

Plasma levels of IL-6 in patients with untreated major depressive disorder: comparison with catecholamine metabolites

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Objective: IL-6 and catecholamines play roles in the pathophysiology of major depressive disorder (MDD).

Aim: The present study investigated associations between plasma IL-6 and plasma catecholamine metabolites in patients with MDD.

Participants and methods: A total of 148 patients (male/female 65/83, age 49.5±12.1 years) who met the criteria for MDD based on the *Diagnostic and Statistical Manual of Mental Disorders IV* and 40 participants as healthy controls (HC; male/female 23/17, age 44.0±10.5 years) were enrolled in the present study. Plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA) were analyzed using high-performance liquid chromatography, and plasma IL-6 levels were measured using ELISA.

Results: No correlations were observed among plasma IL-6 levels, MHPG levels, and HVA levels in patients with MDD. Plasma IL-6 levels in patients with MDD were significantly higher than in the HC. A positive correlation was found between plasma IL-6 levels and Hamilton Rating Scale for Depression-17 scores.

Conclusion: No correlations existed between plasma IL-6 levels and plasma catecholamine metabolite levels in patients with MDD, and the severity of depressive state was related to plasma IL-6 levels in MDD.

Keywords: IL-6, 3-methoxy-4-hydroxyphenylglycol, homovanillic acid, major depressive disorder, Hamilton Rating Scale for Depression

Introduction

Major depressive disorder (MDD) is an important cause of reduced quality of life worldwide.¹ It has been speculated that monoamines play a role in MDD,² but the actions of monoamines during the pathophysiology of MDD remain incompletely understood. Drugs that inhibit the serotonin transporter (5-HTT) and/or the noradrenaline transporter exhibit antidepressive efficacy. Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are first-line treatments for patients with MDD.³ MDD has been shown to be associated with increased levels of circulating cytokines and their soluble receptors.^{4–10} We recently reported that higher plasma IL-6 activity is associated with refractory depression, and plasma IL-6 levels might be a predictor of the response to SSRIs or SNRIs.¹¹ We also reported that plasma IL-6 levels were significantly higher in patients with dysthymic disorder and MDD than in control subjects.¹²

We proposed plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of noradrenaline, as a candidate biomarker for predicting the response

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to antidepressants. Responders to milnacipran and duloxetine demonstrated lower plasma MHPG levels than nonresponders. In contrast, responders to paroxetine demonstrated higher serum MHPG levels than nonresponders.^{13,14} Since MDD is a heterogeneous disease, its pathophysiology might be divided into two groups by serum MHPG levels. We also reported that MDD patients who had higher scores for anxiety and agitation on the Hamilton Rating Scale for Depression-17 (HAM-D17) had better responses to paroxetine, whereas those who had higher scores for psychomotor retardation on the HAM-D17 had better responses to milnacipran.¹³ Taking these findings into account, it is possible that the dynamics of plasma IL-6 and serum MHPG are altered in patients with MDD, and these factors might be biomarkers for predicting the response to antidepressants. Brydon et al¹⁵ reported that stress altered plasma IL-6 levels, suggesting that psychological and immune stressors may act synergistically to promote inflammation and pathological behavior in humans. Parrado et al¹⁶ reported that dopamine agonists upregulate IL-6 production in human keratinocytes. Aguilar-Valles et al¹⁷ reported that IL-6 alters the function of mesolimbic dopamine neurons in rodents. Therefore, catecholamines influence IL-6 and vice versa.

The synergistic effect between immune activation by lipopolysaccharide and methamphetamine, a dopamine stimulant could have important implications in the treatment of neuroimmune-compromised and dopamine dysfunctional populations such as MDD or schizophrenia.¹⁸ Raison et al¹⁹ reported peripherally administered interferon-alpha increased cerebrospinal fluid (CSF) IL-6 levels, and which were associated with decreases in the serotonin metabolite, 5-hydroxy-indoleacetic acid (5-HIAA), but not MHPG or homovanillic acid (HVA). This in turn was correlated with depressive symptoms. Thus, we hypothesized that interactions exist between catecholamines and IL-6 in patients with MDD. If so, drugs targeting IL-6 might be effective for MDD. Zhang et al²⁰ demonstrated blockade of IL-6 receptor promotes rapid and sustained antidepressant actions in mice via influencing gut-brain axis. We investigated the associations between serum catecholamine metabolite and plasma IL-6 levels in patients with MDD to confirm this hypothesis.

Subjects and methods

Participants

A total of 148 patients (male/female 65/83, age 49.5±12.1 years) were continuously recruited from 2004 to 2012 at the Neuropsychiatry Branch of the University Hospital of

University of Occupational and Environmental Health, Kitakyushu, Japan. The patients were screened for axis I psychiatric disorders using the Japanese version of the Mini-International Neuropsychiatric Interview and blood sampling was performed by Reiji Yoshimura (a board certified psychiatrist with over 30 years of experience) on the first day the patients visited our branch of the hospital. In short, major depressive episodes were diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders IV*, Text Revision.²¹ The severity of depression was evaluated using the HAM-D17.²² All patients had not taken antidepressants for at least 1 month before the evaluation. MDD patients whose HAM-D17 scores were 17 or greater were enrolled in the present study. The exclusion criteria included any history of neurological disease or other physical diseases and comorbidity with other psychiatric disorders. Forty participants as healthy controls (HC) were enrolled in the present study. All of them were recruited from nearby communities via an interview conducted by the same psychiatrist using Structured Clinical Interview for DSM-IV Axis I Disorders/Non patients (SCID-I/NP). The HC consisted of not only staff from our institution but also their relatives (marriage) and close friends. Biologically related relatives were excluded from the HC. No HC had a history of severe medical or neuropsychiatric illness or a family history of major psychiatric or neurological illnesses. They also had no history of serious physical diseases and use of drugs (steroid, aspirin, or nonsteroidal anti-inflammatory drugs).

The demographic data for the people with MDD and the HC are described in Table 1. The study protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan. Written informed consent was obtained from all subjects who participated in this study and the study was conducted in accordance with the Declaration of Helsinki.

Table 1 Demographic data of the MDD patients and healthy controls

	MDD	Controls
Number	148	40
M/F	65/83	23/17
Age (years), mean (SD)	49.5 (12.1)	44.0 (10.5)
Episode (single/recurrent)	57/91	
Melancholic/non-melancholic	47/101	
With/without psychotic features	34/114	
Duration of illness at the episode (months)	2.3 (1.2)	
smoking/non-smoking	69/79	8/32
continuous alcohol use (yes/no)	41/107	7/33

Abbreviations: F, female; M, male; MDD, major depressive disorder.

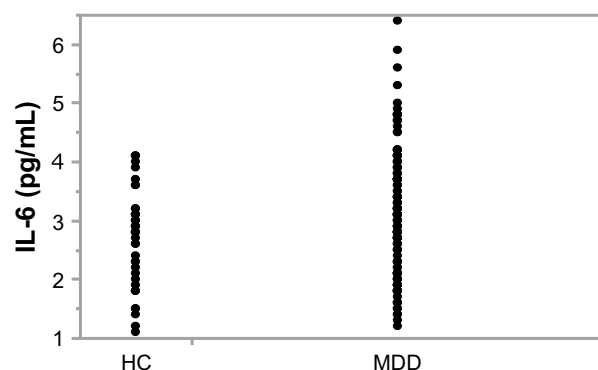


Figure 1 Dot plot of IL-6 between MDD and HC ($P=0.00096$).

Abbreviations: MDD, major depressive disorder; HC, healthy controls.

Assays of plasma levels of MHPG, HVA, and IL-6

Circadian variation was demonstrated in catecholamine and their metabolites. Plasma levels of catecholamines and their metabolites are higher during the day than those during the night.^{23–27} Thus, blood sampling was performed from 9 am to 11 am in the morning after at least 30 minutes after lying in bed. The method used was high-performance liquid chromatography (HPLC). Plasma levels of MHPG and HVA were measured according to the method of Minegishi and Ishizaki²⁸ and Yeung et al,²⁹ respectively. Plasma levels of IL-6 were measured with the methods we previously described.³⁰

Statistical analysis

The Shapiro–Wilk test indicated that IL-6 levels were normally distributed. A generalized linear model was used to explore the association of IL-6 levels with HVA and MHPG levels using potentially confounding variables (age, gender, first episode or not, melancholia or not, duration of untreated illness, and HAM-D17 scores at baseline) as covariates, and the adjusted results were regarded as the study outcomes. All statistical tests were performed using JMP (JMP 12, SAS Japan Inc., Tokyo, Japan), and $P<0.05$ was considered to indicate statistical significance. Non-paired t -test was performed comparing plasma levels of IL-6 between the MDD patients and HC.

Results

The plasma IL-6 level of the patients with MDD (3.11 ± 1.03 ng/mL) was significantly higher than that of the HCs (2.69 ± 0.83 ng/mL) ($P=0.00096$) (Figure 1 and Table 3). A significant positive correlation was found between plasma IL-6 levels and HAM-D17 scores in MDD patients ($R^2=0.32904$, $P<0.0001$) (Figure 2) but not between plasma levels of MHPG ($P=0.8630$) (Figure 3) or HVA ($P=0.9860$) (Figure 4) and HAM-D17 scores in MDD patients. No correlations were found among plasma IL-6 levels, plasma MHPG levels, and plasma HVA levels using both raw (Table 4) and adjusted (Table 5) measures in patients with MDD. We also calculated the power of the three measures (Table 6). Moreover, we investigated the correlation between sub-items scores of HAM-D17 according to Seretti et al³¹ and IL6, MHPG, or HVA. A significant correlation was found all sub-items scores and IL-6. On the other hand, no correlations were found between each-item score and MHPG or HVA (Table 2).

Discussion

No correlations were found between plasma IL-6 levels and plasma MHPG levels or plasma HVA levels in patients with MDD. The results do not support the hypothesis that interactions exist between catecholamines and IL-6 in patients with MDD. It has been reported that noradrenaline induces the expression of IL-6 in cell lines.^{32,33} Handley et al³⁴ reported that IL-6 levels were also lower after treatment with haloperidol than after treatment with placebo, but this effect was not observed for aripiprazole. This result suggests that full antagonism of the dopamine two receptor can lead to a reduction of IL-6 levels.

Miller et al³⁵ reported that cytokines and their signaling pathways, including p38 mitogen-activated protein kinase, have significant effects on the metabolism of multiple neurotransmitters, such as serotonin, dopamine, and glutamate, by affecting their synthesis, release, and reuptake. Felger et al³⁶ reported that connectivity between the striatum and the ventromedial prefrontal cortex was associated with increased plasma levels of IL-6, IL-1 beta, and IL-1 receptor antagonists,

Table 2 Relations between HAM-D17 sub-items scores and IL-6, MHPG, or HVA

	Core	Sleep	Activity	Psychic anxiety	Somatic anxiety
MHPG	0.9039	0.5194	0.9676	0.3964	0.326
HVA	0.5527	0.4481	0.5359	0.2944	0.0504
IL-6	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001

Abbreviations: HAM-D17, 17-item Hamilton Depression Rating Scale; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Table 3 Comparison of IL-6 between the MDD patients and HC

	MDD	SD	Min	Max	HC	SD	Min	Max	t-test	Mean difference	95% CI	Cohen's d
	Mean				Mean				P-value			
IL-6	3.12	1.04	2.95	3.29	2.7	0.831	2.43	2.96	0.0192	0.419	0.0692-0.770	0.45

Abbreviations: MDD, major depressive disorder; HC, healthy controls.

which suggests that decreased corticostriatal connectivity may serve as a target for anti-inflammatory or prodopaminergic treatment strategies to improve motivational and motor deficits in patients with increased inflammation, including depression. These findings were inconsistent, and we considered that noradrenaline and dopamine may enhance IL-6 levels. We reported that plasma IL-6 levels were significantly higher in patients with MDD and dysthymic disorder than in HC.³⁷

We also reported that among patients with MDD, patients who responded to paroxetine and sertraline had higher plasma IL-6 levels than nonresponders to those antidepressants.¹¹ Fluvoxamine decreased plasma IL-6 levels, which was associated with improved depressive symptoms, as evaluated by the HAM-D17.³⁸ Manoharan et al³⁹ also reported a significant correlation between the percentage change in plasma IL-6 levels and the percentage change in HAMD scores among MDD patients who responded to treatment with fluoxetine. In contrast, Fornaro et al⁴⁰ reported that plasma IL-6 levels increased significantly only in responders to duloxetine using a very small sample of only nine patients. Based on our previous unpublished experiments, no significant differences were observed in plasma MHPG and plasma HVA levels between MDD patients and HC because of their broad

distribution (data not shown). A recent report demonstrated that HVA levels, but not MHPG, and 5-HIAA in the CSF were significantly decreased in MDD patients.⁴¹ Another report also demonstrated a significant reduction in HVA levels, but not MHPG in the CSF between MDD patients and HC.⁴² Sasayama et al⁴³ reported that both the patients with schizophrenia and MDD had significantly higher CSF IL-6 levels compared to the HC. IL-6 levels were significantly higher in the CSF than in the serum. The authors also demonstrated that no significant correlation was observed between CSF and serum IL-6 levels. The present findings suggest that IL-6 of central origin is associated with the pathophysiology of schizophrenia and MDD. We interpret the results as follows. Since MDD is heterogeneous, it is reasonable that the levels of plasma IL-6, MHPG, and HVA vary widely. Moreover, individual levels of IL-6, MHPG, and HVA are regulated by both genetic factors and epigenetic factors. Therefore, complicated mechanisms might link IL-6 and catecholamines. We can categorize MDD patients into several subtypes according to plasma levels of IL-6, MHPG, and HVA. SSRIs and SNRIs both work on the serotonin transporter. We reported no differences in baseline IL-6 levels or the change in plasma IL-6 levels between patients who were serotonin transporter

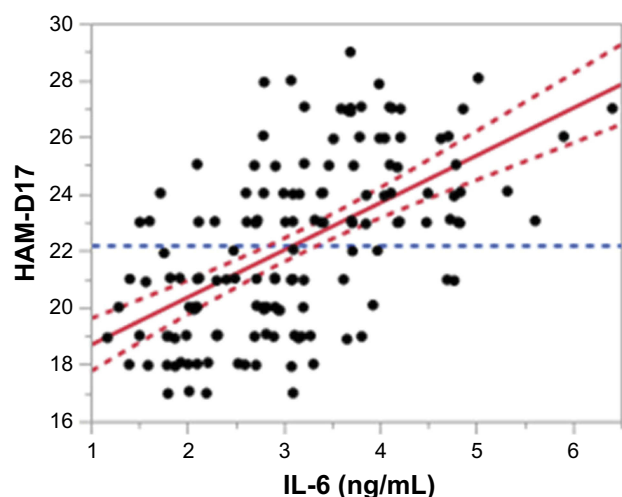


Figure 2 Partial regression residual leverage plot of plasma IL-6 levels and HAM-D17 scores ($P < 0.0001$, $R^2 = 0.33$).

Abbreviation: HAM-D17, 17-item Hamilton Depression Rating Scale.

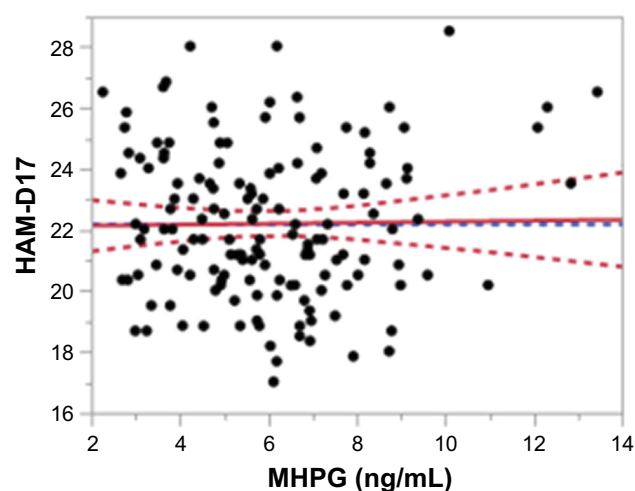


Figure 3 Partial regression residual leverage plot of plasma MHPG levels and HAM-D17 scores ($P = 0.8630$).

Abbreviations: HAM-D17, 17-item Hamilton Depression Rating Scale; MHPG, 3-methoxy-4-hydroxyphenylglycol.

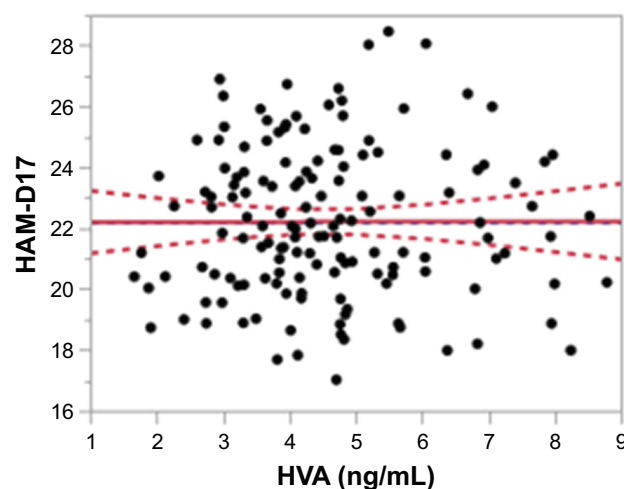


Figure 4 Partial regression residual leverage plot of plasma HVA levels and HAM-D17 scores ($P=0.9860$).

Abbreviations: HAM-D17, 17-item Hamilton Depression Rating Scale; HVA, homovanillic acid.

(5-HTT) gene L carriers and those who had the S/S genotype, which indicates that the plasma IL-6 level is independent of the 5-HTT genotype.¹¹

We confirmed our preliminary results that plasma IL-6 levels are significantly higher in MDD patients than in HC and that there is a positive correlation between plasma IL-6 levels and HAM-D17 scores. Furthermore, we additionally reported significant correlations between sub-items scores of HAM-D17 according to Seretti et al³¹ and plasma IL-6 levels. Several recent reports demonstrated a positive correlation between plasma IL-6 levels and HAM-D17 scores.^{38,44–46} The results of the present study were in accordance with those of recent studies, including our previous study. Thus, it is possible that plasma IL-6 is a biomarker of MDD severity. This preliminary study had several serious limitations, such as a small sample, heterogeneous participants, and a cross-sectional design. In addition, we should correct the plasma IL-6 levels with body mass index, because body mass index was reported to influence plasma IL-6 levels.⁴⁷ Thus, we are performing a longitudinal study with a large sample, with age-, sex-,

Table 4 The raw correlations among the biological measures

	Estimated value	Standard error	T-value	P-value	Standard beta
IL-6	1.664207	0.198104	8.4	$P<0.00001$	0.573533
MHPG	0.0162167	0.093842	0.17	0.863	0.011857
HVA	0.0023559	0.133953	0.02	0.986	0.001207

Abbreviations: HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Table 5 The adjusted correlations among the biological measures

	Standard error	T-value	P-value	Standard beta
IL-6	0.200328	8.52	<0.00001	0.588139
MHPG	0.095001	0.15	0.882	0.010331
HVA	0.134012	0.03	0.9749	0.002165
Age	0.016002	-1.43	0.1554	-0.09866
Gender	0.417227	-0.14	0.8881	-0.00975

Abbreviations: HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Table 6 Calculated power for three biomarkers

IL-6				
α	σ	δ	Number	Power
0.05	2.48562	1.740565	148	1
MHPG				
α	σ	δ	Number	Power
0.05	2.48562	0.03039	148	0.0525
HVA				
α	σ	δ	Number	Power
0.05	2.48562	0.006442	148	0.0501

Abbreviations: HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

and BMI-matched control groups, to reconfirm these preliminary results.

Conclusion

No correlations existed between plasma IL-6 levels and plasma MHPG or HVA levels in patients with MDD. Plasma IL-6 levels were significantly higher in MDD patients than in HC, and a positive correlation was observed between plasma IL-6 levels and HAM-D17 scores in patients with MDD.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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