Neuropsychopharmacology (2006) 31, 2568–2569

www.neuropsychopharmacology.org

Letter to the Editor

Olanzapine Upregulates Genes for S100A8 and S100A9 in the Frontal Cortex of Rats

S Hossein Fatemi*[,1], Teri J Reutiman[1] and Timothy D Folsom[1]

[1]*Department of Psychiatry, Division of Neuroscience Research, University of Minnesota Medical School, Minneapolis, MN, USA*

Neuropsychopharmacology (2006) **31,** 2568–2569. doi:10.1038/sj.npp.1301187

Sir

We read with interest the comments by Drs Manev and Manev (2006) concerning upregulation in two S100 genes, namely S100A8 and S100A9 in the frontal cortex of rats treated chronically by olanzapine (Fatemi *et al*, 2006).

The S100 proteins consist of a superfamily of EF-hand calcium binding proteins, which contribute to various cell signaling pathways by modulating Ca levels and regulating cellular growth, transcription and differentiation, and cell-cycle progression (Heizmann *et al*, 2002). Several members of S100 family like S100A8/A9 and S100B can be secreted from cells and exhibit cytokine-like extracellular functions related to inflammation (Heizmann *et al*, 2002). S100A8 is involved in inflammatory response and associated with oxidative defense (Hsu *et al*, 2005). Glucocorticoids increase constitutive levels of both A8 and A9 forms of S100 mRNA in human monocytes (Hsu *et al*, 2005). Moreover, increases in S100A8 have been associated with several acute and chronic inflammatory conditions and involved in inflammatory demyelination (Chen *et al*, 2002). More recently, significant elevations in levels of several S100 genes (S100A6, A8, A9, A11, A12, S100P, and S100Z) were observed in lymphocytes of patients with Kawasaki disease (Ebihara *et al*, 2005). A recent study implicates S100A9 and S100A12 as being involved in brain plaques observed in Alzheimer's cases (Shepherd *et al*, 2005) alluding to the inflammatory nature of these proteins.

Additionally, a recent report by Svenningsson *et al* (2006) indicated an increase in levels of S100A10 protein (p11) in mouse brains in response to administration of antidepressants. It was also suggested that S100A10 levels were reduced in brains of subjects with depression (Svenningsson *et al*, 2006) and that deficiency in S100A10 protein may be the cause for lack of availability of 5-HT1B receptors in the brain. As to whether elevations in S100A8 and A9 genes are owing to antidepressant effects of olanzapine, or are simply markers of inflammation and oxidative response by brain, will remain to be determined in future studies. Finally, as noted cogently by Drs Manev and Manev, involvement of several members of S100 proteins as markers of brain response to psychotropic agents like fluoxetine (Manev *et al*, 2001), olanzapine (Fatemi *et al*, 2006), imipramine, tranylcypromine, and ECT (Svenningsson *et al*, 2006) may bode well for potential beneficial effects of these proteins in the treatment of several mental disorders.

*Correspondence: Dr SH Fatemi, Department of Psychiatry, Division of Neuroscience Research, University of Minnesota Medical School, MMC 392, 420 Delaware St. SE, Minneapolis, MN 55455, USA,
Tel: +1 612 626 3633, Fax: +1 612 624 8935,
E-mail: fatem002@umn.edu
Received 16 June 2006; accepted 10 July 2006
Online publication: 13 July 2006 at http://www.acnp.org/citations/Npp07130606413/default.pdf

ACKNOWLEDGEMENTS

We acknowledge the generous grant support by Stanley Medical Research Institute to SH Fatemi and the clerical assistance by Ms L Iversen.

REFERENCES

Chen Z, Ge B, Hudson TJ, Rozen R (2002). Microarray analysis of brain RNA in mice with methylenetetrahydrofolate reductase deficiency and hyperhomocysteinemia. *Gene Expr Patterns* **1**: 29–93.

Ebihara T, Endo R, Kikuta H, Ishiguro N, Ma X, Shimazu M *et al* (2005). Differential gene expression of S100 protein family in leucocytes from patients with Kawasaki disease. *Eur J Pediatr* **164**: 427–431.

Fatemi SH, Reutiman TJ, Folsom TD, Bell C, Nos L, Fried P *et al* (2006). Chronic olanzapine treatment causes differential expression of genes in frontal cortex of rats as revealed by DNA microarray technique. *Neuropsycopharmacology* (in press).

Heizmann CW, Fritz G, Schafer BW (2002). S100 proteins: structure, functions and pathology frontiers. *Bioscience* **7**: d1356–d1368.

Hsu K, Passey RJ, Endoh Y, Rahimi F, Youssef P, Yen T *et al* (2005). Regulation of S100 A8 by glucocorticoids. *J Immunol* **174**: 2318–2326.

Manev R, Uz T, Manev H (2001). Fluoxetine increases the content of neurotrophic protein S100β in the rat hippocampus. *Eur J Pharmacol* **420**: R1–R2.

Manev H, Manev R (2006). Olanzapine and S100 proteins. *Neuropsychopharmacology* **31**: 2567.

Shepherd CE, Goyette J, Utter V, Rahimi F, Yang Z, Geezy CL *et al* (2005). Inflammatory S100A9 and S100A12 proteins in Alzheimer's disease. *Neurobiol Aging* (in press).

Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, Yacoubi ME *et al* (2006). Alterations in 5-HT1B receptor function by p11 in depression-like states. *Science* **311**: 77–80.