

Changes in glucose level with age and its correlation with severity of plaque deposition in a transgenic model of Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in elderly population [1]. Glucose uptake and metabolism has been shown to be impaired during AD and has been proposed to be an important cause of neurodegeneration [2,3]. However the cause of impairment of glucose uptake/metabolism in AD brain and its correlation with plaque deposition is not clear. Transgenic mouse models of AD offer the possibility to systematically follow the correlation between plaque deposition and changes in glucose levels *in vivo*. Till now *in vivo* analysis of glucose in transgenic mouse models of AD has not been attempted. In this study, we applied *in vivo* magnetic resonance spectroscopy (MRS) in combination with *in vivo* magnetic resonance microimaging (μ MRI) to longitudinally monitor the temporal relationship between changes in glucose level and plaque deposition with age in APP_{TG2576} mouse model of AD [4]. Our results clearly show that decline in glucose occur primarily in brain areas which are severely affected with plaque load.

Methods

Ten transgenic (APP_{TG2576}) mice and 9 none-transgenic littermates (WT) were used in this study. All MR measurements were performed at 9.4 T vertical wide-bore imaging systems equipped with a Bruker Avance console and 1000 mT/m gradients. A 20-mm volume imaging coil was used for μ MRI and MRS study. The MR images were acquired using the rapid acquisition with the relaxation enhancement sequence as described previously [5]. *In vivo* spectroscopic data were acquired from the same animals at age 10, 14, 16, and 18 months from hippocampus (hipp), thalamus (thal) and hippocampus cortex (hipp + ctx) regions using the point resolved spectroscopy sequence with TE = 15 ms, TR=3500 ms, number of averages (NA) = 512. Metabolite concentrations were quantified using the LC model and the unsuppressed water signal was used as an internal reference [6]. Metabolites quantified with Cramer-Rao lower bounds (CRLB, estimated error quantification) $\geq 50\%$ were classified as not detected. For immunohistology a WT and an APP_{TG2576} mouse were sacrificed and brain slices (40 μ m) were stained with anti-amyloid β (6E10) antibody [5]. High-resolution magic angle spinning proton MRS (HR-MAS ¹H MRS) was performed with intact hippocampi from 21 month old WT and APP_{TG2576} mice at 4°C at a spinning rate of 2500 rpm using a Carr-Purcell-Meiboom-Gill pulse sequence with RT= 3500 ms and TE= 0.4 ms. 2D spectra were acquired with a correlated spectroscopy sequence.

Results

In vivo analysis of glucose levels with age in the same mice at different brain regions (hipp, hipp+ctx and thal) is shown in Fig. 1. A trend of decrease in glucose/tCr level was clearly observed in hipp and hipp+ctx region between 10 and 18 months of age in transgenic mice as compared to wild-type mice (Fig. 1a-b). A significant decrease in the level of glucose was evident at the age of 18 months in hipp+ctx region (Fig. 1b). This decline was nicely correlated with the severity of the plaque deposition which occurs mainly at the age of 18 month in these mice as was evident in previous longitudinal μ MRI studies [5] (Fig. 2). The decline in glucose in hipp region of APP_{TG2576} mice was also evident in 2D HR-MAS ¹H MR spectrum (data not shown). Interestingly, the level of glucose was not changed in thal region of APP_{TG2576} mice as compared to WT mice at any age (Fig. 1c). Also the thal region did not show any plaque deposition as is evident in Fig. 3. Our results suggest that the decline in glucose level occurs mainly in plaque affected areas of the brain of APP_{TG2576} mice and show that a decline in glucose can be temporally correlated with the increase in plaque deposition in the AD brain.

References: [1] Frank and Galaske et al. Neurobiol Aging 2003; 24: 521-36; [2] Liu and Liu et al., FEBS Lett 2008; 582:359-64; [3] Liu and Iqbal et al., PNAS 2004; 101:10804-09; [4] Hsiao and Chapman et al. Science 1996; 274:99-103; [5] Braakman and Matysik et al., J Magn Reson Imaging 2006; 24: 530-36.

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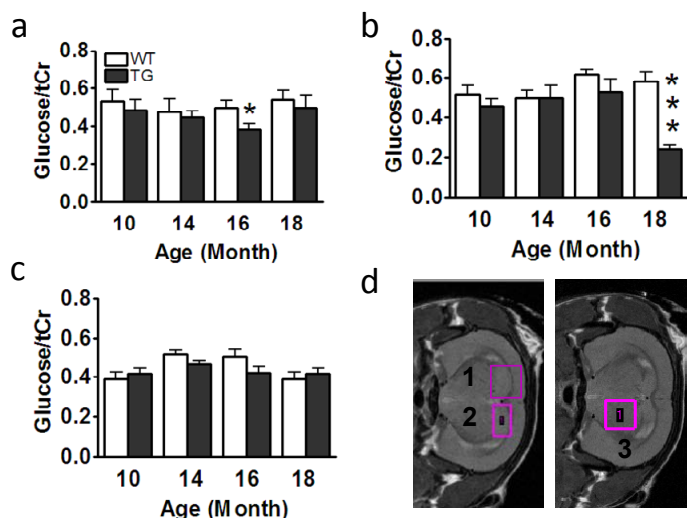


Fig. 1: Change in glucose level in (a) Hipp (1.4x2.2x2 μ L), (b) Hipp+Ctx (2x2x2 μ L), (c) Thal (2x2x2 μ L) regions in WT (open bars) and APP_{TG2576} (gray bars) mice measured longitudinally between 10 and 18 months. (d) MR images showing position of the voxel in: hipp+ctx [1], hipp [2] and thal [3]. Error bars shown are standard deviation of mean. Levels that are significantly different ($p < 0.05$) in APP_{TG2576} mice than control groups at a particular age are marked with a star; * $p < 0.05$, *** $p < 0.001$.

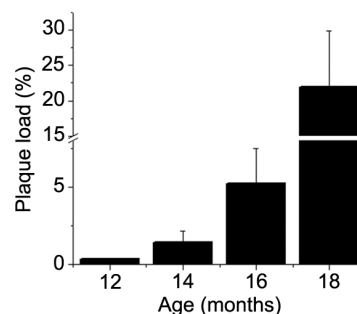


Fig. 2: Age dependent changes in A β plaques load in ctx/hipp region of APP_{TG2576} detected by *in vivo* μ MRI. Data represent mean of n=5 (\pm SD). Plaque load was quantified using SCIL-image software [5].

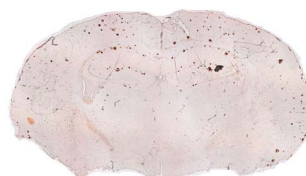


Fig. 3: Immunohistochemical detection of A β plaques in APP_{TG2576} mouse. Plaques are visible in hippocampus and cortex region. However there are no plaques in thalamus region.