Proton MRS at 3 tesla reveals altered neurochemistry in smokers

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Introduction

Tobacco smoking is the largest preventable cause of disease and premature death world wide [1]. While insight into the neurobehavioral mechanisms of nicotine action is growing, little has been done to determine the vulnerability of adult brain tissue to nicotine exposure. In rodents nicotine reduces neurogenesis and increases cell loss in both hippocampus and cortex. The first investigation in smokers employing voxel based morphometry and region of interest analyses reported reduced gray matter volumes and densities in the prefrontal cortex bilaterally, the left dorsal anterior cingulate cortex, and the cerebellum, as compared to nonsmokers [2]. Except for one published study employing in vivo MR spectroscopy in alcohol dependent tobacco smokers [3], to our knowledge no reports exist of neurochemical brain alterations associated with chronic smoking in otherwise healthy subjects.

Methods

Thirteen smokers and 13 nonsmokers matched for age, gender and education were recruited through newspaper advertisements. All subjects gave written informed consent. They were free of medical, neurological, psychiatric and substance abuse disorders other than nicotine dependence. Smoking behavior was measured using a dedicated questionnaire. MR measurements were carried out with a 3T-scanner (MEDSPEC 30/100, Bruker Medical) using a birdcage coil. Following T_1-weighted imaging of the brain at a resolution of 1 x 1 x 1.5 mm^3, MR spectra were acquired using PRESS (T_R = 3 s, T_E = 80 ms, n = 128) from two brain voxels, one (2 x 3 x 2 cm^3) including the left hippocampus, the other (2.5 x 4 x 2 cm^3) including the anterior cingulate gyrus (AC). Metabolite quantification relied on a time domain-frequency domain program package [4] involving automatic retrospective frequency drift correction, non-parametric background estimation, and uncertainty assessment using a Bayesian approach [5]. Choline-containing compounds (tCho), total creatine (tCr), NAA, and glutamate concentrations were quantified, including phantom spectra and prior knowledge for frequency, linewidth and phase. For quantification an external water phantom was used, and fitted amplitudes were corrected for relaxation times (measured in vivo), coil loading differences, and CSF content of the voxels as deduced from segmentation of the T_1-weighted images using SPM99, thus giving concentrations in mmol per liter of brain tissue.

Results and Discussion

No significant differences in the mean metabolite levels between smokers and nonsmokers were found in the AC voxel. Fig. 1 shows the respective values for the left hippocampus voxel. The only significant difference in concentrations was the NAA level in this voxel being lower in smokers than in nonsmokers ((11.2 ± 1.2) mmol/l *vs.* (12.2 ± 0.8) mmol/l, p = 0.023, mean uncertainty for NAA quantification, 2.6 %). The data were tested for correlations between brain metabolite concentrations and the magnitude of lifetime exposure to active tobacco smoking (pack-years, with one pack per day for 10 years equaling 10 pack-years). The concentration of tCho in the AC voxel was positively correlated with the amount of smoking (Fig. 2, p = 0.002). No statistically significant correlations between the other metabolites and smoking parameters were detected.

The observed reduction in hippocampal NAA concentration is in line with growing evidence that hippocampal neurons are susceptible to neurotoxic effects of nicotine. Since nicotine has a pivotal role in the formation of dendrite branches and spine density, the reduced hippocampal NAA concentration may reflect disturbed synaptic formation following the chronic nicotine exposure in smokers. The lack of a similar finding for the AC is consistent with data showing that adult rats exhibit a hierarchical brain vulnerability to nicotine with the highest sensitivity of the hippocampus, followed by the cerebral cortex and the midbrain [6]. The observed higher tCho levels in the AC of subjects with higher lifetime cigarette consumption may indicate membrane alterations or gliosis in cortical regions of heavy smokers.

References

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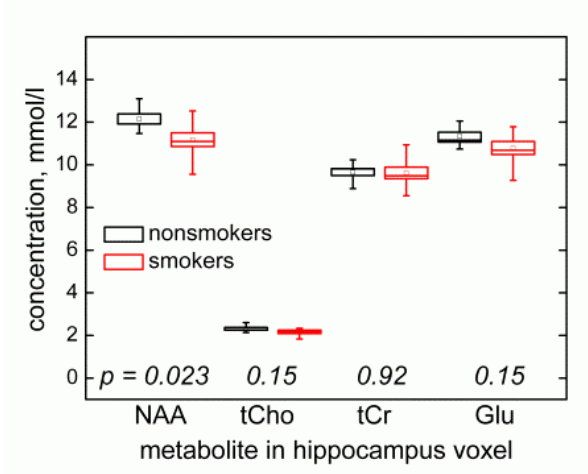

Fig. 1. Comparison of metabolite levels in the hippocampus voxel of smokers and nonsmokers.

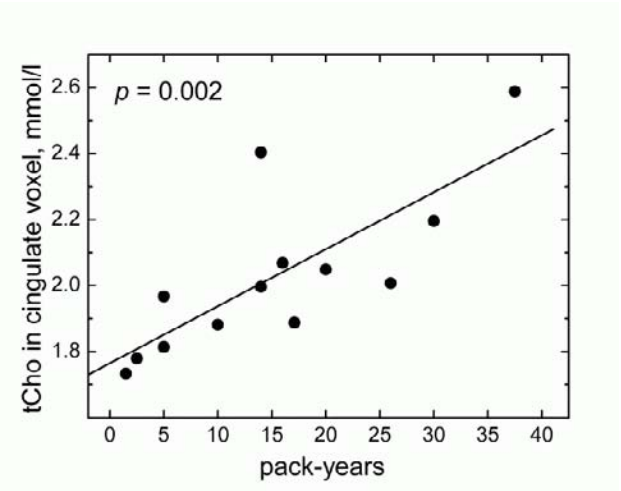

Fig. 2. Correlation of tCho concentration in AC with amount of smoking.