CHANGES OF RATE CONSTANT OF CREATINE KINASE REACTION IN HUMAN BRAIN DURING HYPOGLYCAEMIA MEASURED BY ^{31}P NMR SATURATION TRANSFER

Š. Zbýn[1,2], M. Mandl[2], V. Mlynárik[3], M. Promintzer[2], A. Luger[2], M. Krebs[2], C. Anderwald[2], E. Moser[1], and M. G. Bischof[2]

[1]MR Centre of Excellence, Medical University of Vienna, Vienna, Austria, [2]Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria, [3]Laboratory for Functional and Metabolic Imaging (LIFMET), Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Introduction/Purpose:

The forward rate constant of creatine kinase (CK) reaction was found to be a sensitive parameter for characterizing acute metabolic demands in the brain [1]. The reduced phosphocreatine (PCr)/ATP ratio found in type 1 diabetes mellitus patients (T1DM) [2] indicated at an involvement of the CK reaction. In this study we tested how plasma glucose levels influence the velocity of CK reaction in the brain of T1DM and healthy controls (CON) by using the method of ^{31}P NMR saturation transfer.

Subjects and Methods:

11 T1DM and 6 CON matched for gender, age and body mass index were included in this study. Since the level of glycosylated haemoglobin (HbA1c) in the blood is a suitable long-term marker of hyperglycemia we used it to classify T1DM into two subgroups, well-controlled patients (T1DM-w) with HbA1c < 7% (n=6) and poorly-controlled T1DM patients (T1DM-p) with HbA1c > 8% (n=5). Hyperinsulinemic (1.5 mU·kg^{-1}·min^{-1}) hypoglycemic clamp tests were used to induce hypoglycemia in both CON and T1DM. Saturation transfer measurements were performed at basal conditions, during hypoglycemia and in the subsequent recovery period. For ^{31}P NMR spectroscopy, participants were positioned in a 3-T Medspec DBX (Bruker Biospin, Ettlingen, Germany) whole body system in the supine position, with their heads resting on a 10 cm ^{1}H/^{31}P double tuned transmit/receive standard surface coil. To measure the forward chemical exchange rate constant (k_{for}) of the CK reaction, eight ^{31}P NMR spectra (Fig.1) were recorded with different times of saturation achieved by the BISTRO pulse train repeated 1 to 5 times [3,4]. The k_{for} was calculated according to equation: $k_{for} = (1 - M_\infty/M_0) / T_{1S}$, where M_∞ is the steady-state magnetization of PCr after 10s saturation of γ-ATP, M_0 is the equilibrium PCr magnetization in the absence of γ-ATP irradiation, and T_{1S} is the relaxation time of the PCr resonance in the presence of γ-ATP saturation. For more accurate results, all PCr amplitudes were referred to the amplitude of signal provided by a reference standard sample containing 1M triphenylphosphate + Cr(acac)$_3$ (TPP) and measured with each subject.

Results:

At basal conditions, k_{for} values were not significantly different between T1DM and CON groups (Fig.2). During hypoglycemia, k_{for} remained unchanged in CON and T1DM-w, but was substantially increased in T1DM-p, when compared to CON (p=0.006), T1DM-w (p=0.03), and baseline conditions (p=0.03) (Fig.2). In the post-hypoglycemic recovery period, T1DM-p showed considerably higher k_{for}, when compared to CON (p<0.05), and T1DM-w (p=0.03) (Fig.2). It was found that HbA1c levels of all three groups were positively correlated with k_{for} during hypoglycemia (r=0.47, p=0.02) (Fig.3). HbA1c values were neither significantly related to k_{for} at baseline (r=0.20, p=0.37), nor during recovery period (r=0.39, p=0.07).

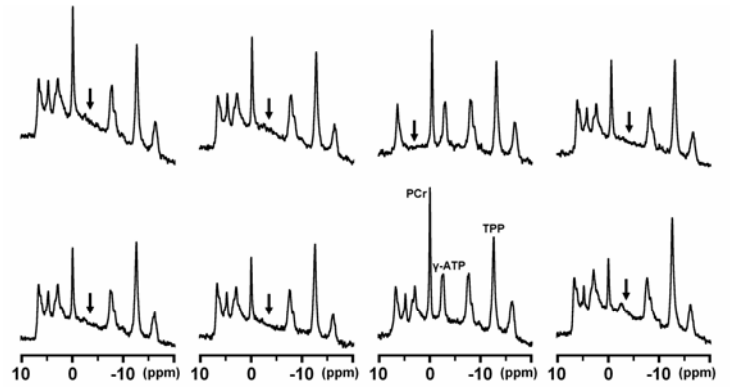

Fig. 1. A series of ^{31}P NMR spectra of human brain obtained using a progressive saturation method. Top from left to right: spectra with saturation time of 0.378 s, 0.756 s, 1.134 s (with the saturation offset symmetric relative to the PCr resonance) and spectrum with 1.134 s irradiation. Bottom: spectra with saturation periods of 1.512 s, 1.890 s, 1.890 s with the saturation offset of 100 kHz and the steady-state spectrum with 10 second saturation. TPP denote a signal of external reference and arrows indicate location of saturation pulses.

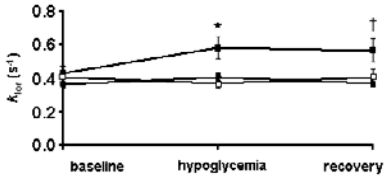

Fig. 2. Values of k_{for} in CON (white boxes), T1DM-w (black circles), and T1DM-p (black boxes) at baseline, during hypoglycemia, and in the recovery period, *p=0.03 vs. baseline, p=0.006 vs. CON, p=0.03 vs. T1DM-w, †p<0.05 vs. CON, p=0.03 vs. T1DM-w.

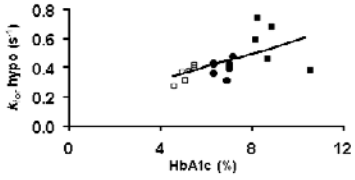

Fig. 3. Correlation (r=0.47, p=0.02) of k_{for} with values of HbA1c during hypoglycemia.

Discussion/Conclusion:

The major finding of this study was an increase of k_{for} in T1DM-p during hypoglycemia while no change was seen in CON and T1DM-w. HbA1c levels were positively correlated with k_{for} during hypoglycemia but not at baseline nor during recovery period. Our findings suggest that the synthesis of ATP from PCr in the brain of T1DM-p patients is increased during hypoglycemia.

References:

[1] Chen W. et al., *Magn Reson Med*, 1997; 38: p. 551-557. [2] Bischof M.G. et al., *Diabetologia*, 2004; 47: p. 648-651.
[3] Luo Y. et al., *Magn Reson Med*, 2001; 45: p. 1095-1102. [4] Mlynárik V. et al., *ISMRM*, 2004