NAA Is Reduced During the Latent Period Preceding Pilocarpine-Induced Epilepsy

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Introduction:

Reductions in N-acetyl aspartate (NAA) have proven useful for the lateralization and localization of seizure foci in patients with intractable temporal lobe epilepsy (TLE) (1). Substantial evidence also indicates that metabolic defects may contribute to the development of epilepsy (2), suggesting that hippocampal NAA content might serve as a useful prognostic indicator for epileptogenesis. Since most TLE patients to date have been studied only after years of intractable seizures, it is unclear, if the deficits in NAA precede the onset of overt seizures or, alternatively, are solely a consequence of chronic, intractable seizures. To determine when the reductions in NAA occur, we used the pilocarpine rat model of human TLE (3). This model shares many common cellular and behavioral changes with human TLE including: an initial insult, a protracted latent period largely free of overt seizures and ultimate progression to chronic, spontaneous seizure activity.

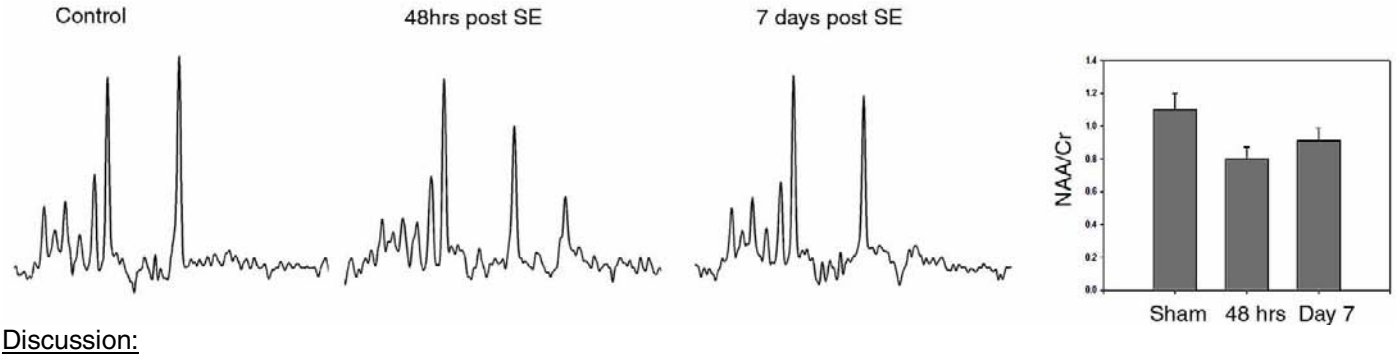
Methods:

Male Sprague-Dawley rats (275-300g) were pretreated with scopolamine (1 mg/kg in 0.9% saline s.c.) 30 minutes prior to the induction of status epilepticus (SE) using pilocarpine (375 mg/kg in 0.9% saline i.p.). SE was terminated after 1 hour with diazepam (4 mg/kg i.p.). Control rats received sham-injections of 0.9% saline (n=4 control rats). The severity of the SE was graded according to Racine (4), and rats with severe generalized seizures (stages 3, 4 and 5) were included for analysis (n=11). Two and seven days post-SE, spectroscopic images (SI) were acquired with a Varian INOVA 9.4T system. The SI was acquired with a modified LASER sequence using TE=60 ms to minimize contributions from amino acids and macromolecules with the NAA resonance. SI data were acquired with a slice thickness of 1.25 mm, 24X24 encodes over a field of view of 30x30 mm^2 providing a nominal voxel volume of ~2ul. Data were reconstructed, using voxel-shifting methods to yield spectra confined to 3 voxels within each hippocampus (6 voxels total per rat).

Results:

Displayed in Fig. 1 are spectra summed from the six hippocampal pixels, in a sham injected animal (control) and 2 and 7 days post-SE in a pilocarpine treated rat. NAA is significantly reduced after both 2 days post-SE (27.5±6.9% decrease, $p<0.001$) and 7 days post-SE (17.3±6.9% decrease, $p<0.001$) in comparison to sham-injected controls (Fig. 1).

Fig. 1



Discussion:

Hippocampal NAA content in a rat model of TLE is significantly reduced during the latent period prior to the development of overt spontaneous seizures. It is unlikely that the reduction in NAA is due to solely to neuron loss since neuronal loss is reported to be minimal after the pilocarpine dose used in this study (5). Further, the recovery of NAA observed seven days post-SE suggests that the initial decline cannot be entirely attributed to acute cell loss. While the initial episode of SE causes an acute decline in NAA, the normal turnover time of NAA in rat brain is 13 hours (6) and complete normalization should occur by seven days if NAA synthesis in neuronal mitochondria is maintained. Thus persistent reduction of NAA at seven days post-SE reflects, at least in part, ongoing impairment of mitochondrial function during the latent period, before the onset of spontaneous seizures. The presence of decreased NAA during the latent period suggests that spectroscopic studies of NAA provide an early marker of the processes underlying the development of epilepsy, prior to the manifestation of overt seizures. If validated in patients, this would provide a non-invasive method for evaluating and identifying those patients at risk to develop epilepsy following a first provoked seizure.

References:

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