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Research Report

Metabolic changes in rat striatum following convulsive seizures

Olivier Darbin[a], Jean Jacque Risso[b], Emily Carre[b], Michel Lonjon[c], Dean K. Naritoku[a,d,*]

[a]Department of Neurology, Southern Illinois University School of Medicine, PO Box 19637, Springfield, IL 62794-9637, USA
[b]Department of Neurochemistry, IMNSSA, HIA St Anne, Toulon Naval, France
[c]Department of Neurosurgery, Hopital Pasteur, Nice, France
[d]Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL 62794-9637, USA

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Abstract

Generalized convulsive seizures increase glucose utilization within the brain but their impact on metabolism is not well known. The striatum receives excitatory input from widespread sources in the brain and could potentially reflect energy depletion in the brain resulting from generalized seizures. We utilized multiprobe microdialysis in freely moving rats subjected to maximal electroshock to simultaneously measure glucose, lactate, and pyruvate levels in the interstitial space within striatum and in peripheral subcutaneous tissue. A brief convulsive seizure was associated with marked changes in striatal and peripheral metabolism during the post-ictal state that lasted up to 1 h. There were significant central and peripheral elevations of glucose, pyruvate, and lactate, reflecting increased glucose metabolism. Interestingly, the lactate-to-pyruvate ratio increased significantly in the periphery but remained unchanged in the striatum. Thus, there appears to be brain mechanisms that maintain adequate energy sources and prevent anaerobic shift during the post-ictal state.

Theme: Brain metabolism and blood flow
Topic: Epilepsy: human studies and animal models

Keywords: Epilepsy; Electroshock; Glycolysis; Glucose; Lactate; Pyruvate; Basal ganglia; Sub-cutaneous; Microdialysis; Metabolism

1. Introduction

Generalized convulsive seizures are associated with severe and excessive neuronal firing that place large metabolic demands on the central nervous system but their impact on brain glucose utilization and energy metabolism are not well characterized. Some studies have examined specific parameters of glucose metabolism related to seizures, such as glucose uptake [10], endogenous glucose [27], or lactate [18]. However, measurement of multiple parameters is necessary to provide a better characterization of glucose metabolism, especially with respect to glucose availability and balance between aerobic and anaerobic metabolism. In addition, studies examining glucose uptake have generally utilized prolonged seizures [14] or status epilepticus [15]. This strategy would not provide temporal resolution of metabolic and energetic changes related to a single seizure, and changes occurring during status epilepticus may not applicable to the post-ictal state following a typical seizure.

Under physiological conditions, brain energy demand is met primarily by the consumption of glucose. Thus, increases in pyruvate, the product of glycolysis, reflect increased brain metabolic activity. Subsequently, pyruvate can be metabolized anaerobically into lactate or undergo oxidative phosphorylation. A balance is maintained between aerobic and anaerobic metabolism in order to optimize ATP production and to limit lactate production. Increases in the lactate-to-pyruvate ratio suggest a relative increase of anaerobic metabolism.

* Corresponding author. Department of Neurology, Southern Illinois University School of Medicine, PO Box 19637, Springfield, IL 62794-9637, USA. Fax: +1 217 545 8039.
E-mail address: dnaritoku@siumed.edu (D.K. Naritoku).

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Microdialysis may be used to monitor the extracellular level of energetic metabolites. Simultaneous measurement of glucose, lactate, pyruvate levels, and the lactate/pyruvate ratio in the extracellular space provides pertinent information on local glucose availability and its utilization [11,20,30]. Comparison of changes in the central nervous system (CNS) to the periphery can be used to examine how brain tissue may adapt its energy needs. The ability to perform repeated samplings allows temporal correlation of metabolic changes to specific brain events.

Maximal electroshock (MES) is a well-established model of generalized tonic–clonic convulsions in rodents. As opposed to focal onset seizures, MES evokes widespread involvement of cerebral cortex, possibly secondary to activation of the brainstem reticular core and propagation to the forebrain [7,8,13]. The generalized activity may be observed behaviorally and electrographically and is characterized by hypersynchronous firing activities of cortical neurons. The striatum is a core brain structure that receives excitatory input from most regions of cerebral cortex and thus is affected by cortical firing during a seizure [6]. Benzodiazepine receptors show rapid changes following convulsive seizures in the Mongolian gerbil, which are most pronounced in the striatum [2] and increases in GABA concentration are seen in striatum following electroshock-induced convulsions [5]. In addition, indices of oxidative stress, i.e., lipid peroxidation and protein carbonyls, are reduced in striatum following electroshock [3]. As a result, striatal metabolism would be expected to change greatly following a generalized convulsive seizures [23,24]. To explore the impact of generalized convulsive activity on brain metabolism during the post-ictal state, we administered MES to awake rats and simultaneously measured glucose, lactate and pyruvate levels in the interstitial space of striatum and subcutaneous tissue using multiprobe microdialysis sampling.

2. Materials and methods

2.1. Surgery

Male Sprague–Dawley rats (Harlan) weighing 280–320 g at the time of surgery were used. They were housed at 21 ± 0.5 °C in individual cages under a 12–12-h light–dark cycle (lights on from 07:00 h to 19:00 h) with free access to food and water. At least 1 week prior to experiment, the rats were anesthetized with ketamine (85 mg/kg) and xylazine (3 mg/kg) administered intraperitoneally. Animals were positioned in a stereotaxic apparatus. Small cavities were drilled into the cranial bone for receiving microdialysis guide and screws for mechanical stability. Intracerebral guide cannulas were stereotaxically implanted in the striatum (A: 7.89 mm, L: 2.5 mm, H: 2.5 mm, according the atlas of Koning and Klippel [16]) and fixed with dental cement on the skull surface.

2.2. Equipment stand for multiprobe microdialysis

The apparatus utilized for microdialysis and electrophysiological recording was based on a multiprobe microdialysis stand described previously [11]. In brief, three legs around the rat cage supported a rotating Plexiglas circular plate. A potentiometer located at the center of the plate monitored the rotating behavior of the rat using a fine metal rod attached to the head. As the animal rotated, the signal generated by the potentiometer controlled a servomotor, which turned the rotating plate in the same direction as the rat movement. Both the microdialysis pump (CMA120; Phymep, France) and collector (CMA140; Phymep, France) were located on the plate and turned as a function of the rat behavior. An electrical swivel (Mercator, USA) connected the power supply to the microdialysis equipment and conveyed information to the computer data acquisition system.

2.3. Microdialysis protocol design

Central microdialysis probes (CMA12 3 mm, CMA-USA) were perfused with an artificial CSF at a rate of 1.5 μl/min (composition in mM: 147.0 Na^+, 4.0 K^+, 1.0 Mg^{2+}, 1.2 Ca^{2+}, and 153.2 Cl^-) (CMA, USA). A peripheral microdialysis (CMA 20) probe was implanted subcutaneously in the back and perfused at a rate of 1.5 μl/min with a fluid for subcutaneous tissue (composition in mM: 147.0 Na^+, 4.0 K^+, 2.3 Ca^{2+}, and 156 Cl^-) (CMA, USA). Microdialysis probes were placed under low anesthesia using O_2 (97%) and halothane (3%) breathing mixture during 3 to 5 min. Five hours after anesthesia, samples were obtained for 1 h to measure baseline levels. Samples were collected in 15-min intervals from each location. Test animals were subjected to MES, which consisted in a single train of AC current (50 mA, 500 Hz, 500 ms) provided by a constant current stimulator (Wahlquist, Utah, USA) and delivered by earclip electrodes. Post-ictal sampling of dialysate was performed each 15 min for 1 h following the seizure. Control animals were handled similarly and received application of earclip electrodes, but not electroshock.

2.4. Sample and data analysis

Analysis of CSF dialysate for glucose, lactate, and pyruvate was performed with enzymatic kits (CMA, Phymep, France) and an automatic microdialysis analyzer (CMA600, Phymep, France). Data were expressed in median and 25th–75th percentile. The Mann–Whitney test was used for inter-group comparisons and the Wilcoxon test was used for intra-group comparisons. Post hoc comparisons between groups were performed using the Mann–