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BRAIN RESEARCH

Research Report

Remarkable increase in ^{14}C-acetate uptake in an epilepsy model rat brain induced by lithium–pilocarpine

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ABSTRACT

The present study demonstrates changes in rat brain glial metabolism during the acute phase of epilepsy. Status epilepticus (SE) was induced using the lithium–pilocarpine model. Glial metabolism was measured with ^{14}C-acetate. Local cerebral blood flow and glucose metabolism were also measured using ^{14}C-N-isopropyl-p-iodoamphetamine (IMP) and ^{14}C-2-deoxyglucose (2DG), respectively. At the initiation of the seizure, ^{14}C-acetate uptake did not change significantly. However, a marked increase was observed 2 h after the pilocarpine injection in all brain regions studied. The increase of brain uptake was transient, and the maximum enhancement was seen at 2 h after the pilocarpine injection. The increase of ^{14}C-acetate uptake was almost to the same degree in all regions, whereas ^{14}C-IMP and ^{14}C-2DG uptakes showed a heterogeneous increase. In the case of ^{14}C-IMP, the highest increase was observed in the thalamus (280%), and a moderate increase (120 to 150%) was seen in the orbital cortex, cingulate cortex and pyriform cortex. ^{14}C-2DG uptake increased by 130 to 240% in most regions of the brain, however, an increase of only 40 and 20% was observed in the cerebellum and pons-medulla, respectively. These results demonstrated that glial energy metabolism was markedly enhanced during a prolonged seizure. To our knowledge, this study is the first observation showing large and widespread glial metabolic increases in the rat brain during status epilepticus.

1. Introduction

Although the role of glia in seizures is not well known, it has been suggested that glia may be involved in epileptogenesis. Focal glial dysfunction in the cortex leads to focal epileptiform discharges and sometimes convulsions (Willoughby et al., 2003). Reactive gliosis is a prominent morphological feature of temporal lobe epilepsy (Castiglioni et al., 1990; Garzillo and Mello, 2002). Recent findings have demonstrated that, in the course of temporal lobe epilepsy, glia not only undergo structural alterations, but also display distinct functional changes. A reduction of the inward rectifying potassium currents in glia within epileptic tissue has been identified, which may alter potassium homeostasis (Steinhäuser and Seifert, 2002). The metabolic trafficking between neurons and glia, for example, the glutamine–glutamate cycle, is particularly important for neuroprotection. Glutamate, which is primarily synthesized and stored in glutamatergic neurons,

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is released on excitation, and removed mostly by uptake into astrocytes (Berl and Clarke, 1969). Subsequently, glutamate is converted into glutamine by the astrocyte-specific enzyme glutamine synthetase (Norenberg and Martinez-Hernandez, 1979), and cycled back to neurons. Furthermore, metabolic disturbances in glutamate–glutamine cycle have been reported in a model of temporal lobe epilepsy (Melø et al., 2005).

The cerebral metabolism of acetate takes place in glia (Berl and Clarke, 1969; Muir et al., 1986; Hassel et al., 1992, 1997; Waniewski and Martin, 1998), and incorporation of a label from exogenous acetate has been used to study glial metabolism in the central nervous system (Badar-Goffer et al., 1990; Cerdan et al., 1990). ^{14}C-acetate is converted to ^{14}C-acetyl CoA, and then oxidatively metabolized in the tricarboxylic acid (TCA) cycle. Glutamine is rapidly labeled by the conversion of α-ketoglutarate to glutamate and the subsequent action of the synthetic enzyme, glutamine synthetase. The maximum specific activity of glutamine was seen at 5 min after intravenous injection of ^{14}C-acetate and then declined slowly with a half-life of more than as hour in cat brain (Berl and Frigyesi, 1969). Approximately 80% of label remaining in the tissue at 5 min was contained in the amino acids glutamate and glutamine. Thoren et al.(2005) reported the maximum specific labeling of glutamine was produced at 5 min after injection, with similar valued seen at 10 min in rat brain. Furthermore, with an experimental period of 5 min, ^{14}C-acetate uptake in rat brain was reported to reflect mainly metabolism via the small glutamate compartment (Dienel et al., 2001, Cruz et al., 2005). We previously found that ^{14}C-acetate uptake in the rat brain appears to occur in parallel with glial energy metabolism and reflects glial conditions (Hosoi et al., 2004). Micro-infusion of fluorocitrate, a selective glial toxin (Paulsen et al., 1987, Hassel et al., 1992), into the rat striatum caused a significant and dose-related decrease in ^{14}C-acetate uptake in the same region (Hosoi et al., 2004). Also we have recently reported that the brain uptake of ^{14}C-acetate was very sensitive to brain ischemia (Hosoi et al., 2007). Immediately after only 3 min of middle cerebral artery occlusion (MCAO) and reperfusion, ^{14}C-acetate uptake showed a significant (about 50%) and reversible reduction in the rat striatum (ischemic core), which indicated even such a short-term brain ischemia caused depression of glial metabolism. In this way it seems that ^{14}C-acetate uptake is an appropriate marker for investigating putative abnormalities in glial energy metabolism in intact brain.

It has been reported that there is interictal hypometabolism in temporal lobe epilepsy (TLE) patients as well as in epileptic animals (Ryvlin et al., 1991; Foldvary et al., 1999; Dubé et al., 2001). On the other hand, during status epilepticus (SE), large and sustained increases of glucose metabolism were recorded in various experimental models of severe seizures or SE (Ingvar, 1986; Handforth and Treiman, 1995). Glial metabolism, however, has only been reported as unchanged in the latent phase of the Li–pilocarpine (Melø et al., 2005) and kainate model (Müller et al., 2000). Therefore, the aim of the present study is to examine glial metabolism in acute phase in the SE rat brain. SE was induced in rats by the administration

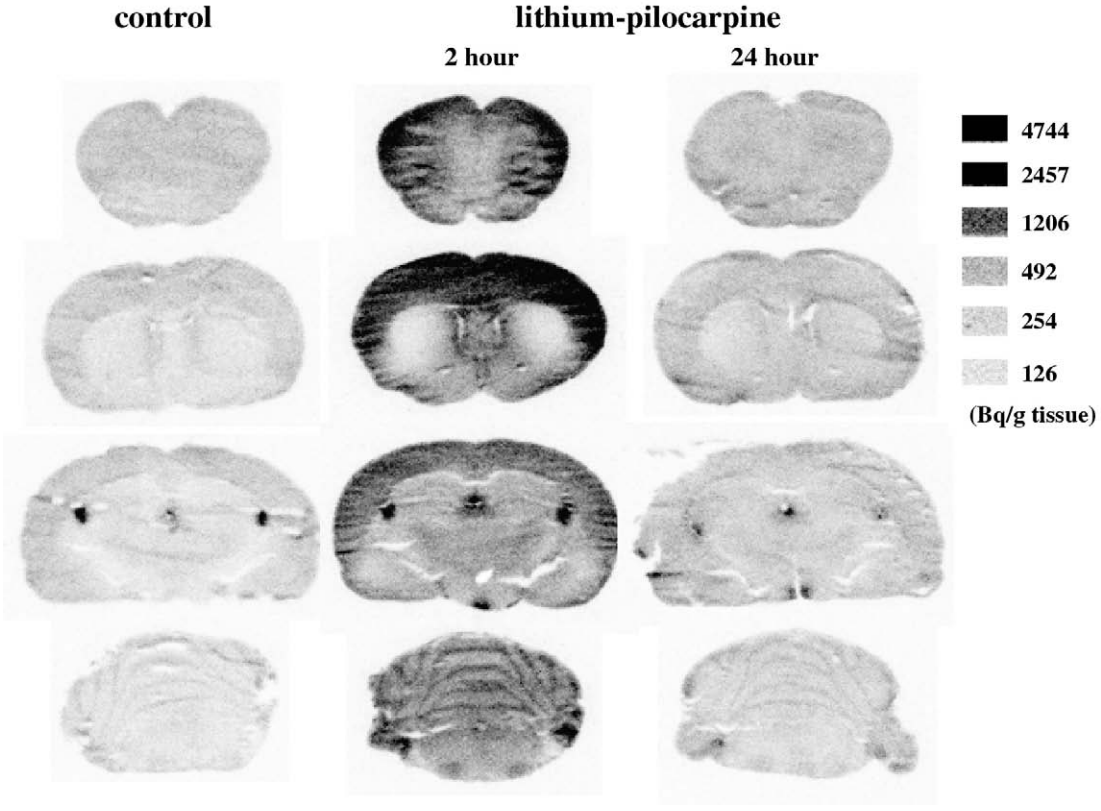

Fig. 1 – Typical autoradiograms of ^{14}C-acetate in the brain of the lithium–pilocarpine model rat.