^{1}H-MRS changes in the rat brain due to circadian cycle

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Introduction

Circadian rhythms have impact in many physiological processes, which can result in different drug response and toxicity, depending on the time of the day. The sensitivity of the central nervous system to various stimuli including pharmacological agents and neurotoxicants may also be dependant on the phase of the circadian cycle and this may be due to variations in the activity of neurotransmitters and other neural systems. The goal of this study was to evaluate diurnal changes in neurometabolite profiles in naïve rats measured using non-invasive magnetic resonance spectroscopy (MRS).

Methods

Male Sprague-Dawley rats (69.0 ± 1.5 days old, 367 ± 31 g) were subjected to MRS starting one hour after light onset (7 am, N = 5, AM group) or offset (7 pm, N = 5, PM group) during the regular light cycle. Animals were anesthetized with isoflurane (1-2% in oxygen at 1 L/min) and the body temperature was maintained at 37.0 ± 0.8°C. MRS was performed using a Bruker BioSpec 7T/30 system with a 72 mm bird-cage transmit and a 4-channel brain phased array receive coil (Bruker BioSpin). PRESS sequence (TE = 8 ms, TR = 2.5 s, NA = 16) was used with VAPOR water suppression and voxel positioned at the left anterior hippocampus. Shimming was performed using FASTMAP. Dynamic spectra were acquired for 2 hours. Individual spectra were summed together in a groups of 16 to provide effective NA = 256 (10.5 min/averaged spectrum). LCModel software was used to extract metabolite concentrations from individual spectra and the statistical analysis was performed using ANOVA.

Results

Averaged results among all animals are shown in Fig. 1. Concentrations of glutamate, N-acetylaspartate, taurine, and choline were all significantly lower in AM group comparing to PM group (2 hrs after light onset or offset, that is 8:00 AM or 8:00 PM). However, at the end of scanning (3 hrs after light onset or offset, 9:00 AM or 9:00 PM) all these differences disappeared. Concentrations of other significant neurometabolites (GABA, creatine, glutamine, and myo-inositol) were not significantly different between groups at any time point.

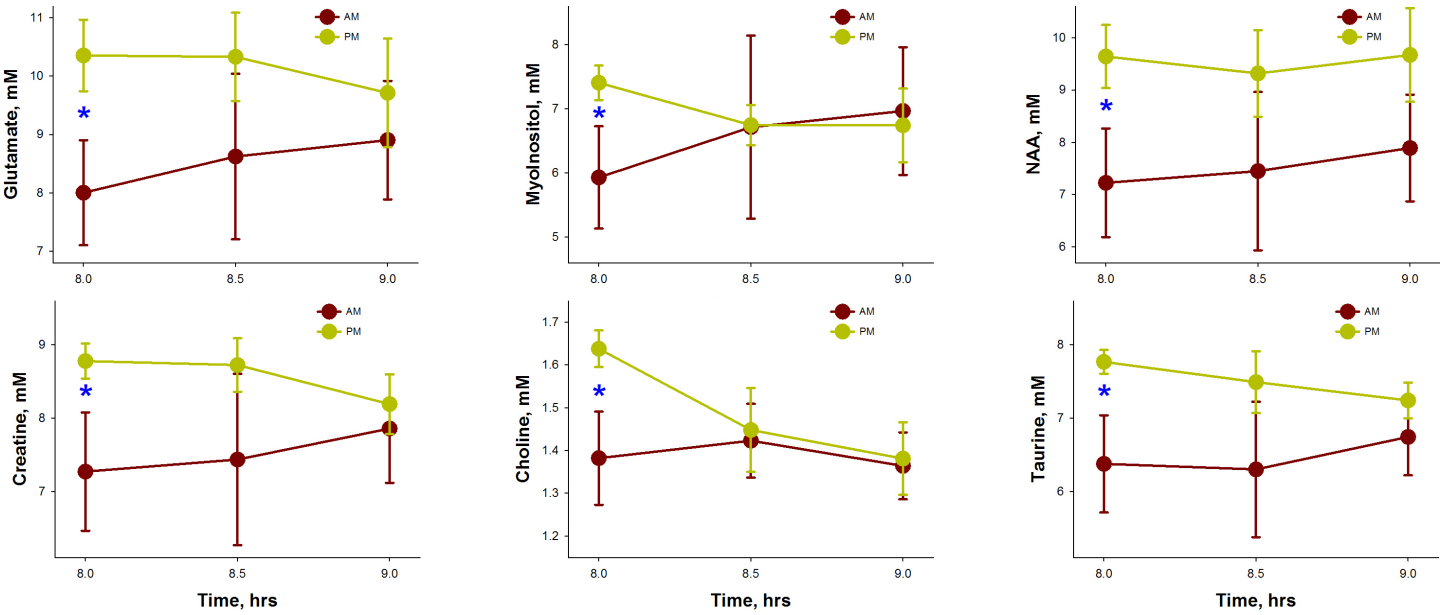

Figure 1. Dynamic changes of neurometabolites measured using proton MRS 2 hours after light onset or offset (8:00 AM or 8:00 PM) in the left anterior hippocampus of naïve rats. * - significant difference between groups (P < 0.05).

Discussion

These data demonstrate that brain neurochemical composition is influenced by diurnal variation which may be one of the mechanisms underlying circadian fluctuations in neurotoxicity and sensitivity to pharmacological neuromodulators. Systemically higher concentrations of measured metabolites may be related to the awaken state of rats after light offset as they are nocturnal animals. The data also suggest that the studies using MRS and especially those related to the development of MRS biomarkers for pharmacological and toxicological research should take the circadian cycle into account.