Neurochemical profile in the hippocampus of aging mice as detected by *in vivo* ^{1}H NMR spectroscopy at 14.1 T</sup>

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Introduction: The concentration of metabolites in different cerebral areas, so called neurochemical profile, can be taken as biomarker of regional development, differentiation or degeneration. The decline in memory and cognitive function is a normal consequence of aging and is accentuated by neurodegenerative pathologies, such as Alzheimer's disease, which cause progressive deterioration of learning and memory, attention and concentration, use of language, and other mental functions. These aging-associated functional losses may be accompanied by neurochemical alterations that are unknown. The aim of this work was to evaluate the neurochemical alterations in the brain of aging mice. For that, high resolution *in vivo* ^{1}H NMR spectroscopy was employed in a longitudinal way to determine the hippocampal content of 18 metabolites composing the neurochemical profile.

Methods: Localized ^{1}H NMR spectroscopy was performed on a 14.1 T, 26 cm VNMRS spectrometer (Varian, Magnex) using a home-built 8 mm diameter quadrature surface coil (used both for RF excitation and signal reception) as previously described [1]. C57BL/6 mice were anaesthetized under 1 to 2% isoflurane in oxygen gas. Field homogeneity was adjusted by FASTMAP [2], and ^{1}H NMR spectra were acquired from VOIs placed in the hippocampus, using SPECIAL [3] with TE of 2.8 ms and TR of 4 s. Typically, spectra were acquired with 400 scans. Metabolite concentrations were estimated with LCModel [4]. The entire neurochemical profile was analyzed over the aging period with ANOVA with Bonferroni correction. In some cases, linear regression was used to describe the age-dependent observed modifications.

Results: The neurochemical profile composed of 18 metabolites was determined *in vivo* in the mouse hippocampus from young adulthood to 2 years old. Mice are being longitudinally scanned at 3 (n=18), 6 (n=18), 12 (n=10) and 24 (n=3) months of age. Although most metabolite concentrations were stable over time, some metabolites varied their content (figure 1). The total concentration of choline-containing compounds increased linearly age at a rate of 0.007 mmol/kg/month (R^2=0.94, F=33.8, P<0.05). Glutamine concentrations increased at 2 years old compared to the other measured ages (+37±18%, P<0.05 analysis with ANOVA), while glutamate levels were largely unaltered (P>0.10). Taurine concentration increased at a rate of 0.048 mmol/kg/month (R^2=0.97, F=71.4, P<0.05). These preliminary results also show that hippocampal levels of *N*-acetylaspartate (NAA) and glutamate were slightly reduced while total creatine tended to increase with age, although not statistically different (P>0.10 for all).

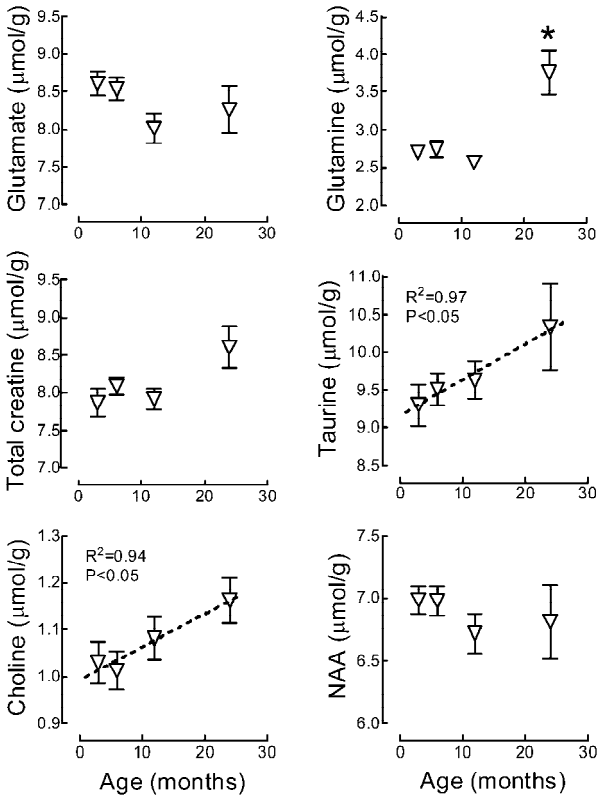

Figure 1. Metabolite concentrations in the mouse hippocampus measured from 3 to 24 months of age. Data shown as mean±SEM. Dashed lines represent significant linear modification of metabolite levels with aging (P<0.05). For glutamine, * P<0.05 compared with the other ages.

Conclusion: The neurochemical profile of the mouse hippocampus has been determined longitudinally for 2 years of age. This is the first report of *in vivo* quantification of 18 metabolite concentrations in the brain of aging mice. These preliminary results suggest that glutamine, taurine and choline-containing compounds can be used as neurochemical markers of brain aging.

References: [1] Kulak (2010) J Neurochem *in press*. [2] Gruetter (1993) MRM 29:804. [3] Mlynárik *et al*. (2008) J Mag Reson 194:163. [4] Provencher (1993) MRM 30:672.

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