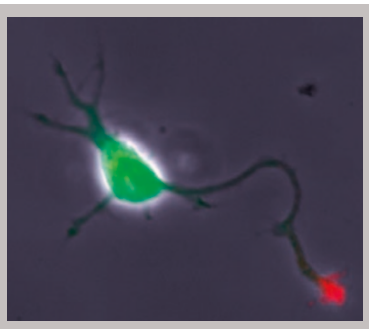
The team found that the number of synaptic vesicles in otoferlin-deficient IHCs was similar to that of wild-type cells and, furthermore, the localization of these vesicles to the presynaptic plasma membrane was also unaffected. Exocytosis of these synaptic vesicles in response to IHC calcium influx, however, was almost completely absent in otoferlin-deficient mice. Otoferlin therefore seems to control the last step in the IHC exocytosis pathway.

The amino acid sequence of otoferlin predicts a transmembranous calcium binding protein, and the team showed that otoferlin was indeed able to bind calcium. In addition, immunoprecipitation and *in vitro* binding experiments revealed that otoferlin interacts with components of the synaptic secretory machinery in a calcium-dependent manner.

It has been reported that depolarization-induced exocytosis is linearly dependent on the amount of presynaptic calcium influx, which in IHCs means a direct relationship between sound intensity and exocytosis. The authors propose that the ability of otoferlin to bind calcium and the dependence on calcium binding for interaction with the synaptic secretory machinery allow otoferlin to act as a calcium trigger, inducing a rapid and precise exocytosis in response to sound vibrations that depolarize the IHC. The authors raise the interesting possibility that otoferlin substitutes for synaptotagmin I and II, which have so far not been detected in IHCs.

Ruth Williams

ORIGINAL RESEARCH PAPER Roux, I. *et al.* Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. *Cell* **127**, 277–289 (2006)



Asymmetrical accumulation of shootin1 in the axonal growth cone. A polarized (stage 3) hippocampal neuron was double-stained with anti-shootin 1 antibody (red) and a volume marker CMFDA (green). Image courtesy of N. Inagaki, Nara Institute of Science and Technology, Ikoma, Japan.

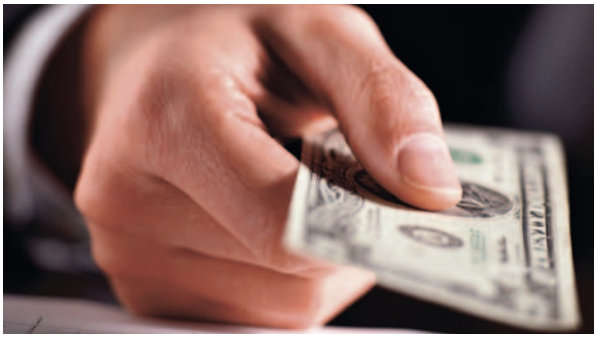
discrete boluses; this was accompanied by passive diffusion of the protein back to the soma. Inhibitors of actin or myosin abolished anterograde transport of shootin 1 and prevented its asymmetrical accumulation in neuronal processes.

As phosphatidylinositol-3-kinase (PI3K) is important for establishing neuronal polarity, the researchers wondered whether shootin 1 interacts with this pathway. They found that shootin 1 bound to PI3K in the rat brain, and that the proteins were also colocalized in axonal growth cones in stage 3 cultured hippocampal neurons. Importantly, abolishing shootin 1 expression reduced PI3K activity in axonal growth cones, whereas shootin 1 overexpression led to ectopic PI3K activation in multiple neurites, indicating that shootin 1 acts upstream of PI3K.

On the basis of these findings, the researchers propose a model in which anterograde transport and passive retrograde diffusion of shootin 1, which acts upstream of PI3K, provide a positive feedback loop that promotes neuronal polarization. So, if a neurite has more shootin 1 than its less fortunate siblings, it will outgrow them. This stretches the retrograde diffusion time of shootin 1, thereby increasing the protein level further and propelling even more neurite growth.

Jane Qiu

ORIGINAL RESEARCH PAPER Toriyama, M. *et al.* Shootin1: a protein involved in the organization of an asymmetric signal for neuronal polarization. *J. Cell Biol.* **175**, 147–157 (2006)
FURTHER READING Yoshimura, T. *et al.* Signalling networks in neuronal polarization. *J. Neurosci.* **26**, 10626–10630 (2006)



BEHAVIOURAL NEUROSCIENCE

It's good to give

Why does it feel good to give — even at a cost to oneself, and even anonymously? In a new study, Jorge Moll and colleagues have used functional neuroimaging to investigate the neural source of the 'joy of giving'. They find that charitable donations activate the same neural systems as those that respond to monetary reward.

In the study, subjects were scanned using functional MRI while they made decisions about whether to donate to a charity (either with a cost to themselves or with no cost to themselves), to oppose the charity (again, with or without personal cost) or to receive a monetary reward. The charities were all associated with societal causes such as abortion, children's rights and euthanasia. The participants were also asked about their feelings towards the causes (compassion or anger) and about their real-life charitable donations.

A monetary reward caused activity in the mesolimbic reward system, including the ventral tegmental area and the striatum. Intriguingly, a decision to donate to charity led to even greater activity in this network. It also activated the subgenual area, which was not activated by monetary reward, and which has been implicated in social attachment. Costly donation and costly opposition — as compared with non-costly decisions — were also associated with activity in the anterior prefrontal cortex. The level of activity here correlated with participants' real-life charitable engagement, supporting the theory that the anterior prefrontal cortex is a key area in altruistic behaviour.

The decision to oppose a cause, whether at a cost or at no cost, was also associated with activity in the lateral orbitofrontal cortex. This region has previously been implicated in aversive responses such as anger and moral disgust, consistent with the subjects' reported feelings about causes they chose to oppose.

These results shed light on the link between altruistic behaviour and reward systems in the brain, and on the role of the anterior prefrontal cortex in resolving conflicts between motivation related to personal gain and moral altruism.

Rachel Jones

ORIGINAL RESEARCH PAPER Moll, J. *et al.* Human fronto-mesolimbic networks guide decisions about charitable donation. *Proc. Natl Acad. Sci. USA* **103**, 15623–15628 (2006)
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