

EXCITABLE BUT LACKING IN ENERGY: CONTRADICTIONS IN THE HUMAN EPILEPTIC HIPPOCAMPUS

Extracellular Metabolites in the Cortex and Hippocampus of Epileptic Patients

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Interictal brain energy metabolism and glutamate–glutamine cycling are impaired in epilepsy and may contribute to seizure generation. We used the zero-flow microdialysis method to measure the extracellular levels of glutamate, glutamine, and the major energy substrates glucose and lactate in the epileptogenic and the nonepileptogenic cortex and hippocampus of 38 awake epileptic patients during the interictal period. Depth electrodes attached to microdialysis probes were used to identify the epileptogenic and the nonepileptogenic sites. The epileptogenic hippocampus had surprisingly high basal glutamate levels, low glutamine/glutamate ratio, high lac-

tate levels, and indication for poor glucose utilization. The epileptogenic cortex had only marginally increased glutamate levels. We propose that interictal energy deficiency in the epileptogenic hippocampus could contribute to impaired glutamate reuptake and glutamate–glutamine cycling, resulting in persistently increased extracellular glutamate, glial and neuronal toxicity, increased lactate production together with poor lactate and glucose utilization, and ultimately worsening energy metabolism. Our data suggest that a different neurometabolic process underlies the neocortical epilepsies.

COMMENTARY

Glutamate is the principal excitatory neurotransmitter in mammalian brain and has long been implicated in the generation of epileptic discharges. Administration of glutamate or glutamate analogues to experimental animals can elicit seizures, whereas glutamate antagonists are both anti-convulsant and neuroprotective (1). Glutamate receptor subunits are upregulated in hippocampal tissue resected from patients with chronic temporal lobe epilepsies; electrophysiological recordings from human epileptic hippocampal slice preparations demonstrate a glutamate-dependent hyperexcitability; and in vivo microdialysis studies show an elevation in extracellular glutamate during seizures (2). These observations point to glutamate as potentially crucial in the generation and maintenance of seizures in localization-related epilepsies.

Glutamate is synthesized from glutamine in glutamatergic neurons via the action of the enzyme glutaminase and, follow-

ing synaptic release, is removed into both nerve terminals and glial cells by selective energy-dependent transporters. Glial cells subsequently reconvert glutamate into glutamine, via the enzyme glutamine synthetase, and glutamine is finally transferred to glutamatergic neurons, completing the so-called glutamate–glutamine cycle (3). Glutamate homeostasis is critical to the normal functioning of the nervous system, and in this regard, glial glutamate uptake is believed to be of principal importance (4). Glutamate is not only a neurotransmitter but also an excitotoxic agent that, in high concentrations, has the potential to cause cell death. As a result, it is maintained at low levels in the extracellular fluid of the brain by efficient, but energetically expensive uptake into glial cells.

The evidence to support glutamatergic dysfunction in temporal lobe epilepsies is compelling and yet, until recently, has been largely circumstantial. Although seizures are almost certainly associated with increased extracellular glutamate concentrations, with the potential for localized glial and neuronal damage, the source of elevated glutamate and the distinction between cause and effect have proved elusive. Much of the understanding to date has come from animal models, which may not adequately mirror the human situation, or from the ex vivo

analysis of surgical and postmortem tissue, which is subject to a multitude of confounding factors. However, recent advances in brain imaging and the ongoing development of intracerebral microdialysis for human use, pioneered by During and Spencer in the 1990s (5), have significantly improved the ability to perform real-time investigations of brain neurochemistry in disease states.

A recent study by Cavus and colleagues employed intracerebral microdialysis to investigate extracellular concentrations of glutamate, glutamine, and the major energy substrates, glucose and lactate, in epileptogenic and nonepileptogenic regions of the hippocampus and cortex in conscious epilepsy patients during the interictal period. The investigators reported elevated glutamate levels in the epileptogenic hippocampus, together with a low glutamine/glutamate ratio, increased lactate, and evidence of reduced glucose utilization. Interestingly, these phenomena did not extend to epileptogenic regions of the cortex. This is the first study to report concentrations of multiple seizure-related neurometabolites in conscious epilepsy patients and serves to confirm many previously held suspicions. The authors hypothesized that an unspecified energy deprivation, possibly related to mitochondrial injury, could be responsible for the neurochemical profile observed. Energy deficiency could, in theory, lead to functional impairment of both glutamate transporters and glutamine synthetase, which could in turn result in poor glutamate clearance from the synapse and an increase in the nonvesicular release of glutamate from the glial compartment, leading to neurotoxicity and poor utilization of available glucose and lactate.

This hypothesis is supported by previous observations of hypometabolism in the epileptic focus (6) and reduced activity of glutamine synthetase in surgically excised epileptic tissue (7). However, several questions remain to be answered. Because glutamate is causal to the generation of seizures and is chronically elevated in the epileptogenic hippocampus, one would expect seizures and neurotoxicity to propagate uninterrupted—unless some type of protective mechanism is equally upregulated. Similarly, the suggestion that energy deprivation leads to glutamatergic dysfunction, and thereby impaired glucose utilization, would appear to be a circular argument and difficult to reconcile in the absence of evidence to support ever-worsening energy metabolism and the catastrophic failure of local neuronal function. The 10-fold variation in basal glutamate concentrations in the epileptogenic hippocampus, from low normal values to neurotoxic levels, would suggest considerable heterogeneity in the study population, sufficient to question the experimental

design and statistical power of the investigation. Finally, the potentially confounding influence of antiepileptic drug treatment cannot be taken lightly. Although the authors did not observe any specific drug-related effects, possibly as a result of the low number of patients analyzed and the use of combination therapy, subanalyses based on principal drug mechanisms or comparison with untreated individuals may have been more revealing.

Intracerebral microdialysis may offer significant advantages over previous investigational approaches by providing a direct measure of brain metabolite concentrations in living subjects, without the confounding influence of general anesthesia or the inherent limitations of *ex vivo* tissue analysis. The differences in hippocampal and cortical neurochemistry reported in this study are intriguing and not only merit further investigation but also may, in time, encourage consideration of focal epilepsies in terms of their distinctive neurobiology rather than just their anatomical localization. If nothing else, the use of microdialysis in conscious epilepsy patients should begin to offer unprecedented insights into the neurochemistry of the epileptic focus.

by Graeme J. Sills, PhD

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