CELL BIOLOGY OF THE NEURON

Fuelling transport

Glycolysis, which largely occurs in the cytosol, generates a small proportion of cellular ATP compared with mitochondrial ATP production. In neurons, however, mitochondria are unevenly distributed along axons, leading to the question of how neurons maintain a constant energy supply in axons for fast axonal transport (FAT), a process whereby cargo-carrying molecular motors hydrolyse ATP to 'walk' along microtubules. Now, Saudou and colleagues show that the ATP needed for the FAT of vesicular cargoes may be generated by glycolytic machinery located on the vesicles themselves.

In line with previous studies, the authors found that, in cultured rat cortical neurons, axonal mitochondria were unevenly distributed but glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a key enzyme in glycolysis, exhibited a diffuse axonal presence. The ATP/ADP ratio also remained constant over long stretches of the axons.

Despite their axonal distribution, mitochondria were responsible for generating most axonal ATP, as application of oligomycin — a mitochondrial inhibitor — dramatically decreased axonal ATP levels, whereas iodoacetate-mediated inhibition of GAPDH led to only

a moderate decrease in ATP. Interestingly, iodoacetate but not oligomycin inhibited the FAT of vesicles containing brain-derived neurotrophic factor (BDNF), indicating that GAPDH activity but not mitochondrial activity is crucial for vesicular FAT.

Knockdown of GAPDH expression in cortical neuron cultures by small interfering RNAs (siRNAs) impaired the FAT of vesicles containing BDNF, the amyloid precursor protein or tropomyosin-related kinase B (also known as NTRK2), suggesting that GAPDH may be important for the FAT of different types of vesicles.

GAPDH is largely found in the cytosol, although some studies have suggested that it may also be located in other cellular compartments. The authors showed that mouse GAPDH could be localized to motile brain BDNF vesicles, possibly on their cytosolic face. Moreover, they showed that purified BDNF vesicles exhibited GAPDH activity and generated ATP, indicating that vesicles can harbour their own ATP-generating machinery.

Huntingtin (HTT) can act as a scaffolding protein and is found on vesicles. siRNA-mediated knockdown of HTT expression led

to a specific loss of co-localization of GAPDH with vesicles (without affecting the cytosolic levels of GAPDH), suggesting that HTT tethers GAPDH to vesicles. Interestingly, HTT knockdown also impaired FAT, indicating that vesicular GAPDH is necessary for FAT.

Together, these findings show that, for at least certain types of vesicles, vesicular FAT is powered by 'on-board' glycolytic machinery rather than cytosolic GAPDH or mitochondrion-generated ATP.

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ORIGINAL RESEARCH PAPER Zala, D. *et al.*
Vesicular glycolysis provides on-board energy for fast axonal transport. *Cell* **152**, 479–491 (2013)

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