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Plasma levels of interleukin-6 and 3-methoxy-4-hydroxyphenylglycol and treatment with milnacipran in major depression

Reiji Yoshimura, Naomichi Okamoto and Atsuko Ikenouchi

Dear Editor,

Milnacipran is a serotonin–noradrenaline reuptake inhibitor (SNRI) that is effective in treating patients with major depression (MD).[1] Antidepressant treatment in MD has been associated with alterations in peripheral cytokine levels.[2] Monoamine levels in the cerebrospinal fluid are also altered after treatment with antidepressants in MD.[3] Thus, we investigated the plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of noradrenaline or interleukin-6 (IL-6), and the clinical response to milnacipran in MD. We also examined the correlation between plasma MHPG and IL-6 levels before and after milnacipran treatment.

Twenty-four patients who met MD criteria per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) were enrolled in this study (ages 48.7 ± 13.9 years; male/female 12/12; single/repeated episode 6/18). Improvement in depressive symptoms was evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD). The detection of plasma IL-6 and plasma MHPG was done by sandwich enzyme-linked immunosorbent assay (ELISA) and high-performance liquid chromatography, respectively. The maximum dose of milnacipran at week 4 was 77.0 ± 19.3 mg/day. Changes in plasma MHPG or IL-6, and HAMD scores are shown in Table 1.

The plasma levels of MHPG and IL-6 were not altered before or 4 weeks after milnacipran treatment. HAMD scores significantly decreased after milnacipran treatment. No correlation was found between the changes in plasma MHPG and the changes in HAMD scores before and 4 weeks after milnacipran treatment (r = -0.0030, p = 0.98, Pearson correlation coefficient). No correlation was found between the changes in plasma levels of IL-6 and changes in the HAMD scores (r = 0.00030, p = 0.99, Pearson correlation coefficient). Moreover, there was no correlation between changes in plasma MHPG levels and changes in plasma IL-6 levels (r = 0.021, p = 0.92, Pearson correlation coefficient).

We previously reported a positive correlation between changes in plasma MHPG levels and changes in HAMD scores in first-episode MD patients,[4] which was not confirmed in this study. The discrepancy between our former study and this study may be due to 18 patients of 24 had a history of recurrent, multiple episodes of MD and their average depressive episode was 3.1 in this study. Another report determined that serum levels of IL-6, IL-8, and macrophage inflammatory protein-1β could be used as biomarkers to predict response to milnacipran.[5] In short, the authors suggested that serum levels of IL-6 and IL-8 might be potential blood biomarkers for response to milnacipran in MD patients. Our results show no association between changes in plasma IL-6 levels and response to milnacipran treatment, which was not in accordance with other reports.[5] Our present study only focused on the relationship between plasma levels of IL-6 and response to milnacipran, but not adverse effects. The effect of noradrenaline on induced IL-6 release is primarily mediated by β2-adrenergic receptors, suggesting interaction between noradrenaline and IL-6.[6] Our present study showed no correlation between levels of plasma MHPG and plasma IL-6.[6] Milnacipran improved depressive symptoms at least until week 4. Since we could not detect successfully other cytokines, including IL-1β, IL-8, and tumor necrosis factor (TNF)-α, in this study, we are now

Correspondence to:
Reiji Yoshimura
Department of Psychiatry, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, Fukuoka 8078555, Japan.

yoshi621@med.uoeh-u.ac.jp

Naomichi Okamoto
Atsuko Ikenouchi
Department of Psychiatry, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Table 1. Parameter changes.

	0 week	4 weeks	*p* value
MHPG	3.64 (1.08)	3.60 (0.93)	0.94
IL-6	1.79 (0.61)	1.73 (0.38)	0.42
HAMD	21.5 (3.59)	12.4 (4.72)	<0.001*

Data are expressed as mean (SD).
HAMD, Hamilton Rating Scale for Depression; IL-6, interleukin-6; MHPG, 3-methoxy-4-hydroxyphenylglycol.
*Wilcoxon signed-rank sum test.

undergoing the study measuring these cytokines and response to several antidepressants.

All descriptive statistics and statistical analyses were performed using Python ver. 3.0.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the University of Occupational and Environmental Health (approval code UOHECRB21-057). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Author contributions

Reiji Yoshimura: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Naomichi Okamoto: Data curation; Formal analysis; Methodology.

Atsuko Ikenouchi: Conceptualization; Data curation; Formal analysis; Methodology; Project administration.

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Availability of data and materials

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ORCID iDs

Reiji Yoshimura https://orcid.org/0000-0002-7637-5576

Atsuko Ikenouchi https://orcid.org/0000-0001-8328-4608

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