1H MRS profiling at 9.4T in prefrontal cortex and hippocampus of ethanol dependent rats during intoxication, withdrawal and protracted abstinence

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Introduction

Understanding the pathophysiology of addictive disorders is critical for development of new treatments. Alcohol-induced systems adaptations that persist independently of continued drug use are particularly relevant for susceptibility to relapse, the major clinical problem in alcoholism, but biomarkers for such a 'post-dependent' state are lacking. Experimental alcohol vapor intoxication of laboratory animals allows us to emulate a level, pattern and duration of brain exposure that shares key features with what occurs in clinical alcoholism. Thus, daily exposure cycles for seven weeks with intermittent alcohol intoxication leads to persistent neuroplasticity, functional tolerance to alcohol and changes in behavioral responses, similar to key symptoms seen in alcoholics. Alterations in brain metabolism associated with long-term abstinence have so far not been identified.

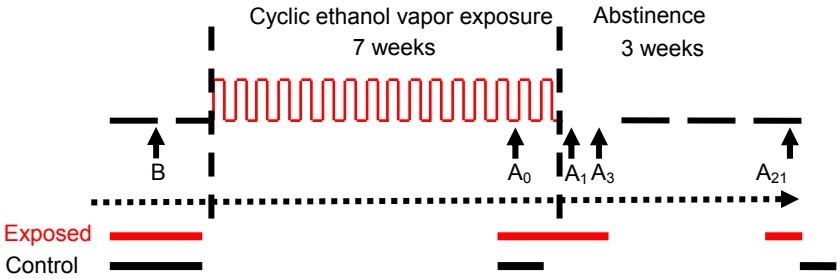

Fig. 1: Experimental design and timecourse of MRS- measurements

Here, we assessed metabolic profiles in two brain regions with functional importance for dependence, i.e. medial prefrontal cortex (PFC) and hippocampus (HI), using in vivo single-voxel 1H magnetic resonance spectroscopy on a 9.4 T scanner

Methods

Animals (8 exposed, 9 controls) were made dependent by exposure to 45 daily exposure cycles with peak levels up to 4 g/l blood alcohol concentration. Five in vivo MRS recordings were obtained in a within subject, repeated measurement design, i.e. at baseline, during alcohol intoxication (at cycle 41/42), during withdrawal (12 and 60 hr after the last exposure cycle) and after 3 weeks of abstinence. Non-exposed control subjects were assessed in a similar manner. Spectra were acquired using Point Resolved Spectroscopy (PRESS) at an echotime of 10 ms from a 12l and a 16µl Volume fro the PFC and HI respectively. Quantification was done with LCMODEL by fitting the in vivo spectra to phantom data of 16 different metabolites. Concentration values were referenced to an unsupressed water signal acquired from the same voxel.

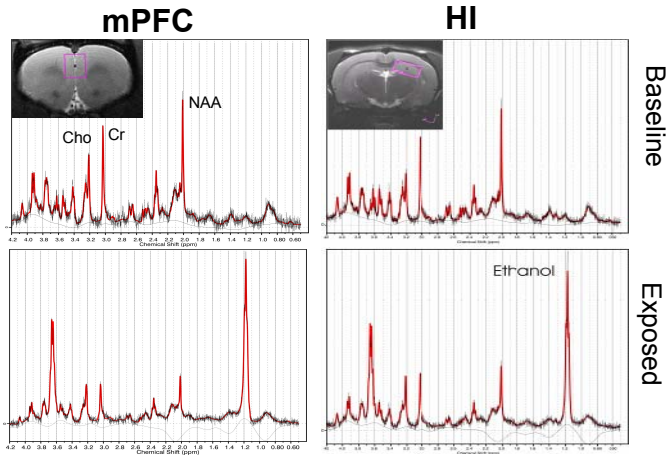

Fig. 2: Typical 1H MRS Spectra before and during ethanol exposure

Results

Preliminary results confirm findings from human alcoholics, i.e. reduced myoinositol and N-acetylaspartate levels as well as increased total choline-containing compounds during intoxication [1,2]. Raised glutamate levels are found during early withdrawal, which is in line with the well-established hyperexitability during alcohol withdrawal. Interestingly, with the exception of taurine, all metabolites returned to control levels in the animals after 3 weeks of abstinence. Whether taurine is an informative marker for the 'post-dependent' state needs further exploration. Furthermore, alterations in the metabolic profile appear more pronounced in the medial prefrontal cortex compared to hippocampus confirming region-specific transcriptome analysis from this model.

Discussion

These results demonstrate the validity of our experimental approach for studying mechanism associated with the pathophysiology of alcoholism, and potentially to monitor the efficacy of pharmacotherapeutic interventions.

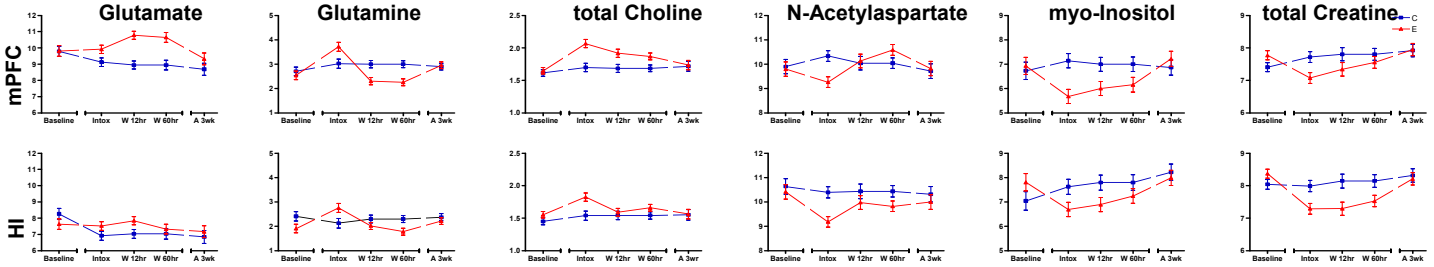

Fig. 3: Timecourse for the measured Metabolite concentrations in both brain regions for exposed animals (red) and controls (blue)

References

[1] Ende G et al. Neuroimage. 2006 Aug 15;32(2):740-6.
[2] Biller A et al. J Cereb Blood Flow Metab. 2009 May;29(5):891-902.