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Novel Anticonvulsant, Antiepileptic, and Neuroprotective Actions of 2dg – an update

Thomas P. Sutula MD, PhD
Department of Neurology, University of Wisconsin, Madison, WI
Neurogenomex, Inc., Madison, WI

2-deoxy-D-glucose (2DG) is a reversible activity-dependent inhibitor of glycolysis and has acute anticonvulsant actions against seizures in preclinical *in vivo* models of 6 hz and audiogenic stimulation in mice. The acute *in vitro* actions of 2DG include suppression of epileptic discharges evoked by a variety of cellular mechanisms of network synchronization, implying a broad spectrum mechanism of acute anticonvulsant action. 2DG also has chronic antiepileptic “disease-modifying” effects in rats consisting of 2-fold slowing of kindling progression of seizures evoked from different brain sites. These chronic actions have been associated with therapeutically favorable alterations in seizure-induced expression of neural genes such as BDNF and trkB implicated in kindling and adverse chronic consequences of seizures. 2DG undergoes uptake in brain regions as a function of neural activity and local circuit energy demands, enabling local therapeutic delivery during and immediately after seizures and by focal brain stimulation. The chronic “disease-modifying” actions against kindling progression are observed when 2DG is administered as long as 10 minutes *after* a seizure, suggesting that favorable therapeutic effects may occur with post-seizure administration. Recent magnetic resonance and diffusion tensor imaging studies in rat strains bred for susceptibility or resistance to kindling-induced plasticity have demonstrated that brief treatment with 2DG after traumatic brain injury (TBI) reduced the progression of focal and generalized damage and structural alterations evolving for 6 months after initial injury, implying that 2DG could modify long-term consequences of TBI dependent on injury-induced plasticity such as post-traumatic epilepsy and post-traumatic stress disorder. These distinctive preclinical mechanistic and efficacy studies suggest that 2DG could be a significant addition to therapy for seizures, epilepsy, and TBI. Continuing preclinical studies are underway to evaluate potential toxicity of 2DG including recent evidence of cardiac autophagy in association with chronic dietary administration, and to further define therapeutic opportunities for 2DG not only for sporadic seizures, but for clusters of seizures, status epilepticus, intractable epilepsies, status epilepticus, in combination with device and stimulation therapy, and for TBI.

T. Sutula is Chief Scientific Officer and holds equity interests in Neurogenomex, Inc.