Effect of Acamprosate on Glutamate Level of Alcoholic Subjects

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Introduction

Increased alcohol preference and self-administration have been related, in rodents, to repeated cycles of intoxication and withdrawal. High EtOH preference is suggested to cause a hyperglutamatergic state, which persists beyond acute withdrawal. In alcoholics, such a hyperglutamatergic state might link the acute symptoms of individual withdrawal, which may increase craving and potential for relapse. Therefore, we have hypothesized that by reducing the glutamate level we may reduce the withdrawal symptoms and hence increasing the success of abstinence. Acamprosate both reduces ethanol consumption in alcoholics and purportedly modulates glutamatergic signaling. We present results from an ongoing investigation of this effect on human alcoholic subjects.

Methods

Subjects: We recruited alcoholics with a history of significant withdrawals. All subjects were evaluated to ensure no history of major physical or psychiatric illness in our recruits. The subjects were then randomized to Acamprosate or placebo group for 28 days beginning when the blood alcohol level (BAL) became 0%. A 1,332 mg dose of Acamprosate was initially given every 8 hours for the first three doses to yield a steady state level plasma level in 40 hours when the first Magnetic Resonance Spectroscopy (MRS) was performed.
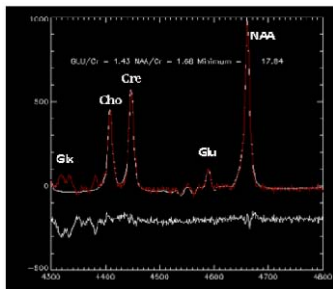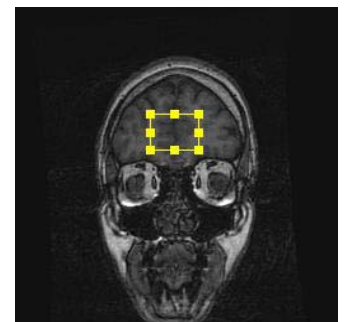
MR Spectroscopy: MRS were collected on a 3T scanner using the echo-time-averaged PRESS sequence [1] with repetition time= 3 s, echo interval = 6 ms, echo number =32, average number = 4. A 2.5x2.5x2.5 cm^3 voxel was placed in the area of anterior cingulate of each subject (Fig. 1). The quantification was performed using an in-house written program (Fig. 2) developed by IDL. The program used individually simulated spectra linearly combined to fit the experimental data, giving the relative ratios of glutamate (Glu) to creatine (Cre) and NAA to creatine.

Results

We have quantified glutamate level of 13 alcoholic subjects on placebo and 11 alcoholic subjects on Acamprosate 48 hours after admission and 28 days after being on placebo or medication. Though no significant differences were observed at the first scan, we found significantly lower glutamate level of those on Acamprosate with respect to those on placebo.
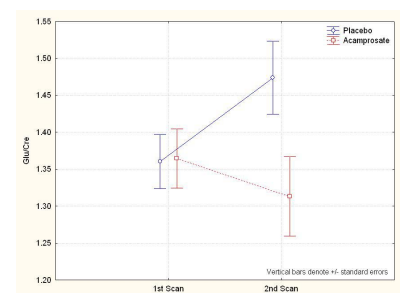
Conclusions

Our early analyses indicate that Acamprosate treatment may indeed reduce brain glutamate offering potential for a surrogate marker for clinical efficacy that could be applied to the evaluation of novel candidate treatments for alcoholism.

[1] Hurd et al, MRM, 51:435, 2004.