Effects of DTNBP1 (dysbindin) gene variants on hippocampal glutamate concentration determined by MRS at 3 T

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Introduction

In linkage and association studies the DTNBP1 gene has been identified as a major susceptibility gene for schizophrenia [1]. Reduced expression of DTNBP1 was found in the hippocampus and prefrontal cortex in post mortem brains of schizophrenic patients [2]. In vitro and animal models provide evidence that the DTNBP1 gene product dysbindin modulates the activity of the neurotransmitter glutamate in hippocampal neurons and is crucial for cell functioning and synaptogenesis [3]. This study aims to investigate the effects of genetic variants of DTNBP1 on the status of the glutamate system as well as neuronal integrity (NAA) in the hippocampus and a cortical region, the anterior cingulate cortex (ACC), in humans.

Subjects and Methods

In 79 healthy subjects (43 f, age 33.3 ± 9.4 y) the association of single nucleotide polymorphisms (SNPs) rs760665 and rs909706 with absolute concentrations of glutamate and NAA in the left hippocampus (HC) and the ACC were investigated using proton magnetic resonance spectroscopy at 3 tesla. All subjects gave written informed consent. MR examinations were performed on a 3T-scanner (MEDSPEC 30/100, Bruker Medical) using a circularly polarized head coil. Following $T_1$-weighted imaging of the whole brain at a resolution of 1 x 1 x 1.5 mm³, proton spectra were acquired using PRESS ($T_E = 80$ ms [4], $T_R = 3$ s, $n = 128$) from voxels of 2 x 3 x 2 cm³ including the left HC and 2.5 x 4 x 2 cm³ including the ACC. For glutamate and NAA quantitation a time domain-frequency domain method was employed involving automatic retrospective frequency and phase drift correction, non-parametric background estimation, and uncertainty assessment using a Bayesian approach that accounts for background fit uncertainty [5]. A measured metabolite basis set and prior knowledge for frequency, linewidth and phase were used in the fitting. For quantitation an external water phantom was used; fitted amplitudes were corrected for effects of $T_2$ (determined in 3 volunteers), coil loading differences, and cerebrospinal fluid content of the voxels (computed from segmentation using SPM2).

Results and Discussion

The genotype distributions were similar to previously reported samples [6]. Hippocampal glutamate concentrations were significantly affected by genotype of rs909706 and rs760665 (figures). For the concentration of NAA, a weak association with rs760665 was observed in the contrast analysis. None of the metabolites measured in the ACC showed a significant connection with the genotypes.

The results support a role of DTNBP1 gene variants for glutamate neurotransmission in the human hippocampus. This is compatible to the view that the association of dysbindin genetic variants in schizophrenia may constitute a dysfunction in glutamatergic neurotransmission in this disorder.

References


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