Direct comparison of glycolytic and oxidative brain metabolism measured by ^{18}FDG-PET and NMR spectroscopy using ^{13}C-labeled glucose

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Introduction

Since the early 90[ies], NMR spectroscopy has proven a unique tool to quantitatively measure the rate of brain TCA cycle (V_{TCA}) using ^{13}C-labeled glucose [1-4]. This *in vivo* approach relies on isotopic labeling of brain metabolites, and is therefore very similar to the measurement of regional cerebral metabolic rate of glucose (rCMRglc) based on ^{18}FDG detection by positron emission tomography (PET). Although the first PET measurements of rCMRglc have been performed more than 25 years ago [5], no direct comparison between NMR spectroscopy and PET has been performed yet. Our purpose has been to perform both measurements in the same area of the monkey brain under identical experimental conditions. NMR-derived V_{TCA} and PET-derived rCMRglc are compared and the interest of a simultaneous measurement is discussed.

Materials and Methods

Animals. Studies were conducted on 2 macaque monkeys (2 NMR and 1 PET experiment for each monkey). Animals were anaesthetized using i.v. infusion of propofol (~200 µg/kg/min), intubated and ventilated.

NMR Data acquisition. NMR Experiments were performed on a 3 Tesla whole-body NMR system (Bruker, Ettlingen, Germany) equipped with a surface ^{1}H probe. T1-weighted MR images were acquired for proper positioning of the 30×10×13mm^3 voxel of interest (VOI) in the center of the brain (Fig.1). After shimming, a baseline ^{1}H PRESS spectrum was acquired (TE/TR = 8/1000ms, 512 transients). Then ^{1}H PRESS spectra were collected during ^{13}C-glucose infusion i.v. (3-min bolus of [U-$^{13}C_6$]glucose followed by 120-min continuous infusion). During the acquisition, blood samples were collected to measure glucose ^{13}C fractional enrichment using high resolution NMR spectroscopy. Finally, 3D proton density MR images (matrix 128x128x128, resolution 1x1x1mm^3) were acquired for registration with ^{18}FDG PET images.

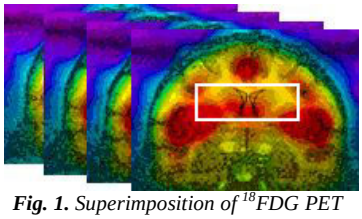

Fig. 1. *Superimposition of ^{18}FDG PET images and T_1 MR images showing the voxel of interest*

PET Data acquisition. PET experiments were performed on a CTI HR+ Exact tomograph (CTI PET Systems, Knoxville, TN) allowing for simultaneous acquisition of 63 slices with an isotropic intrinsic resolution of 4.5mm. Transmission scans were acquired before each study for attenuation correction. Then PET emission scans were collected for 60-min following ^{18}FDG injection i.v. (110 ± 5 MBq). A total of 24 emission scans was obtained. During the acquisition, arterial blood samples were withdrawn to measure arterial radioactivity in a cross-calibrated γ-counter (Cobra Quantum D5003, Perkin-Elmer, France). Time-activity curves were corrected for [^{18}F] decay from the time of injection

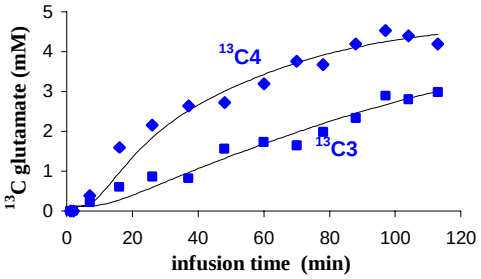

Fig. 2. *Glutamate ^{13}C4 and ^{13}C3 time-courses measured by NMR and best fits (average time-courses, n=4)*

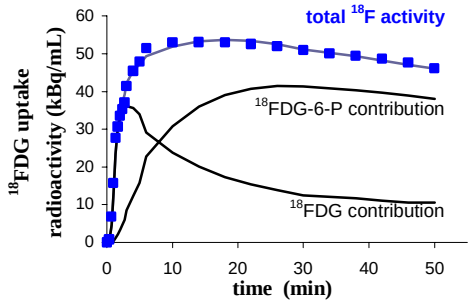

Fig. 3. *^{18}FDG PET time-activity curve measured in the same VOI for one monkey and best fit by the 2-compartment model*

NMR Data processing. ^{13}C incorporation into brain glutamate C4 appeared on ^{1}H PRESS spectra as a decrease in ^{12}C-bonded protons (at 2.35ppm) and a simultaneous increase in ^{13}C-coupled protons (satellite peaks appearing 135Hz away from each other in the absence of ^{13}C decoupling). Glutamate C3 enrichment was detected the same way. Details on the acquisition procedure and on ^{13}C enrichment determination by LCModel have been submitted separately (Boumezbeur, this symposium). A mathematical model was used to fit the experimental data [1], leading to V_{TCA}.

PET Data processing. 3D proton density MR images were registered with 3D reconstructed PET scans (128x128x128) using rigid transformation. Proper superimposition was achieved by maximizing mutual information criterion [6]. The VOI detected by NMR was extracted from the 24 PET images and the corresponding time-activity curve was generated with regional activity calculated for each frame and plotted versus time. For kinetic analysis, a two tissue compartmental model was used (FDG and FDG-6-P respectively) [7,8]. Arterial plasma radioactivity was used as input function. Model constants were identified with a non-linear least square fitting procedure (Pmod software [9]) and the rCMRglc was calculated.

Results

The best fit to Glutamate ^{13}C4 and ^{13}C3 time-courses measured by NMR is shown on Fig. 2. The resulting TCA cycle flux was V_{TCA} = 0.55±0.04 µmol.g^{-1}.min^{-1} (*n=4*). Fig. 3 shows the best fit to ^{18}F activity measured by PET in the same VOI. ^{18}FDG uptake analysis lead to rCMRglc = 0.24±0.01 µmol.g^{-1}.min^{-1} (*n=2*). Both NMR and PET analysis showed a good agreement of experimental data with mathematical models, as demonstrated by the quality of the fits. The corresponding rCMRglc/V_{TCA} ratio was 0.44.

Discussion

Compared with literature values in gray matter, both V_{TCA} and rCMRglc values obtained in this study are rather low [10,11]. The slow metabolism of white matter (46% of brain tissue within the VOI) is very likely to explain these numbers. The [rCMRglc/V_{TCA}] ratio is consistent with the near 1:2 stoichiometry between glycolytic and oxidative metabolisms of glucose. For proper interpretation of this ratio, it must be kept in mind that the V_{TCA} measured using ^{13}C-labeled glucose includes the contribution of all possible substrates of acetyl coenzyme A oxidation. In this context, possible explanations for the [rCMRglc/V_{TCA}] ratio being smaller than 0.5 include the contribution of other substrates to the TCA cycle. Indeed it has been shown recently that acetate and ketone bodies could contribute to 5-10% of brain oxidative metabolism in humans [12,13].

This work is the first reported comparison of metabolic NMR spectroscopy and ^{18}FDG PET measurements performed on the same animals under identical experimental conditions. V_{TCA} directly reflects oxidative metabolism whereas rCMRglc reflects glycolytic metabolism. Therefore combination of both measurements should prove useful for studying possible metabolic uncoupling between glycolytic and oxidative pathways under various conditions (cerebral activation or energy impairment).

References

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