Diabetes drug may hold potential as treatment for epilepsy, using same mechanism as ketogenic diet

April 8 2008

Two years ago, University of Wisconsin-Madison scientists reported they had suppressed epileptic seizures in rats by giving them a glycolytic-inhibitor, inhibiting the brain's ability to turn sugar into excess energy and blocking the expression of seizure-related genes. The discovery was greeted with excitement and hope for a new class of drugs for epilepsy, which afflicts more than 50 million people worldwide.

Now, in a presentation at Experimental Biology 2008 in San Diego, Dr. Avtar Roopra describes a next step in this research that may mean a drug already widely used by people with diabetes could also be an effective and safe therapy for epilepsy, especially for that one third of patients who have recurrent seizures despite therapy with the best available antiepileptic drugs.

Dr. Roopra's presentation on April 8 is part of the scientific program of the American Society for Biochemistry and Molecular Biology (ASBMB).

Although the earlier work by Dr. Roopra and his colleagues marked the first time a compound had been used for metabolic regulation of neuronal genes, epilepsy patients had been attempting to achieve the same goal - fewer seizures - for centuries through severe dietary restriction, in some cases with near starvation, more often with a high-fat, high-protein diet completely free of starches and sugars. Half of all

drug-resistant people with epilepsy experience seizure control with this kind of severe ketogenic diet (although even a mild lapse can sometimes result in seizures).

The mechanism was completely unknown but the researchers reasoned it had to involve glycolysis, the recognition of sugar and its conversion to energy. And if that were correct, they asked, could they tap into this same biological pathway, bypassing dietary requirements altogether? The answer, published in Nature Neuroscience in October 2006, was 2-Deoxy-D-glucose, a compound that tricked the body into thinking it was sugar so that the cells stopped using the real thing as an energy source.

Now, in the new work reported at Experimental Biology, the researchers have identified a small molecule in the neurons that senses how much energy in available. Glucose turns on this sensor – but so does Metformine, a FDA-approved prescription drug used by millions of people with diabetes to control their blood sugar. Dr. Roopra and his colleagues are now testing Metformine in the brains of mice to see how it affects the functioning of the hippocampus, the part of the brain involved with learning and memory and also the seat of seizures for many patients with epilepsy. The goal is to tamp down a mechanism called Long Term Potenciation enough to reduce the rate of epilepsy but not enough to affect the brain's ability to learn and remember.

At this early stage of the research, it appears to be hitting the right balance, says Dr. Roopra. In the meantime, he points out, there have been no reports of learning and memory side effects in any of the adults or children who have used Metformine for years.

The next step will be to take Metformine to a mouse model of epilepsy. It's still early, says Dr. Roopra, but the researchers already are pleased with the increased understanding of the likely mechanism of the positive

effect of the ketogenic diet on epileptic seizures and the focus on new drug targets for this often-devastating disease.

Source: Federation of American Societies for Experimental Biology