Neurobiology

Signals that make waves

Louis F. Reichardt

Neurons in the brain release proteins called neurotrophins, which bind to glial cells and unleash a wave of calcium ions inside them. This could be the missing link in a communication circuit between glia and neurons.

Our brains contain billions of nerve cells, woven together in an intricate network. But another class of brain cells, glial cells, vastly outnumbers the neurons. These cells provide essential support, forming a scaffold to hold the neurons in place, insulating the neuronal protrusions, providing nutrients and clearing debris. On page 74 of this issue, Rose *et al.*[1] reveal another link between glial cells and neurons. Neurotrophins — proteins that bind to and promote the survival of neurons — also bind to astroglial cells. Rose *et al.* find that this binding triggers the release of calcium ions inside these cells. This might regulate communication between neurons.

Neurotrophins are crucial for the normal development and functioning of the brain. These proteins bind directly to neurons, triggering intracellular signals that culminate in survival, growth or the modulation of neuronal function. About a decade ago, the major receptors to which neurotrophins bind on neurons were shown to be a subfamily of 'receptor tyrosine kinases', named Trks (ref. 2). These receptors span the neuronal membrane; neurotrophin binding at the outside of the cell causes them to dimerize, which in turn activates the intracellular tyrosine-kinase portion of the receptor. This portion then phosphorylates other intracellular proteins, initiating signalling cascades inside the neurons. These lead to changes in protein function and gene expression that promote neuronal survival and maturation. The Trk receptors can also directly regulate other proteins in the neuronal membrane, including ion channels and receptors for neurotransmitters, which are essential for neuronal function[3,4] (Fig. 1a).

There are three *trk* genes, and each encodes more than one protein product. For instance, the *trkB* and *trkC* genes encode not only full-length TrkB and TrkC proteins, but also truncated forms lacking the intracellular tyrosine-kinase domain. However, little was known about the function of the truncated forms, as most studies of Trk receptors had involved the full-length, kinase-containing forms, which are abundant in neurons. The truncated forms are found mainly in glial cells, which lack the kinase-containing receptors. And the truncated form of TrkB is widely expressed both during development and in the adult brain.

What is the function of these truncated receptors, and why are they present on glial cells? Some clues, but no clear answers, have come from several studies. As the brain matures, the ratio of truncated to kinase-containing forms of TrkB increases dramatically in the outer layer of the brain (the cerebral cortex), indicating that the functions of the truncated receptors are developmentally

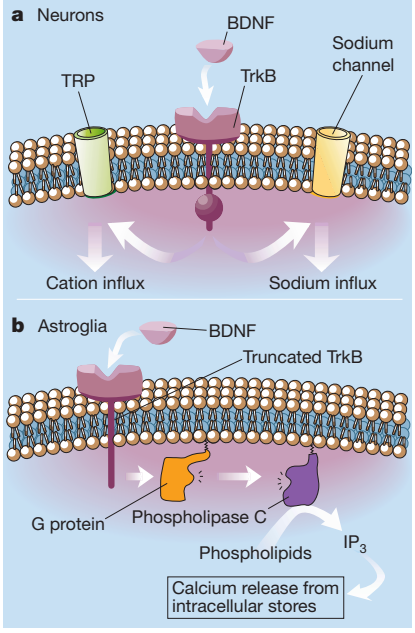

Figure 1 **A multifunctional receptor. The TrkB receptor has various ways of regulating the ion concentrations in different brain cells.** a, **The full-length receptor occurs abundantly on the surface of neurons. When it binds its ligand, BDNF, the receptor's intracellular 'kinase' domain phosphorylates the enzyme phospholipase C, activating the transient receptor channel TRP. TrkB can also activate a sodium channel (Na(v)1.9) via a faster but less well understood interaction that probably does not require kinase activity.** b, **Astroglia contain a truncated form of the TrkB receptor (TrkB-T1). Its function was unclear, but Rose *et al.*[1] now show that BDNF binding to this receptor activates the release of calcium from intracellular stores, through a signalling pathway that involves an as yet unidentified 'G protein'. This in turn promotes the generation of inositol trisphosphate (IP_3) through phosphopholipase C. When IP_3 binds to its intracellular receptor, calcium is released.**

100 YEARS AGO

It is announced by the *Electrician* that this year it is proposed to award the Nobel physics prize to Signor Marconi, the chemistry prize to Prof. Arrhenius, and the medicine prize to Prof. Finsen. Each prize is worth about 8000*l.*

From *Nature* 5 November 1903.

50 YEARS AGO

The Nobel Prize for Medicine and Physiology for 1953 has been awarded jointly to Prof. H. A. Krebs, professor of physiology in the University of Sheffield and director of the Medical Research Council Unit for Research in Cell Metabolism, and Dr. F. Lipmann, head of the Biochemical Research Laboratories, Massachusetts General Hospital.

***Prof. H. A. Krebs, F.R.S.:* Prof. Krebs has mostly been concerned with the study of metabolic processes by experiments *in vitro*. The first of his two greatest contributions to biochemistry was from Freiburg in 1932, when he elucidated the mechanism of urea synthesis in the liver, by discovering the participation of ornithine, citrulline and arginine through a cyclical process — a concept of unprecedented nature. His subsequent observations on the deamination of amino-acids demonstrated D-amino-acid oxidase, and laid foundations for future studies of the L-acids. In Cambridge in 1935 he proved the synthesis of glutamine from glutamic acid and ammonia in tissue slices. After moving to Sheffield, he announced in 1937 his second major contribution, the citric-acid cycle.**

***Dr. Fritz Lipmann:* After studying problems of muscle metabolism in Meyerhof's laboratory and of fermentation in the Carlsberg laboratory, Lipmann set the pattern for his future work when in 1937 he began to analyse the oxidation of pyruvate to acetate by bacteria. He found that the oxidation is accompanied by phosphorylation, and announced from Cornell University in 1939 that the 'energy-rich' ester acetyl phosphate is an intermediate… Moving to Boston, Lipmann realized that acetyl phosphate is not formed in pyruvate oxidation in animal tissues; some other substance had to be sought… Studying the biological acetylation of sulphanilamide, he discovered a new coenzyme, coenzyme *A*… Finding that it is a derivative of the vitamin pantothenic acid and a general constituent of living organisms, he quickly realized that it is of fundamental importance in carbohydrate and fat metabolism.**

From *Nature* 7 November 1953.

regulated[5]. Truncated TrkB and TrkC have also been shown to form dimers with, and thereby inhibit the activation of, the full-length forms of these receptors. And truncated TrkB can rapidly bind and internalize the neurotrophins BDNF and NT4, preventing their diffusion[6]. Studies of cultured astroglia (matrix-forming glial cells in the brain) and Schwann cells (glial cells that insulate nerve-cell projections in the peripheral nervous system) have also revealed that truncated TrkB promotes both the internalization and subsequent release of BDNF. This suggests that these cells could act as a reservoir of BDNF to promote the growth and maturation of adjacent neurons[7]. Finally, several groups have shown that the truncated receptors can, through more direct mechanisms, regulate the neurons' intracellular pH and maturation, but what these mechanisms might be has been somewhat enigmatic[8–10].

Rose *et al.*[1] now take a step towards solving this enigma. They show that when BDNF is applied to cultures of astroglia and slices of brain, it generates waves of calcium release inside the glial cells. Calcium is an important 'second messenger' that regulates the release of neurotransmitters and other molecules from cells, as well as controlling the activities of several signalling proteins and ion channels. BDNF is released by neurons and is present in the brain at the sub-nanomolar concentrations required to generate calcium waves, so this protein might be a means by which neurons signal to glia.

The authors show that the BDNF-induced production of calcium waves in astroglia requires truncated ('T1'), but not kinase-containing, TrkB. And wave generation requires intracellular but not extracellular calcium — waves are prevented by inhibiting a receptor, the inositol trisphosphate receptor, through which calcium is released from intracellular compartments. Rose and colleagues' study also implicates several other signalling molecules in the pathway from receptor activation to wave generation (Fig. 1b). These include an as yet unidentified G protein (a class of protein that often couples cellular receptors to intracellular signalling pathways) and phospholipase C (an enzyme that generates inositol trisphosphate from phospholipids). It will be important to identify the G protein involved in this signalling cascade.

What is the significance of the waves of calcium release in astroglia? In so-called pyramidal neurons of the cerebral cortex, both the expression and release of BDNF are induced by calcium and electrical activity. And in adjacent astroglia, increased levels of calcium evoke the release of the excitatory neurotransmitter glutamate, enhancing the activity of the synapses formed by neighbouring neurons[11]. (Synapses are the connections through which electrical impulses can pass from one neuron to the next.) Calcium waves can also propagate through many astroglia and regulate synapses over wide areas by means of gap junctions, which are connections between cells that allow molecules to move from one cell to another[11].

It was known that BDNF promotes both short- and long-term enhancement of synaptic strength, but the underlying mechanisms were poorly understood. Rose and colleagues' findings[1] suggest that it may exert its effects on neuronal synapses in part by triggering calcium signalling in astroglia. The physiological functions of this signalling pathway, and which of the other truncated forms of TrkB and TrkC can initiate it, remain to be discovered. ■

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1. Rose, C. R. *et al. Nature* **426,** 74–78 (2003).
2. Huang, E. J. & Reichardt, L. F. *Annu. Rev. Neurosci.* **24,** 677–736 (2001).
3. Chao, M. V. *Nature Rev. Neurosci.* **4,** 299–309 (2003).
4. Blum, R., Kafitz, K. W. & Konnerth, A. *Nature* **419,** 687–693 (2002).
5. Allendoerfer, K. L. *et al. J. Neurosci.* **14,** 1795–1811 (1994).
6. Biffo, S., Offenhauser, N., Carter, B. D. & Barde, Y. A. *Development* **121,** 2461–2470 (1995).
7. Alderson, R. F., Curtis, R., Alterman, A. L., Lindsay, R. M. & DiStefano, P. S. *Brain Res.* **871,** 210–222 (2000).
8. Hapner, S. J., Boeshore, K. L., Large, T. H. & Lefcort, F. *Dev. Biol.* **201,** 90–100 (1998).
9. Yacoubian, T. A. & Lo, D. C. *Nature Neurosci.* **3,** 342–349 (2000).
10. Baxter, G. T. *et al. J. Neurosci.* **17,** 2683–2690 (1997).
11. Haydon, P. G. *Nature Rev. Neurosci.* **2,** 185–193 (2001).

Ecology

Palms in motion

Peter D. Moore

Being eaten alive then dumped with the resulting droppings can be all to the good — if you are a palm fruit in the Amazonian tropical forest, that is, and the consumer is a large mammal.

Getting away from one's parent has its advantages. When animals disperse plant seeds, for instance, the seeds avoid competing with their well-established parent and also escape the organisms that home in on the ready source of nutrition that an older tree represents. When the animal is large, and the seeds are ingested, the distances covered can be considerable. And the seeds conclude their journey securely buried in faeces that may further protect them from parasites and predators. The dispersal of palms by tapirs in the forests of Brazil, described by José Fragoso and colleagues in *Ecology*[1], provides a good example of this process and also explains aspects of the patterns in which palms grow.

Most models of seed dispersal, based on direct demographic studies, tend to consider long-distance dispersal as relatively rare, and as insignificant[2]. Genetically based research, in contrast, recognizes its importance in the spread of genes[3]. A model that has proved most useful for tree-seed dispersal in tropical

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Figure 1 **Passing through: the Brazilian tapir, *Tapirus terrestris*.**