**Introduction**

Thiamine deficiency (TD), a frequent complication of alcoholism, interferes with normal ingestion of food and may result in brain damage. In chronic alcoholics, neurobehavioral deficits related to TD has been shown to recover during abstinence. However, the mechanism(s) whereby thiamine treatment facilitates recovery of brain functions during detoxification and continued abstinence are not fully understood. Our previous work (1) suggests that TD induced by pyrithiamine causes reliable reductions in brain choline containing compounds, which are reversed in a dose-dependent fashion subsequent to thiamine administration. These studies are also consistent with findings in detoxifying alcoholic patients during abstinence. In this work we examine the changes in brain Cho-containing compound(s) during pyrithiamine-induced TD in the rat and its reversal with the administration of thiamine, followed by chemical identification of specific choline compounds derived from brain extracts.

**Experiments**

In-vivo localized proton MRS experiments were performed using a 4.7T/440 Spectroscopy Imaging Systems Corporation (SISCO) imaging spectrometer. Localized proton spectra were acquired from a ROI (4x4x4 mm) inside the brain by using a STEAM sequence (TR/TE:3000/68ms). Body temperature was kept at 37°C throughout the experiment by using a circulating heated water. Normal (n=6), TD (n=6), and thiamine treated (n=6) rats were prepared as before (1). Rats were sacrificed by microwave irradiation (5kW) focused on the head for a duration of 2sec. The brain was removed immediately and ground in a mortar containing liquid N2. Metabolite extraction was done according to a modification of the Blight-Dyer technique (2), using a mixture of chloroform/methanol/water at a proportion of 2:2:1. In vitro spectra were acquired on a DRX500 Bruker spectrometer with TR=15sec, NA=8, 450 pulse width, and TSP as an internal standard for chemical shift and concentration.

**Results**

The change in Cho-containing compounds was reliably present in all animals by 12 days of pyrithiamine injection, while no significant change occurred in either Cr or NAA peaks. It also shows an increase/recovery in Cho when TD rats were scanned 2 hours after administration of thiamine (lower dosage was used in this study (1)). GPC, PC, and choline could be easily identified by their peaks at 3.24, 3.23, and 3.21 ppm, respectively, in the brain extract spectra. Table 1 shows the concentration of metabolites in three different groups of rats, demonstrating GPC was the main component responsible for the observed decrease in Cho peak in TD rat brain.

**Discussion**

TD, a frequent complication of alcoholism, contributes significantly to alcohol-induced brain damage. TD is accompanied by diverse changes in intermediary metabolism, including decreased lipid incorporation into myelin and marked alterations in the biosynthesis and turnover of several putative neurotransmitters, all of which may contribute to the neurotoxic effects of ethanol. TD results in decreased decarboxylation by ketoglutarate dehydrogenase and pyruvate dehydrogenase leading to failure of ATP synthesis, and in diminished transketolase activity which impairs cellular capacity to produce sufficient quantities of biosynthetic reducing equivalents. In pyrithiamine-induced TD in the rat monitored over time with proton magnetic resonance spectroscopy, we have shown a decrease in brain concentration of GPC and recovery in Cho with thiamine replenishment. These findings suggest that a reduction in GPC may be relevant to the primary biochemical lesion in TD, and are compatible with reduced catabolism of choline metabolites (4). Consequently, this data is compatible with the hypothesis that a decrease in choline compounds is the cause of the biochemical abnormalities which precedes neuroanatomical damage characteristic of Wernicke's encephalopathy (5).

**References**


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| Table 1. Concentration of metabolites in rat brain. * thiamine treatment, mean±SD (μmol/wet g) |
|--------------------------------------|--------------|----------------|----------------|----------------|
| GPC       | PC           | Cho           | PCr/Cr         | NAA            |
| norm      | 0.46±0.06   | 0.23±0.04    | 0.05±0.02      | 8.00±0.91      | 5.90±0.77       |
| TD        | 0.12±0.03   | 0.24±0.03    | 0.08±0.04      | 7.72±0.84      | 5.52±0.89       |
| thiamine* | 0.25±0.06   | 0.24±0.04    | 0.06±0.02      | 7.57±1.10      | 5.33±0.64       |