NEUROLOGICAL DISORDERS

Food for thought

> Development of antiglycolytic inhibitors as a new class of anti-epileptic therapy warrants further investigation.

Previous observations that a carbohydrate-restrictive diet controls seizures in patients with drug-resistant epilepsy have led researchers to propose a link between seizures and energy metabolism. Now, a paper in *Nature Neuroscience* reports that an inhibitor of glycolysis reduced seizures in a mouse model of epilepsy by modulating a metabolism-regulated transcriptional pathway that controls the expression of neuronal genes.

Temporal lobe epilepsy is a common drug-resistant form of epilepsy that can be modelled in rodents using 'kindling' — the repeated application of electrical stimuli which causes electrographic seizures known as 'after-discharges'. Kindling reproduces the progression from focal seizures to more severe generalized seizures and, although it is not known how this progression occurs, studies in mice show that it is abrogated by deletion of the gene encoding brain-derived neurotrophic factor (BDNF) or blockade of the BDNF receptor, TrkB. Given that many genes implicated in epilepsy are often regulated by neuronal activity that in turn regulates metabolism, Garriga-Canut *et al.* decided to study the effects on seizures of perturbing the glycolytic pathway using a rat kindling model and a glycolytic inhibitor, 2-deoxy-D-glucose (2DG).

The researchers found that treatment of rats with 2DG increased the intensity of electrical currents required to induce the same level of after-discharge observed in control rats, and increased the number of evoked after-discharges required to reach certain classes of seizure. So, 2DG is acting as an anticonvulsant in two ways: reducing the occurrence of initial after-discharges and slowing the progression to more generalized seizures by inhibiting the kindling effect.

The authors next looked at the expression of BDNF and TrkB in the 2DG-treated rats. Control rats that were not treated with 2DG showed a marked increase in BDNF and TrkB expression after five after-discharges; this increase was blunted in rats treated with 2DG, suggesting that these genes have a role in progression to more severe seizures.

Transcription of BDNF and TrkB is regulated by neural restrictive silencing factor (NRSF), which binds to the neuron restrictive silencing element (NRSE) present in neuronal genes. Like many transcription factors, NRSF recruits co-repressors that alter chromatin structure and prevent transcription. Using a scanning chromatin immunoprecipitation assay, the authors showed that the downregulation of BDNF is caused by increased methylation of histones at its NRSE in the presence of 2DG, suggesting that NRSF mediates the effects of 2DG on *Bdnf* gene expression.

To confirm this, the authors measured NRSF-driven expression of a reporter gene under conditions of increased or decreased glycolysis. Addition of the glycolytic inhibitors pyruvate, citrate or 2DG increased NRSF-mediated repression of the reporter gene, and further analysis showed that this repression involves CtBP, a metabolic regulator of several transcription factors, which binds to NRSF in an NADH-labile manner.

Together, these findings show that seizure threshold is affected by glycolysis *in vivo* by NRSF–CtBP-mediated regulation of neuronal genes. As 2DG had antiepileptic and anticonvulsant properties and is well tolerated in humans, the development of antiglycolytic inhibitors as a new class of anti-epileptic therapy warrants further investigation.

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ORIGINAL RESEARCH PAPER Garriga-Canut, M. *et al.* 2-Deoxy-D-glucose reduces epilepsy progression by NRSF–CtBP-dependent metabolic regulation of chromatin structure. *Nature Neurosci.* **9**, 1382–1387 (2006)