CURRENT LITERATURE

HYPERGLYCEMIA LOWERS SEIZURE THRESHOLD

Correlation between Extracellular Glucose and Seizure Susceptibility in Adult Rats

Schwechter EM, Veliskova J, Velisek L

Ann Neurol 2003;53:91–101

In adult diabetic patients, periods of hyperglycemia may be associated with exacerbation of focal seizures. Our objective was to determine in the adult rats the correlation between seizure susceptibility and extracellular glucose concentration in two models of seizures. Male rats were injected with two doses of streptozocin (40 mg/kg, IP) on consecutive days to induce diabetic hyperglycemia. Controls either received vehicle or were not injected. After 2 weeks, blood glucose concentration was measured, and the rats were subjected to flurothyl seizure test. Another group of rats received glucose solution (20%, 5 mL, IP) 30 minutes before testing to induce nondiabetic hyperglycemia. Thresholds for flurothyl-induced clonic and tonic–clonic seizures were determined. Finally, in vitro epileptiform activity was induced in the entorhinal cortex–hippocampal slices from naive rats by perfusing with magnesium-free medium with various glucose concentrations. In additional slices, the paired-pulse paradigm was determined in the perforant path. Susceptibility to clonic and tonic–clonic flurothyl-induced seizures positively correlated with blood glucose concentrations, as the increased glucose concentration was associated with proconvulsant effects. Similarly, in the in vitro experiments, epileptiform activity was promoted by increased and suppressed by decreased glucose concentrations. Data indicate that, in the adult rats, high glucose concentrations are associated with proconvulsant effects.

COMMENTARY

Abnormal glucose levels, whether too high or too low, can cause seizures. The problem is especially pertinent to individuals with diabetes, whose blood glucose levels can fluctuate widely over the course of a day, as a result of intercurrent illness, variations in insulin levels, or other metabolic factors. Clinical studies show that adults with hyperglycemia have an increased predisposition to experiencing seizures. Experimental studies, both in vivo and in vitro, suggest that a threshold glucose concentration is necessary to support synaptic transmission. Conversely, it appears that elevated extracellular glucose is associated with neuronal hyperexcitability, indicating that glucose balance is necessary for normal neurotransmission. The importance of glucose balance has been identified in studies demonstrating that hyperglycemia exacerbates ischemia-induced brain damage, whereas fasting-induced hypoglycemia protects against this neurotoxicity. The present study, by Schwechter and coworkers, hypothesizes that the reduction of extracellular glucose could ameliorate seizure activity by decreasing neuronal excitability.

First, Schwechter et al. examined the relation between extracellular glucose levels and seizure susceptibility in adult rats in vivo. They tested the hypothesis that elevated glucose is proconvulsant in the flurothyl model of generalized seizures (flurothyl is a gaseous convulsant capable of inducing seizures by inhalation). Hyperglycemia was induced in two ways: (a) streptozocin (STZ) administration, which reliably produces hyperglycemia and simulates diabetes; and (b) short-term intraperitoneal injection of 20% glucose to create a condition of nonketotic hyperglycemia independent of diabetes. A variety of well-chosen controls were used to compare outcomes. The three groups comprising "nondiabetic controls" included rats injected with the STZ vehicle, STZ-injected rats that did not develop diabetes, and rats that received no injection but otherwise were handled identically to the other animals. A final comparison group consisted of rats that underwent a 24-hour fast and thus were *hypo*glycemic.

Testing with flurothyl demonstrated a negative correlation between blood glucose level and clonic seizure threshold—with STZ-induced diabetic rats having significantly lower seizure thresholds than did nondiabetic controls. Fasted, hypoglycemic rats had the highest thresholds. To control for other metabolic or hormonal effects resulting from STZ injection, an additional group of rats was injected with 20% glucose, 30 minutes before flurothyl testing, and then were compared with saline-injected controls. Again, the hyperglycemic rats had significantly lower thresholds for clonic flurothyl seizures, suggesting

that hyperglycemia itself is proconvulsant, in both diabetic and normal rats. Furthermore, no damage to hippocampal neurons was seen in any of the experimental conditions, as assessed by Fluro-Jade and silver stain techniques, suggesting that neither STZ or elevated glucose causes structural neuronal injury.

Next, Schwechter and colleagues evaluated the effects of elevated extracellular glucose on epileptiform activity in vitro. Slices of entorhinal cortex–hippocampus were exposed to a Mg^{2+}-free extracellular medium, causing epileptiform bursts for which amplitude and frequency can be measured and compared under different experimental conditions. In Mg^{2+}-free medium with 10 m*M* extracellular glucose (i.e., the usual glucose concentration used in slice experiments), typical epileptiform discharges occurred. When the glucose was increased to 20 m*M*, epileptiform burst frequency did not change; however, the burst amplitudes increased significantly, suggesting enhanced neuronal firing. The effect was reversed when the glucose was switched back to 10 m*M*. In addition, no epileptiform discharges were seen in normal cerebral spinal fluid (CSF), that is 2 m*M* Mg^{2+}, plus a 20 m*M* glucose solution. As a caveat—consider the fact that nearly all brain-slice electrophysiology experiments have used a CSF-glucose concentration of 10 m*M*, rather than the physiologic concentration, which is closer to 5 m*M*. The conventionally accepted practice of using the higher-glucose-level solutions is based on empiric experience, showing that the synaptic viability of slices is optimized with the higher concentration (1).

This well-designed study confirms previous work with several animal models of diabetes, which show a reduction in seizure threshold. The important new finding from Schwechter and colleagues is that hyperglycemia, itself, is proconvulsant. How can elevated glucose enhance seizure susceptibility? The answer to this crucial question regarding the mechanism of action awaits further research, as the mechanism per se is not addressed in this report. However, one clue to the answer might be gleaned from the authors's observation that hypoglycemia was associated with a higher seizure threshold. Other studies have indicated that restricting calories, thus inducing hypoglycemia, in the epilepsy-prone EL mouse also reduces seizure susceptibility (2). With any model that induces hypoglycemia, the role of ketosis must be excluded, as ketones themselves can affect seizure threshold (3). Moreover, multiple other mechanisms could explain hypoglycemia- and hyperglycemia-induced alterations of neuronal excitability. Furthermore, the effects of age on glucose balance and neuronal excitability must be delineated, as children with diabetes tend to develop seizures with hypoglycemia rather than with hyperglycemia. In addition to clarifying further the relation between hyperglycemia and seizures, Schwechter et al. highlight the link between metabolism and neuronal excitability and emphasize the need for further research on the long-term effects of hyperglycemia on various aspects of brain function (4).

by Carl E. Stafstrom, M.D., Ph.D.

References

1. Schwartzkroin PA. Characteristics of CA1 neurons recorded intracellularly in the hippocampal in vitro slice preparation. Brain Res 1975;85:423–436.
2. Greene AE, Todorova MT, McGowan R, Seyfried TN. Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. Epilepsia 2001;42:1371–1378.
3. Stafstrom CE. Effects of fatty acids and ketones on neuronal excitability: implications for epilepsy and its treatment. In: Mostofsky DI, Yehuda S, and Salem N Jr, eds. Fatty acids: physiological and behavioral functions. Totowa, NJ: Humana Press, 2001:273–290.
4. Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. Trends Neurosci 2000;23:542–549.