Coupling ^{18}F-deoxyglucose PET imaging and MRS at 14T of the in vivo GLUT8 knockout mouse brain

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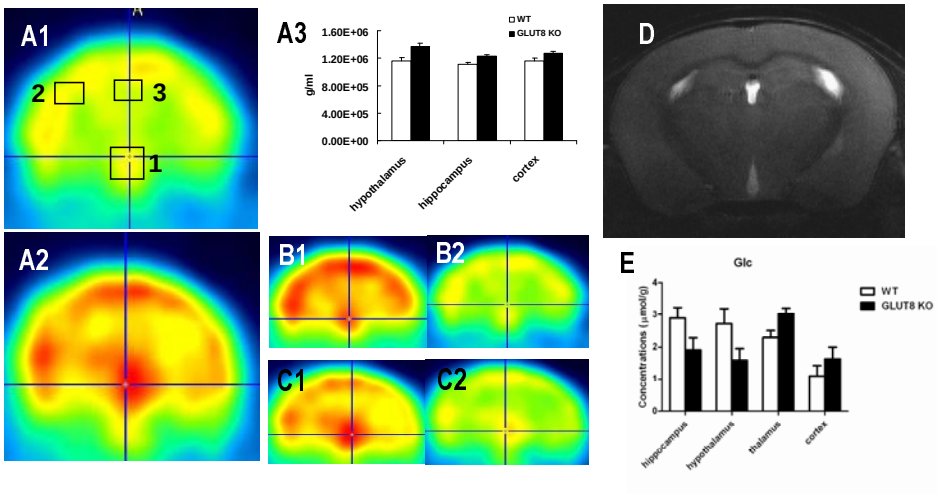
Introduction

The physiological function of GLUT8, a recently characterized high-affinity (2mM) glucose transporter expressed in brain, heart, testis and liver (1) still remains uncertain. The goal of this study was to explore whether GLUT8 functions as a glucose transporter under resting physiological conditions using high resolution, in vivo dynamic and steady-state imaging of ^{18}FDG in brain of GLUT8 knockout (GLUT KO) mice and their wild type (WT) counterparts.

Methods

Subsequent to magnetic resonance spectroscopic measurements and imaging in a 14.1T/26cm scanner (Varian/Magnex Scientific) mice underwent positron emission tomographic imaging using an avalanche photodiode detector-based LabPET 4 scanner (GammaMedica, Sherbrooke, Canada) achieving a reconstructed volumetric spatial resolution of better than 2.2 µl. For this study we used the glucose analogue 2-[18F]Fluoro-2-deoxy-D-glucose (FDG), a biochemical marker of glucose uptake. ^{18}FDG dynamic scans (45 min) followed by ^{18}FDG steady-state scans (60 min) were acquired of the brain after an IV bolus injection (30s) in the femoral vein of ~ 50MBq. Storage of coincidence events in list mode files underwent histogramming for image reconstruction (2). Post processing of images was performed using PMOD. GLUT8 KO mice were backcrossed with C57Bl/6 (n=5) and WT (C57Bl/6, n=4) mice (1) were anesthetized with isofluorane (1%, 1 L/min O_2) and vital signs were continuously monitored throughout the scans. Images were semi-quantitated of accumulated intracellular ^{18}FDG-6-phosphate using standardized uptake values (SUV), expressed as [mean ROI activity (kBq/cm^3)]/[injected dose (kBq)/body weight (g). The injected dose per body weight was comparable between WT and GLUT8 KO mice, indicating comparable amounts of ^{18}FDG entering the systemic blood. Values of SUV therefore allowed comparisons of accumulated intracellular ^{18}FDG-6-phosphate at steady state between WT and GLUT8 KO mice, as well as comparisons between dynamic (D) and steady-state (st-st) phases of glucose uptake in a given animal. SUV was appropriately color-scaled in the figures, red being maximum.



Panel A: full field view at steady-state of ^{18}FDG PET images in the coronal plane of brain from WT (A1) and GLUT8 KO (A2) mice, located approximately at Bregma position -2.30mm (3). Regions: 1, hypothalamus; 2, cortex; 3, hippocampus; SUV values (A3) by brain region. **Panel B**: Dynamic phase of ^{18}FDG imaging of WT brain, i.e. substrate uptake and substrate phosphorylation (B1) compared to steady-state phase (B2), i.e. accumulation of phosphorylated substrate and washout of excess ^{18}FDG. **Panel C**: the same as in Panel B but for GLUT8 KO mouse brain. **Panel D**: T_2-weighted image corresponding to the Bregma position in panel A. **Panel E**: Localized ^{1}H MRS (4) determined levels of glucose (Glc) by brain region in WT (white bar) and GLUT8 KO mice.

Results and Discussion

The distribution and magnitude of phosphorylated ^{18}FDG, and thereby of glucose uptake in brain at steady-state in GLUT8 KO mice was heterogeneous and *increased* in hypothalamus, cortex and hippocampus (panel A2) relative to WT mice (panel A1). This increase is quantitatively summarized in panel A3. ^{18}FDG uptake was also modulated in the heart and endocrine organs in GLUT8 KO mice relative to WT mice (results not shown). These observations were unexpected and surprising in light of: (1) the current view that GLUT8 is localized to an intracellular storage site (5); and (2) that regions where modulation of ^{18}FDG uptake in GLUT KO mice was measured correspond to regions where GLUT8 is expressed, e.g. hypothalamus, hippocampus and heart. These differences could not be attributed to excess extracellular ^{18}FDG judging from washout of non-phosphorylated substrate that occurs during the transition from dynamic to steady-state phases of ^{18}FDG uptake (panels B and C), nor to differences in glycemia between WT and GLUT8 KO mice (1). Glucose content in hippocampus, hypothalamus and cortex (panel E) was not statistically significant ($p>0.05$) between groups suggesting that normal glucose homeostasis is maintained in the absence of GLUT8. It remains to be explored whether ^{18}FDG uptake in brain of GLUT8 KO mice may in part reflect up-regulation of other GLUT isoforms or alternatively of glucose transport across intracellular membranes (6).

References (1) Membrez et al., Molecular and Cellular Biology, 2006, 26, 4268-4276; (2) Lecomte et al., IEEE Transactions on Nuclear Science, 2004, 51, 696-704; (3) Paxinos and Franklin, The mouse brain in stereotaxic coordinates, Academic Press 2004; (4) Mlynarik et al., MRM, 2006, 19, 544-553; (5) Widmer et al., Endocrinology, 2005, 146,4727-4736; (6) Augustin et al., Traffic, 2005, 6, 1196-1212. Supported by the Centre d'Imagerie Biomédicale (CIBM) of the UNIL, UNIGE, CHUV, EPFL and the Leenaards and Jeantet Foundations.