



**Figure 1 | On-board energy generators.** Neurons have long axonal processes that require a constant supply of energy in the form of ATP molecules to transport cargo-carrying vesicles along microtubules from the cell body to axonal terminals (red arrow) and back (blue arrow). The prevalent assumption is that mitochondria (not shown) are the source of ATP for this purpose. Zala *et al.*<sup>1</sup>, however, find that the glycolytic enzyme GAPDH, which is bound to transport vesicles through the huntingtin protein and possibly other factors (question marks), powers the motor proteins cytoplasmic dynein and kinesin on microtubules by locally generating ATP through glycolysis.

might contribute to disease development and progression. Nonetheless, therapeutic targeting of GAPDH will probably require the development of drugs that specifically modulate only a subset of its functions<sup>6</sup>, as indicated by the failure of a GAPDH-directed molecule in a clinical trial for treating ALS<sup>9</sup>.

The uncoupling of vesicular axonal transport from mitochondrial ATP production is the most intriguing yet puzzling aspect of this work. For instance, Zala *et al.* describe an alternative energy source for fast transport across axonal areas devoid of mitochondria, yet they did not detect any overt variation in ATP levels in the axons they analysed. Another mystery arises from the authors' observations that mitochondrial ATP plays no part in fast axonal transport, and that motors associated with vesicular cargoes cannot access this source of ATP. This finding cannot be explained by intrinsic properties of the motor complexes, because the same types of molecular motor can hydrolyse mitochondrial ATP for mitochondrial transport, which was not affected by inhibition or reduced expression of GAPDH<sup>1</sup>.

Similarly, a direct link between GAPDH and motor complexes is unlikely. The authors report that GAPDH association with transport vesicles is necessary for axonal transport, although its binding to molecular motors is not: in huntingtin-depleted cells, GAPDH targeting to vesicles by other means was sufficient to recover transport. A direct link

between GAPDH and motor complexes is also unlikely because GAPDH-mediated axonal transport was shown to occur with different motors moving in different directions (Fig. 1). To resolve this conundrum, *in vitro* studies are required that examine the effects of GAPDH on the biophysical properties of isolated motor complexes moving along microtubules. Such studies might reveal additional functions for GAPDH in regulating these molecular nanomachines. For example, it could be that other enzymatic activities of GAPDH, such as S-nitrosylation and mono-ADP-ribosylation<sup>6,8</sup>, are also necessary for transport.

Whether GAPDH is required for the axonal transport of non-vesicular complexes, such as RNA granules, is also unknown. And does a similar GAPDH-dependent mechanism apply to other cellular ATP-hydrolysing enzymes, such as ion pumps and remodelling enzymes<sup>8</sup>? Whatever the answers, Zala and co-workers' findings place alternative energy sources in the axonal domain, calling for a re-examination of fundamental assumptions and pointing the field in intriguing and unexplored directions. ■

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## 50 Years Ago

Mr. A. J. Kirkman has recently argued in *Nature* that it was mainly up to teachers of science and technology to give the guidance and impose the standards necessary for their students to improve their written English ... All the errors he mentioned were fairly easy to spot, easy to correct, and of a kind which the teacher could easily mark; but they were all irrelevant to the main problem of helping scientists to write better English and express themselves more fluently. The damage is done in the classes called 'English', and is not the fault of science teachers who accept low standards ... One is led to suspect that a teacher of English can hope to find only the superficial deficiencies in scientific English unless he learns more about the subject-matter. Perhaps Mr Kirkman is right after all in passing responsibility to the science teachers because most English teachers cannot bear it. But the scientist's task is so often rendered well-nigh impossible by English teachers who inoculate pupils interested in science with a distaste, or at least a disdain, for the subject known as 'English'.

From *Nature* 16 March 1963

## 100 Years Ago

Some readers of *Nature* will be interested to learn that tadpoles with large suctorial oral discs, enabling their possessors to adhere firmly to the rocks and boulders of mountain streams, have recently been discovered at Krantzloop, in Natal, at an elevation of about 1500 to 1600 ft. They were found by the Rev. Fr. P. Boneberg, of Mariannahill, who kept them alive for some time, and observed their peculiar leech-like habit of sticking to one's fingers or to the sides of the vessel in which they were contained.

From *Nature* 13 March 1913