Implication of myo-inositol metabolic level in an animal model of depression

S-Y. Kim[1,2], C-B. Choi[3], H-S. Lee[4], S-H. Lee[5], D-C. Woo[1,2], and B-Y. Choe[1,2]

[1]Department of Biomedical Engineering, The Catholic University of Korea, Seoul, Korea, Republic of, [2]Research Institute of Biomedical Engineering, Seoul, Korea, Republic of, [3]Department of Radiology, Kyunghee University Medical Center, Seoul, Korea, Republic of, [4]Korea Basic Science Institute, Korea, Republic of, [5]Department of Veterinary Surgery, Konkuk University, Seoul, Korea, Republic of

INTRODUCTION

Animal models for depression are indispensable tools in the search to identify new antidepressant drugs and to provide insights into the neuropathology that underlies the disease state of depression. The forced swimming test (FST) is the most widely used tool for assessing antidepressant activity in rodents due to its reliability across the laboratories. To date, however, the efficiency of antidepressants has been evaluated by only behavioral changes in FST. ^{1}H-MRS has proved to be an extremely versatile technique for detecting metabolic changes in various neuropsychiatry diseases and/or evaluating therapeutic effects. Despite extensive preclinical and clinical investigation for several years, the specific neurobiological processes associated with depression and mechanisms of action of antidepressants are not clearly understood. The purpose of the present study is to assess neurochemical response induced by FST and to evaluate the effects of desipramine (DMI) on left dorsolateral prefrontal cortex (DLPFC) of rat exposed to the FST by using *in vivo* ^{1}H-MRS.

MATERIALS AND METHODS

Animal The design of the FST was very similar to that described by Porsolt et al [1]. The thirty Sprague-Dawley rats (Charles River, Yokohama, Japan) were randomly assigned into three groups (control: N=10; FST + saline: N=10; FST + DMI: N=10). The DMI (10 mg/kg) was dissolved in distilled water (constant volume: 0.5 ml) and administered subcutaneously. The whole experimental protocols are depicted schematically in Fig. 1.

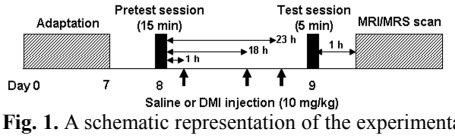

Fig. 1. A schematic representation of the experimental protocols used in this study. DMI: desipramine

In vivo ^{1}H-MRS acquisitions and quantification *In vivo* MR experiments were conducted using a 4.7 T BIOSPEC scanner (Bruker Medical GmbH, Ettlingen, Germany). The position of the VOI was carefully selected based on multislice axial T2-weighted MR images obtained using RARE sequence (TR/TE= 5000/22 ms, mm, NEX = 2) (Fig. 2). All ^{1}H-NMR spectra were obtained from left DLPFC (volume: 27 µl) using PRESS localization technique (TR/TE=3000/20 ms, NEX=512, number of data points=2048, scan time=25 min). *In vivo* proton spectra were analyzed using LCModel [2]. The following 17 metabolites were included in basis set: Ala, Asp, Cr, GABA, Glc, Glu, Gln, GSH, GPC, PCho, mIns, Lac, NAA, NAAG, PCr, Scy, Tau. Metabolite spectra were quantified as ratios to Cr + PCr.

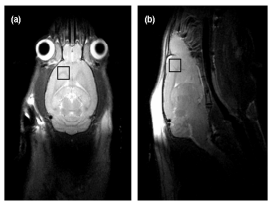

Fig.2. T_2-weighted MR images of the rat brain indicating voxel position in the left DLPFC.

RESULTS

In vivo ^{1}H NMR spectra from the left DLPFC shown in Fig. 3 represents the spectral quality that was consistently achieved in the present study. LCModel analysis of *in vivo* proton spectra obtained from the left DLPFC of the three groups showed significantly higher mIns/(Cr+PCr) ratio in the FST + saline group as compared to control group. In addition, there were significantly lower mIns/(Cr+PCr) ratios in the FST + DMI group as compared to the FST + saline group (Fig. 4). No other metabolites ratios were significantly different among the three groups. Table 1 summarizes our results.

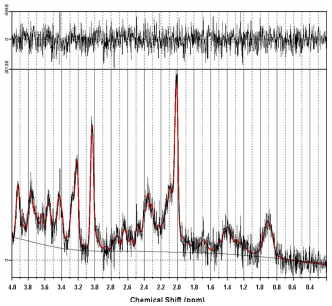

Fig.3. Representative *in vivo* proton spectra obtained from left DLPFC of rat using PRESS localization technique. At the top of plot, the residual signal following LCModel fitting is displayed.

DISCUSSION AND CONCLUSION

To our knowledge, no previous studies have used ^{1}H-MRS to assess neuronal response induced by FST and to evaluate the effects of DMI on brain metabolism of rat. Explanations for the observed higher levels of mIns in the FST + saline group compared to control group include a possible perturbation in the coupling metabolism of the receptor-secondary messenger system complex, thereby providing an important biological substrate to mood disorders [3]. In addition, lower mIns metabolic level in FST+DMI group comared to FST+saline group may be interpreted as that inhibitory effect by DMI treatment modulated the downstream of intracellular events, leading to lowering mIns level. In conclusion, our findings suggest a possible role of altered mIns level within the left DLPFC of rat model for depression.

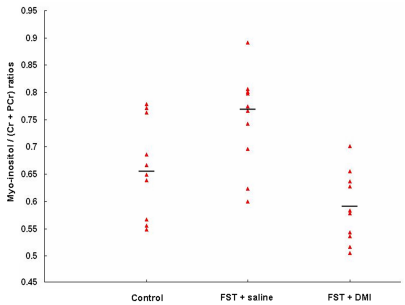

Fig.4. Individual mIns/(Cr+PCr) ratios in left DLPFC of the three group (Control, FST+saline, FST+DMI)

ACKNOWLEDGEMENT

This study was supported by the Korea Health 21 R and D Project, Ministry of Health and Welfare, Republic of Korea (02-PJ3-PG6-EV07-0002) (A081057) and a grant (R01-2007-000-20782-0) from the Purpose Basic Research Grant of the KOSEF and the Korea Research Foundation Grant funded by the Korean Government (KRF-2008-313-D01324 and MEST-2009-0074472) and the program of Basic Atomic Energy Research Institute (BAERI)

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Table 1. Proton metabolites ratios in the left DLPFC of rat and the Cramer-Rao lower boundary

Metabolites	Control (N=10)		FST + saline (N=10)		FST + DMI (N=10)		P-value
	Ratios (/Cr + PCr)	CRLB (%)	Ratios (/Cr + PCr)	CRLB (%)	Ratios (/Cr + PCr)	CRLB (%)	
Glu + Gln	2.1 ± 0.12	6	1.91 ± 0.28	7	1.96 ± 0.21	8	NS
mIns	0.66 ± 0.09	8	0.77 ± 0.08	9	0.59 ± 0.07	10	0.020[a], 0.000[b]
Tau	0.90 ± 0.10	7	0.78 ± 0.13	9	0.78 ± 0.11	10	NS
GPC + PC	0.18 ± 0.02	6	0.17 ± 0.02	8	0.16 ± 0.02	10	NS
NAA	1.32 ± 0.05	3	1.31 ± 0.06	6	1.29 ± 0.07	5	NS

[a] Significant difference between control and FST + saline group

[b] Significant difference between FST + saline + FST + DMI group; NS indicates not significant values.