

2-DEOXY-D-GLUCOSE

K. Rejdak

Department of Neurology, Medical University of Lublin & Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

krejdak@yahoo.com

Despite major advances in the treatment of epilepsy with the introduction of new and better tolerated antiepileptic drugs in recent years, about 30% of people with epilepsy have uncontrolled disease. This leads to somewhat frustrating conclusion that novel and more effective third-generation AEDs are needed (Perucca et al., 2007). All new drugs approved for the treatment of epilepsy display variable mechanisms of action, mainly targeting voltage-gated cation channels and modulating the major neurotransmitter systems in the CNS. However, there is still need and space for novel compounds with unique characteristics in order to enhance the seizure control. Metabolic regulation of neuronal excitability is increasingly recognized as a factor in seizure pathogenesis and control and there is growing interest in using different metabolic modifications to treat epilepsy. One such metabolic approach is dietary modification and the high fat, low carbohydrate ketogenic diet (KD) has gained acceptance for treating refractory epilepsy (Bailey et al., 2005). Although no single mechanism has been identified to explain the seizure protection conferred by the KD (Nylen et al., 2009), it has been suggested that the inhibition of glycolysis might play the role in the anti-seizure mechanism. First of all, mild hypoglycemia, significant ketosis, and a shift in cellular metabolism wherein ketone bodies replace glucose as the primary carbon source in the Krebs cycle represent the most fundamental metabolic changes produced by the KD. Moreover, the observation that the consumption of carbohydrates during the KD can lead to the rapid relapse of seizures supported that concept. Above background inspired studies to determine if approaches that specifically decrease glucose utilization through the glycolytic pathway can also produce anticonvulsant effects. An interesting candidate for pharmacological modulation of glycolysis is 2-deoxy-D-glucose, a glucose analog that accumulates in cells and interferes with carbohydrate metabolism by inhibiting glycolytic enzymes. Our group was the first to report that chronic 2DG treatment in mice resulted in a moderate but significant decrease in mortality rate after status epilepticus evoked by toxic doses of bicuculline and a tendency toward a lower seizure score (Rejdak et al., 2001). Mechanisms of such protective effects of 2DG were not clear but we proposed it could be related to metabolic stress (glucose deprivation)-evoked chemical preconditioning with subsequent induction of the brain tolerance. It is of note that in our experiments protein synthesis inhibitor cycloheximide attenuated protective effects of the 2-DG (Rejdak et al., 2001). Further studies confirmed and extended our observations, reporting that 2DG reduced epileptiform discharges in vitro and protected against seizures in several animal models (Garriga-Canut et al., 2006; Stafstrom et al., 2009). Especially important seems the fact that 2DG potently reduced the progression of kindling and blocked seizure-induced increases in the expression of brain-derived neurotrophic factor and its receptor, TrkB. This reduced expression was mediated by the transcription factor NRSF, which recruits the NADH-binding co-repressor CtBP to generate a repressive chromatin environment around the BDNF promoter (Garriga-Canut et al., 2006).

It is not certain if 2DG would prove effective in clinical trials in humans and the safety of such treatment still needs to be demonstrated. However reported effects of 2DG and other compounds inhibiting glycolysis pave the way for studying new pharmacological "metabolic" target for refractory epilepsy but also other neurological conditions where induction of the brain tolerance might be of importance to protect the central nervous system tissues against acute or chronic insults (Rejdak et al., 2001; Cadet et al., 2009), in particular those involving excitotoxicity.

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