The brain ethanol binding potential and its effect on the ethanol ^{1}H methyl MRS amplitude

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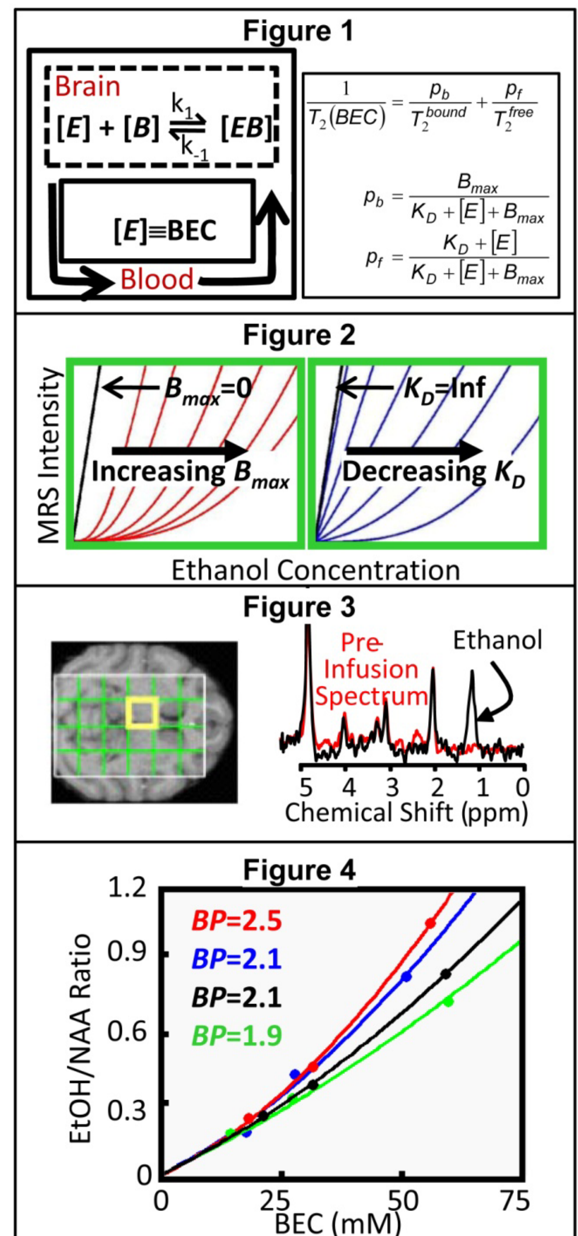
Introduction *In vivo* magnetic resonance spectroscopy (MRS) can provide a direct quantitative measure of brain ethanol following its systemic administration [1]. Through this approach, it has been reported that the amplitude of the methyl ^{1}H resonance relates to tolerance to ethanol's intoxicating effects. Specifically, ethanol tolerance is associated with increased MRS signal intensity per unit brain ethanol concentration [2]. It has been suggested that ethanol MRS amplitude could vary with tolerance through changes in the methyl ^{1}H T_2 value [3], however no biophysical mechanism linking ethanol pharmacology to ethanol methyl ^{1}H spin relaxation has been described. Herein, a relationship between the ethanol brain binding potential (*BP*) and methyl ^{1}H T_2 value is proposed based on the assumption that brain ethanol exchanges rapidly between macromolecule-bound and unbound states. Experimental support for the proposed relationship is provided from MRS measurements following intravenous (I.V.) administration of varying quantities of ethanol in four ethanol-naïve rhesus macaques.

Model Ethanol is presumed to exert its pharmacological effect by binding to brain macromolecular constituents (Fig. 1). In the bound state, rotational diffusion is hindered, which is expected to result in a reduced methyl ^{1}H T_2 value relative to free ethanol. Under conditions of fast exchange, $1/T_2^{free} - 1/T_2^{bound} << k_1 + k_{-1}$, the ethanol methyl ^{1}H T_2 dependence on ethanol concentration may be expressed in terms of the concentration of ethanol binding sites in the brain, $B_{max} = [B] + [EB]$, and the dissociation constant $K_D = [E][B]/[EB]$, as given by the formulas in Fig. 1 (right). The brain ethanol binding potential is equal to the ratio $BP = B_{max}/K_D$. As shown in Fig. 2, non-zero *BP* manifests as a non-linear increase in MRS intensity with increasing ethanol concentration, measured via the blood ethanol concentration (BEC).

Methods Four macaque monkeys served as subjects. Each was I.V. infused with 0.5, 1.0, and 1.5 g/kg ethanol on three occasions (separated in time by a minimum of 1 week). Using a Siemens 3T trio with an extremity RF coil, T_1-weighted images were acquired, followed by single-plane chemical shift imaging (8 mm isotropic voxels, TE=150 ms, TR=1770 ms). Following acquisition of baseline spectra, CSI data were acquired following ethanol infusion for 1 hour. Ethanol MRS amplitude was quantified from pre/post-infusion difference spectra integrated between 1.0 and 1.5 ppm (Fig. 3). A blood sample was obtained from the saphenous vein within 45 minutes following ethanol injection. Due to differences in the ethanol ^{1}H methyl T_2 between brain tissue, and CSF [3], image segmentation procedures were implemented to subtract the estimated CSF contribution of ethanol MRS amplitude [4].



Results and Conclusion In Fig. 4, the ethanol methyl resonance amplitude, expressed relative to *N*-acetylaspartate (NAA) methyl resonance amplitude, is shown following three separate I.V. infusions for four rhesus macaques. *BP* values using the Fig. 1 expressions are given for each monkey, and the fitted result is shown (Fig. 4 solid lines). In each case, the ethanol MRS amplitude exhibits a non-linear dependence on BEC. These results are consistent with a non-zero brain ethanol *BP*. The possibility therefore exists that tolerance to the intoxicating effects of ethanol is mechanistically linked to large MRS amplitude at a given ethanol concentration through a reduction in brain ethanol *BP*.

References **1.** Mason, G, et al., ACER, 2005,29:150-158. **2.** Chiu, T-M, et al., MRM, 1994,32:511-516. **3.** Sammi, MK, et al., MRM, 2000,44:35-40. **4.** Hetherington, HP, et al., MRM, 1999,42:1019-1026.