Effects of antidepressants and mood stabilizers on serum levels of adiponectin

Naoto Omata [1], Tetsuhito Murata [1], Kosuke Narita [2], Nobuyuki Maruoka [1], Hironori Mitsuya [1], Kayo Mita [1], Takefumi Nishimoto [1], Makoto Sato [3], Yuji Wada [1]

1 Department of Neuropsychiatry, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
2 Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, Maebashi, Japan
3 Division of Cell Biology and Neuroscience, Department of Morphological and Physiological Sciences, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

Correspondence to: Naoto Omata, MD., PhD.
Department of Neuropsychiatry, Faculty of Medical Sciences, University of Fukui, 23-3 Matsuokashimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193, Japan.
TEL: +81-776-61-8363; FAX: +81-776-61-8136; E-MAIL: omata@u-fukui.ac.jp

Submitted: 2011-12-09 Accepted: 2011-12-28 Published online: 2012-03-10

Key words: **adiponectin; antidepressant; fluvoxamine; mood stabilizer; lithium**

Neuroendocrinol Lett 2012; **33**(1):1–2 **PMID:** 22467103 NEL330112L01

Abstract

The effect of antidepressants and mood stabilizers on serum levels of adiponectin was investigated. Fluvoxamine (30 and 50 mg/kg/day) or lithium (40 and 60 mg/kg/day) was dissolved in distilled water and administered orally to rats every day for 4 weeks. Fluvoxamine (50 mg/kg/day) alone significantly elevated the serum level of adiponectin, but no significant difference was found between other drug-treated groups and the control group. This difference of these drugs' effectiveness on serum adiponectin might contribute to their differences of action mechanisms and therapeutic effects.

The report by Zeman *et al.* (2009) published in this journal investigated the blood level of adiponectin of depression patients (Zeman *et al.* 2009). Adiponectin, an adipokine derived from adipose tissue, has an anti-inflammatory activity performed through inhiwbition of inflammatory cytokines (Shimada *et al.* 2004). Depression can be regarded as a kind of inflammatory disorder because stressful life events engender microdamage in the brain, which might trigger damaging neuroinflammation and thereby induce depressive symptoms (Wager-Smith & Markou 2011). Chronic vascular inflammation followed by atherosclerosis is related to the onset and severity of the depressive symptoms (Pizzi *et al.* 2010). Therefore, the level of the anti-inflammatory adiponectin in the blood of depression patients probably differs from that of healthy controls. Zeman *et al.* (2009) have described that the severity of depression correlated negatively with the blood level of adiponectin. Furthermore, we showed that the blood level of adiponectin of patients with remitted depression receiving medication was higher than that of healthy controls (Narita *et al.* 2006). Nevertheless, it remains unclear whether this elevation of the blood level of adiponectin is the effect of medication, or if this elevation is accompanied with the remission of the depression. To resolve this question, it is necessary to evaluate the effect of the drugs for the treatment of depression on the blood levels of adiponectin directly without the factor of depression. Antidepressants or mood stabilizers are used to treat depression. In this study, we investigated the effects of an antidepressant and a mood stabilizer, fluvoxamine and lithium, on serum levels of adiponectin using experimental animals.

All protocols were consistent with the NIH policy on the use of animals in experimental research. The Institutional Animal Care Commit-

tee at the University of Fukui approved the experiments. Seven-week-old male Sprague-Dawley rats (Sankyo Labo Service Corp., Tokyo, Japan) that had been bred under standard conditions were housed at 24±1 °C with a light-dark cycle set to 12 h/12 h. They had free access to food and water.

Fluvoxamine was a gift from Abbott Japan K.K. (formerly Solvay Seiyaku K.K.) (Tokyo, Japan) and Meiji Seika Pharma Co. Ltd. (formerly Meiji Seika Kaisha Ltd.) (Tokyo, Japan). Lithium chloride was purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Fluvoxamine (30 and 50 mg/kg/day) or lithium (40 and 60 mg/kg/day) was dissolved in distilled water and administered orally every day for 4 weeks. Control animals were given distilled water only. After the finish of treatment with each drug, body weight was measured, and a blood sample was collected. The serum levels of adiponectin were measured using Human Adiponectin Latex Kit (Mitsubishi Chemical Medience Corp., Tokyo, Japan).

After treatment with each drug for 4 weeks, neither the body weight of fluvoxamine-treated group rats (30 mg/kg/day; 392.61±15.31 g, 50 mg/kg/day; 366.43±11.69 g) nor that of lithium-treated group rats (40 mg/kg/day; 379.55±11.13 g, 60 mg/kg/day; 373.50±6.71 g) was significantly different from that of control group rats (397.03±11.29 g). Serum levels of adiponectin after treatment with each drug for 4 weeks are presented in Figure 1. Fluvoxamine (50 mg/kg/day) alone significantly elevated the serum level of adiponectin. But no significant difference in serum levels of adiponectin was found between rats of other drug-treated groups and those of the control group.

Adiponectin exerts its anti-inflammatory effect by inhibiting inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) (Shimada *et al.* 2004), but TNF-α also inhibits adiponectin. They also mutually inhibit each other's expression and production (Shimada *et al.* 2004). Antidepressants and mood stabilizers have an anti-inflammatory effect by inhibiting inflammatory cytokines (Lekakis *et al.* 2010; Natsume *et al.* 2011). Therefore, these drugs might exert their therapeutic effect through the inhibition of inflammatory cytokines and elevation of blood levels of adiponectin, with subsequent improvement of neural and vascular inflammation, in addition to the effect on the neurotransmission systems which has already been recognized. This study demonstrated that fluvoxamine, but not lithium, elevated the serum level of adiponectin. Therefore, this clinical mechanism of elevation of adiponectin in the blood might be applicable to antidepressants such as fluvoxamine, not to mood stabilizers. Indeed, results suggest that some antidepressants are effective for the treatment of vascular depression (Wager-Smith & Markou 2011).

To our knowledge, this report is the first of a study comparing the direct effects of antidepressant and mood stabilizer on the serum levels of adiponectin. Results suggest that that fluvoxamine, but not lithium, elevated the serum levels of adiponectin. This difference might contribute to differences of the action mechanisms and therapeutic effects of these drugs.

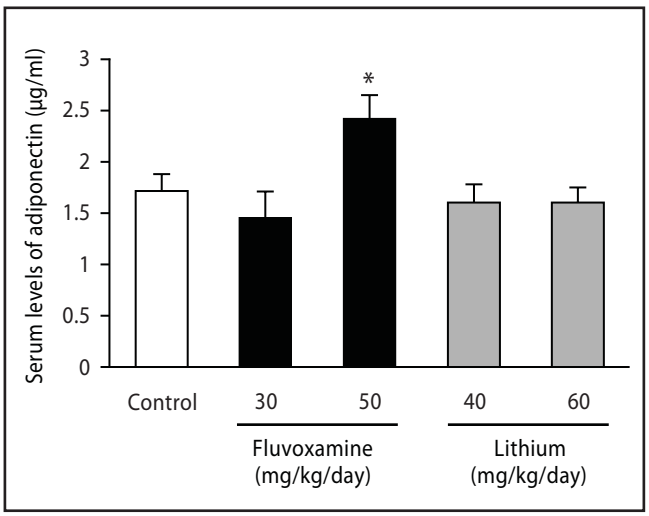

Fig. 1. Serum levels of adiponectin after treatment using each drug for 4 weeks. Data are means ± SEM ($n = 8$). *$p<0.05$; significantly different from control animals (Student's *t*-test).

ACKNOWLEDGEMENTS

This work was supported by FUKUI BRAIN PROJECT, Research and Education Program for Life Science, University of Fukui.

REFERENCES

1 Lekakis J, Ikonomidis I, Papoutsi Z, Moutsatsou P, Nikolaou M, Parissis J, et al (2010). Selective serotonin re-uptake inhibitors decrease the cytokine-induced endothelial adhesion molecule expression, the endothelial adhesiveness to monocytes and the circulating levels of vascular adhesion molecules. Int J Cardiol. **139**: 150–158.

2 Narita K, Murata T, Takahashi T, Kosaka H, Omata N, Wada Y (2006). Plasma levels of adiponectin and tumor necrosis factor-alpha in patients with remitted major depression receiving long-term maintenance antidepressant therapy. Prog Neuropsychopharmacol Biol Psychiatry. **30**: 1159–1162.

3 Natsume H, Tokuda H, Adachi S, Matsushima-Nishiwaki R, Kato K, Minamitani C et al (2011). Wnt3a regulates tumor necrosis factor-α-stimulated interleukin-6 release in osteoblasts. Mol Cell Endocrinol. **331**: 66–72.

4 Pizzi C, Manzoli L, Mancini S, Bedetti G, Fontana F, Costa GM (2010). Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. Atherosclerosis. **212**: 292–298.

5 Shimada K, Miyazaki T, Daida H (2004). Adiponectin and atherosclerotic disease. Clin Chim Acta. **344**: 1–12.

6 Wager-Smith K, Markou A (2011). Depression: a repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition? Neurosci Biobehav Rev. **35**: 742–764.

7 Zeman M, Jirak R, Jachymova M, Vecka M, Tvrzicka E, Zak A (2009). Leptin, adiponectin, leptin to adiponectin ratio and insulin resistance in depressive women. Neuro Endocrinol Lett. **30**: 387–395.