31P MRS study of brain creatine kinase in two different animal models simulating human Alzheimer's disease and vascular dementia

S. Kasparova[1], L. Baciak[1], N. Zilka[2], M. Novak[2], S. Zbyn[3], J. Horecky[4], and T. Liptaj[5]

[1]Analyt. Chemistry, NMR lab, Slovak University of Technology, Bratislava, Slovakia, Slovakia, [2]Institute of Neuroimmunology, Slovak Academy of Science, Bratislava, Slovakia, Slovakia, [3]MR Centre of Excellence, Medical University of Vienna, Viena, Austria, Austria, [4]Slovak Medical University, Bratislava, Slovakia, Slovakia, [5]Slovak University of Technology, Bratislava, Slovakia, Slovakia

Introduction

Creatine kinase (CK) plays a key role in regulation of the ATP level in neural cells. The levels of the brain CK isoform (BB-CK) are reduced in brain due to neurodegeneration in Alzheimer's disease (AD) (1). If the brain CK reaction is inhibited in the model of AD and the ATP turnover correlates with the flux through the CK reaction, then we should be able to monitor cerebral effect of the simulated AD in rats by ^{31}P MRS saturation transfer experiments *in vivo*. Previously we demonstrated that the forward rate constant, k_{for} of the CK in rat brain can be used as an indicator of brain metabolic changes related to an animal model of vascular dementia (VD) (2). To confirm the reduction of the cerebral CK activity, we compared changes of k_{for} in two different AD animal models – in the model of VD and in a transgenic model (TM) based on truncation of the tau protein which is closely associated with AD-typical conformational changes of the tau protein (3).

Materials

The transgene construct was prepared by ligation of a cDNA coding for human tau protein truncated at amino acid positions 151–391, into the mouse Thy-1 gene downstream of the brain promoter/enhancer sequence. Transgenic rats were generated by pronuclear injection of one-day old spontaneous-hypertension-rat (SHR) embryos (3). The rats displayed massive neurofibrillary structures induced by expressed human truncated tau protein (3). The VD model was prepared by 3-vascular occlusion in the rat brain (2). Six groups of Wistar rats (n=8) were used: adult 4-6 and aged >16 month old rats - control groups, adult-SHR as a controls for a transgenic model, adult-TM and finally adult-VD- and aged-VD rats measured on 4th week after occlusion.

Methods

Steady-state parameters of ^{31}P MRS and saturation transfer measurements of k_{for} were performed on a 4.7 T SISCO scanner using 16 mm surface coil with a typical line width of 19-26 Hz in the proton water signal. The saturation transfer measurements were accomplished by DANTE pulse sequence. The k_{for} was fitted to the McConnell equation by nonlinear regression analysis (2): $M_{PCr} = M^0_{PCr}\{1-k_{for}\cdot T_{1sPCr}[1-\exp(-t/T_{1sPCr})]\}$, where M^0_{PCr} is the magnetization of PCr in the absence of γ-ATP saturation, k_{for} is the forward CK reaction rate constant, $(T_{1sPCr})^{-1} = k_{for}+(T_{1sPCr})^{-1}$ is the apparent longitudinal relaxation rate in the presence of γ-ATP saturation, and t is the irradiation time. Quantifications of all ^{31}P MR spectra were provided by jMRUI software AMARES method.

Results & Discussion

We found a significant decrease in k_{for} in both cases of rat model of dementia ($p<0.001$). In TM k_{for} decreased (31%) vs. SHR control rats and surprisingly the same reduction was found in the adult-VD rats (Fig 1, red graph). The VD model in aged rats showed even more significant decrease in k_{for} (42%) relative to aged-controls, however no significant changes in steady-state ^{31}P MRS were observed. The k_{for} remained unchanged in SHR relative to adult rats. In the aged rat brain, k_{for} was also diminished relative to the brain in adult rats perhaps as a consequence of aged related degenerative processes(4). Our findings suggest that k_{for} could reflect a microvascular degeneration in case of aged and aged-VD rats or/and at the same time the dysfunction of the brain CK system under AD conditions which has recently been reported (1) – thus, both models of dementia could be assessed by the same *in vivo* ^{31}P MRS parameter, k_{for}.

We suppose that the CK rate constant could serve as a sensitive *in vivo* MRS indicator of therapeutic efficacy in the case AD and may be used as an early indicator of brain disorders such as cognitive impairment in Alzheimer's disease or vascular dementia.

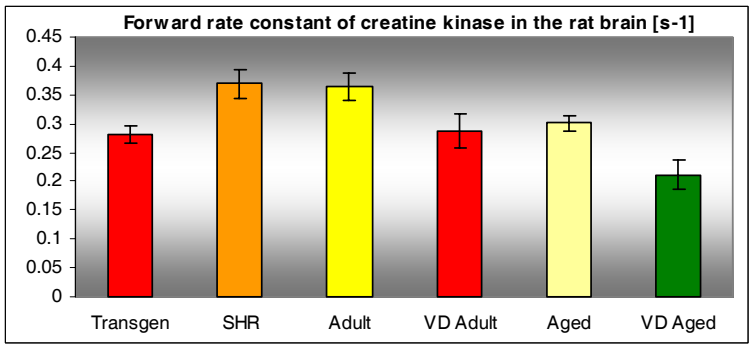

Fig 1. Changes of the rate constant of CK, k_{for} [s^{-1}] in the rat brain by the saturation transfer ^{31}P MRS. ($p<0.001$, AV±SDEV, n=8)

Acknowledgments This work was facilitated by the support of the Slovak State Program of Research and Development No. 2003SP200280203

References

1. Askenov M *et al.* J Neurochem. 74:2520, 2000.
2. Kasparova S *et al.* Neurochem Inter. 46:601, 2005.
3. Zilka N *et al.*FEBS Letters 580:3582, 2006.
4. de la Torre J C. Stroke 33: 1152, 2002.