Glutamate and glutamine concentrations by MRS in adult brain: age and sex dependence

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Introduction

The decline of brain function with healthy aging is accompanied by decreased mitochondrial function including glutamate-glutamine cycle flux [1]. Glutamate induced excitotoxicity is involved in various neurodegenerative disorders. There is evidence that the glutamate+glutamine (Glx) level is altered with the normal aging process of the brain [2], and more advanced studies using higher field strength have shown differential effects on glutamate and glutamine [3]. Steroidal sex hormones have been shown to influence the cerebral glutamate-glutamine metabolism, suggesting sex-related differences of brain glutamate [4]. We sought to determine the effects of age and sex on cerebral glutamate and glutamine concentrations in a large sample of healthy humans using MR spectroscopy at 3 tesla combined with a dedicated quantitation procedure.

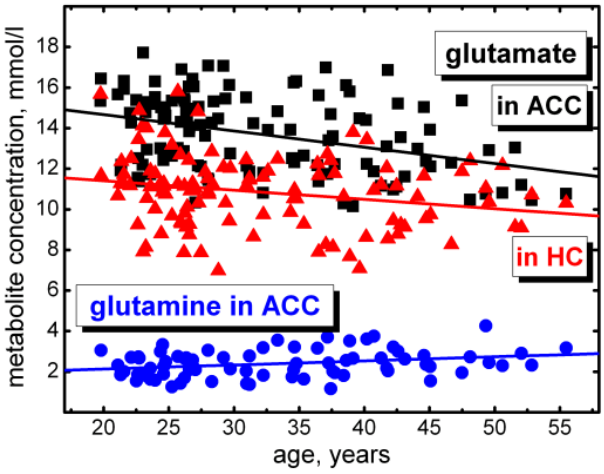
Subjects and Methods

In 118 healthy subjects (age 19.8 – 55.5 y; 32.2 ± 8.8 y; 59 female) ^{1}H-MRS in the left hippocampus and the anterior cingulum was performed. All subjects gave written informed consent. MR examinations were performed on a 3T-scanner (MEDSPEC 30/100, Bruker Medical) using a birdcage coil. Following T_1-weighted imaging of the whole brain at a resolution of 1 x 1 x 1.5 mm^3, proton spectra were acquired using PRESS (T_E = 80 ms, determined as optimal for glutamate detection and separation from glutamine, T_R = 3 s, n = 128) from voxels of 2 x 3 x 2 cm^3 including the left hippocampus (HC) and 2.5 x 4 x 2 cm^3 including the anterior cingulate cortex (ACC). For metabolite 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 accounting for background fit uncertainty [5, 6]. A measured metabolite basis set and prior knowledge for frequency, line width 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, assuming equal values for glutamate and glutamine), coil loading differences, and cerebrospinal fluid content of the voxels (computed from segmentation using SPM2).

Results and Discussion

Uncertainties for the quantification of glutamate were below 20 % for all measurements. Based on this criterion, glutamine in the ACC voxel could be determined in a subset of 79 subjects. A statistically significant sex-related difference of glutamate in the hippocampus ($p < 0.001$) was detected, women exhibiting higher levels. An decline of the concentration of glutamate with age in both voxels was observed (ACC: $r = -0.37$, $p < 0.0001$; HC: $r = -0.227$, $p = 0.016$), whereas glutamine in the ACC was positively correlated with age ($r = 0.288$, $p = 0.01$). In the female subgroup, the age-related decline of glutamate in the ACC was more pronounced than in the male group ($r = -0.551$, $p < 0.0001$). As byproduct, our analysis confirmed the frequently-described drop of the NAA level with age.

The results demonstrate opposite effects of age on glutamate and glutamine, and an effect of sex on glutamate in healthy human cerebellum. They add to the growing evidence for gender specific differences in cerebral neurotransmission, metabolism and structure.



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