

## REGULAR RESEARCH ARTICLE

# Reduced Serum and Cerebrospinal Fluid Levels of Autotaxin in Major Depressive Disorder

Kei Itagaki, Minoru Takebayashi, Hiromi Abe, Chiyo Shibasaki, Naoto Kajitani, Mami Okada-Tsuchioka, Kotaro Hattori, Sumiko Yoshida, Hiroshi Kunugi, Shigeto Yamawaki

Division of Psychiatry and Neuroscience, Institute for Clinical Research (Drs Itagaki, Takebayashi, Abe, Shibasaki, Kajitani, and Okada-Tsuchioka), and Department of Psychiatry (Drs Itagaki and Takebayashi), NHO Kure Medical Center and Chugoku Cancer Center, Kure, Hiroshima, Japan; Department of Psychiatry and Neurosciences, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan (Drs Itagaki, Shibasaki, and Yamawaki); Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan (Dr Takebayashi); Department of Mental Disorder Research, National Institute of Neuroscience (Drs Hattori and Kunugi), and Medical Genome Center (Dr Hattori), National Center of Neurology and Psychiatry, Tokyo, Japan; National Center of Neurology and Psychiatry Hospital, Tokyo, Japan (Dr Yoshida).

Correspondence: Minoru Takebayashi, MD, PhD, Department of Psychiatry and Division of Psychiatry and Neuroscience, Institute for Clinical Research, NHO Kure Medical Center and Chugoku Cancer Center, 3-1, Aoyama, Kure, Hiroshima 737-0023 Japan ([mtakebayashi@kure-nh.go.jp](mailto:mtakebayashi@kure-nh.go.jp)).

## Abstract

**Background:** The autotaxin/lysophosphatidic acid axis is involved in diverse biological processes including neurodevelopment, inflammation, and immunological functioning. The lysophosphatidic acid 1 receptor has been implicated in the pathophysiology of major depressive disorder and in the mechanism of action of antidepressants. However, it is unclear whether central or peripheral autotaxin levels are altered in patients with major depressive disorder.

**Methods:** Serum autotaxin levels were measured by an enzyme-linked immunosorbent assay in 37 patients with major depressive disorder diagnosed using DSM-IV-TR who underwent electroconvulsive therapy and were compared with those of 47 nondepressed controls matched for age and sex between January 2011 and December 2015. Patient serum levels of autotaxin before and after electroconvulsive therapy were also compared. In a separate sample set, cerebrospinal fluid autotaxin levels were compared between 26 patients with major depressive disorder and 27 nondepressed controls between December 2010 and December 2015. A potential association was examined between autotaxin levels and clinical symptoms assessed with the Hamilton Depression Rating Scale.

**Results:** Before electroconvulsive therapy, both serum and cerebrospinal fluid autotaxin levels were significantly lower in major depressive disorder patients than in controls (serum:  $P = .001$ , cerebrospinal fluid:  $P = .038$ ). A significantly negative correlation between serum, but not cerebrospinal fluid, autotaxin levels and depressive symptoms was observed ( $P = .032$ ). After electroconvulsive therapy, a parallel increase in serum autotaxin levels and depressive symptoms improvement was observed ( $P = .005$ ).

**Conclusion:** The current results suggest that serum autotaxin levels are reduced in a state-dependent manner. The reduction of cerebrospinal fluid autotaxin levels suggests a dysfunction in the autotaxin/lysophosphatidic acid axis in the brains of patients with major depressive disorder.

Received: April 22, 2018; Revised: December 13, 2018; Accepted: January 27, 2019

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## Significance Statement

The autotaxin (ATX)/lysophosphatidic acid (LPA) axis is involved in diverse biological processes including neurodevelopment, inflammation, neurological, and immunological functioning. The LPA1 receptor has been implicated in the pathophysiology of depressive disorder and in the mechanism of action of antidepressants. The current study showed decreased levels of ATX, which produces LPA, the endogenous LPA1 receptor ligand, in both serum and cerebrospinal fluid (CSF) in patients with major depressive disorders (MDD) compared with ATX levels of nondepressed controls. Furthermore, serum levels of ATX increased following acute electroconvulsive therapy, which is a highly effective acute treatment for severe forms of depression. These findings indicate that a decline in ATX/LPA axis function, as reflected by reduced expression of ATX, could be associated with the pathophysiology of MDD and that serum and CSF ATX measurements could be used as biomarkers for evaluating the efficacy of treatments in some MDD patients.

**Keywords:** autotaxin, lysophosphatidic acid, major depressive disorder, cerebrospinal fluid, electroconvulsive therapy

## Introduction

Autotaxin (ATX) is a secreted enzyme that produces the lipid mediator lysophosphatidic acid (LPA) from extracellular lysophosphatidyl choline (Umezū-Goto et al., 2002)—it is the primary enzyme responsible for LPA production (van Meeteren et al., 2006). Lysophosphatidic acid exerts its effect through at least 6 LPA G-protein-coupled receptors (LPA1R) (Yung et al., 2015) and is involved in numerous biological processes, including neuroprogenitor cell function (Yung et al., 2011), myelination (Anliker et al., 2013), synaptic transmission (Trimbuch et al., 2009), and the brain's immunologic response (Schilling et al., 2004), which, in turn, influences neural development, function, and behavior. Autotaxin is widely expressed in brain as well as a number of peripheral tissues (van Meeteren et al., 2006)—the expression of LPA1R is tightly linked with ATX (Frugier et al., 2011).

LPA has been implicated in a number of neurophysiological functions and neuropathologies (Yung et al., 2015). For example, LPA1R knock-out mice exhibit depressive-like behaviors, including hippocampal-dependent cognitive alteration (Santin et al., 2009), hypoactivity (Castilla-Ortega et al., 2013), and anhedonia (Moreno-Fernandez et al., 2017). Decreased neurogenesis within the hippocampus of these mice was also observed (Matas-Rico et al., 2008). Interestingly, antidepressants bind to LPA1R expressed in brain astrocytes (Kajitani et al., 2016; Olianas et al., 2016), activation of which leads to expression of glial cell line-derived neurotrophic factor (Kajitani et al., 2016), an important mediator of major depressive disorder (MDD) (Takebayashi et al., 2006; Uchida et al., 2011; Tsybko et al., 2017). These findings suggest a possible association between LPA1R and the pathophysiology of MDD, which, in turn, could be targeted for the treatment of MDD. The linkage between the dysfunction of LPA1R and that of the ATX/LPA axis has not been established, but the existence of such a linkage has been strongly suggested from preclinical findings. Specifically, the association between the ATX/LPA axis and MDD has yet to be clinically defined.

The current study examined whether ATX is altered in patients with MDD and if the alteration reflects the severity of depressive symptoms. While postmortem brain has been used for molecular research of psychiatric disorders, including MDD, CSF and blood from living patients are preferred in order to understand the actual relationship between biomolecules of interest and ongoing symptoms. In human serum, ATX is highly stable and does not greatly vary among healthy subjects (Nakamura et al., 2008). By contrast, direct measurement of LPA is challenging due to its instability (Aoki et al., 2002). Nonetheless, blood levels of ATX and LPA are significantly

correlated (Hosogaya et al., 2008). Thus, levels of ATX could directly reflect LPA levels and therefore serve as a proxy for ATX/LPA axis activity. The current study measured serum and CSF levels of ATX in MDD patients.

Findings from preclinical studies indicate that the pathophysiology of MDD is mediated in part by an abnormality of the ATX/LPA axis and that currently available therapeutic interventions appear to modulate ATX functioning (Matas-Rico et al., 2008; Santin et al., 2009; Castilla-Ortega et al., 2013; Olianas et al., 2016; Kajitani et al., 2016; Moreno-Fernandez et al., 2017). To determine if in fact modulation of ATX in MDD patients is associated with symptom attenuation, the current study measured ATX levels in patients who underwent a therapeutic course of ECT.

## METHODS

### Patients

Serum samples were collected at the Department of Psychiatry of the National Hospital Organization Kure Medical Center (NHOKMC), Hiroshima, Japan between January 2011 and December 2015 (sample Set 1). Patients diagnosed as having MDD were recruited among inpatients who were scheduled for ECT, based on the guidelines of the American Psychiatric Association (American Psychiatric Association, 2001), at NHOKMC (n = 37, Set 1; Table 1). Serum samples were collected just before the first ECT session (Pre-ECT; before any ECT session) and 2 weeks after the final ECT session (Post-ECT). Forty-seven subjects, with no history of past or current mental disorders, were recruited as nondepressed controls matched for age and gender. Most MDD patients at Pre-ECT received antidepressant pharmacotherapy: mirtazapine (15–45 mg/d; n = 16), duloxetine (20–60 mg/d; n = 9), mianserin (10–60 mg/d; n = 6), paroxetine (10–40 mg/d; n = 5), escitalopram (10–40 mg/d; n = 5), nortriptyline (100 mg/d; n = 5), trazodone (25–50 mg/d; n = 3), imipramine (50 mg/d; n = 2), sulpiride (50 mg/d; n = 2), sertraline (100 mg/d; n = 1), and amoxapine (100 mg/d; n = 1). Fifteen patients received a combination of 2 antidepressant drugs (paroxetine and mianserin, 3; paroxetine and mirtazapine, 1; duloxetine and mirtazapine, 4; sertraline and mirtazapine, 1; escitalopram and mirtazapine, 1; imipramine and trazodone, 1; imipramine and mirtazapine, 1; nortriptyline and mianserin, 1; nortriptyline and trazodone, 1; nortriptyline and mirtazapine, 1), and 3 received a combination of 3 antidepressant drugs (escitalopram, mirtazapine, and

Table 1. Patient Characteristics

	Serum Samples (Set 1)			CSF Samples (Set 2)			MDD Set1 vs Set2
	MDD at Pre-ECT	Controls	P value	MDD	Controls	P value	
	(n = 37)	(n = 47)		(n = 26)	(n = 27)		P value
Gender (female)	22 (59.5%)	28 (59.6%)	0.991 <sup>a</sup>	13 (50.0%)	13 (48.2%)	0.893 <sup>a</sup>	.457 <sup>c</sup>
Age (years)	58.7 ± 13.2	58.9 ± 11.4	0.953 <sup>b</sup>	41.2 ± 7.3	41.9 ± 9.1	0.689 <sup>b</sup>	<.001 <sup>d</sup>
Age of onset (years)	53.9 ± 14.2			30.2 ± 10.6			<.001 <sup>d</sup>
Duration of current episode (months)	5.7 ± 6.2			ND			–
Psychotic features	15 (40.5%)			ND			–
Catatonic features	7 (18.9%)			ND			–
Number of episodes	1.5 ± 1.9			1.9 ± 1.2			.168 <sup>d</sup>
Number of ECT sessions per course	10.0 ± 3.5			ND			–
Total HDRS	24.4 ± 8.3			11.8 ± 7.1			<.001 <sup>d</sup>
IMI equivalence (mg/d)	225.4 ± 151.6			207.8 ± 109.6			.923 <sup>d</sup>

Abbreviations: CSF, cerebrospinal fluid; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale-17; IMI, imipramine; MDD, major depressive disorder; ND, not detected.

Serum samples (Set 1) and CSF samples (Set 2) were collected from separate facilities. Data shown as either mean ± SD or number (n) and percent of total (%).

<sup>a</sup>Comparison between MDD and control group by chi-square test.

<sup>b</sup>Comparison between MDD and control group by Mann-Whitney U-test.

<sup>c</sup>Comparison between MDD in Set 1 and Set 2 by chi-square test.

<sup>d</sup>Comparison between MDD in Set 1 and Set 2 by Mann-Whitney U-test.

sulpiride, 2; duloxetine, mirtazapine, and mianserin, 1). The mean imipramine (IMI) dose equivalence according to a previous report (Inada and Inagaki, 2015) at Pre-ECT was 225.7 ± 151.6 mg/d. Three patients did not receive any antidepressant while undergoing the course of ECT.

In Set 2 (Table 1), 26 MDD patients and 27 nondepressed control subjects, matched for age and gender, were recruited through advertisements in a free local magazine and an announcement at the NCNP website, between December 2010 and December 2015. From these subjects, CSF was collected once.

Eight MDD patients received antidepressant pharmacotherapy: milnacipran (75–100 mg/d; n = 2), sertraline (50–100 mg/d; n = 2), paroxetine (20–40 mg/d; n = 2), sulpiride (100–300 mg/d; n = 2), duloxetine (60 mg/d; n = 1), escitalopram (10 mg/d; n = 1), mirtazapine (30 mg/d; n = 1), mianserin (30 mg/d; n = 1), or imipramine (150 mg/d; n = 1). Three patients received a combination of 2 antidepressant drugs (paroxetine and mirtazapine, 1; sertraline and sulpiride, 1; escitalopram and milnacipran, 1), and 1 received a combination of 3 antidepressant drugs (milnacipran, mianserin, and sulpiride). The mean IMI dose equivalence was 207.8 ± 109.6 mg/d. Eighteen patients did not receive any antidepressants.

In both sample sets, a consensus diagnosis was made by either trained psychologists or psychiatrists according to the DSM-IV-TR (American Psychiatric Association, 2000), on the basis of the Mini-International Neuropsychiatric Interview, Japanese version (Sheehan et al., 1998; Otsubo et al., 2005), additional unstructured interviews, and information from medical histories. Exclusion criteria included a past or current history of other psychiatric disorders such as bipolar disorder, schizoaffective disorder or adjustment disorder, significant neurological illness, or any other significant medical illness, including inflammatory diseases such as liver disease, fibrosis, cancer, kidney disease, arthritis, and Alzheimer's disease, as these conditions could be due to changes in the ATX/LPA axis (Umehura et al., 2006;

Benesch et al., 2016; Shimizu et al., 2016). In Set 1, a total of 6 psychiatric patients displayed co-morbidities, including: 2 with generalized anxiety disorder, 2 with somatization disorder, 1 with panic disorder, and 1 with obsessive-compulsive disorder. The severity of the comorbidities was mild. All patients in Set 2 had no comorbidities. As for Set 1, if a patient received 2 or more acute ECT courses during the study period, the serum sample was collected at only the first acute ECT course.

Nondepressed subjects were screened based on either a clinical interview or a structured interview by trained psychologists or psychiatrists using the Mini-International Neuropsychiatric Interview, Japanese version. The person who assessed them was not involved in the subsequent analysis of the data. With all participants, their past medical history, current illness, if any, and current medications were reviewed. Furthermore, hepatic enzyme, renal function, lipid, inflammatory indices, and nutritional status of nondepressed subjects in Set 1 were screened by a blood test. As for Set 2, although subjects in Set 2 were not screened by a blood test, most subjects were younger than those in Set 1. Thus, rather than subject the patients to an unnecessary medical test, we determined that an interview for their past medical history, current illness, and current medication, if any, was sufficient.

Clinical symptoms in MDD patients were scored using the 17-item Hamilton Depression Rating Score [HDRS]. The 17 items of the HDRS were assigned to the following 5 subscales: core symptom (items 1, 2, 7, 8, 10, 13); sleep (items 4, 5, 6); activity (items 7, 8); psychic anxiety (items 9, 10); and somatic anxiety (items 11, 12, 13) in accordance with a previous report (Serretti et al., 1999). For Set 1, each patient's symptoms were assessed at Pre-ECT session (baseline) and at Post-ECT by the same trained psychiatrist. The psychiatrist was not aware that patient ATX levels would be measured in serum or CSF and had no role in patient selection. Responders to ECT were defined as demonstrating a 50% decrease in HDRS score. For

Set 2, each patient's symptoms were assessed by a trained psychologists or psychiatrists at the time of lumbar puncture. While there were 10 patients with moderate or higher depression state (HDRS  $\geq$  13), there were 10 patients with mild depression state (HDRS  $\leq$  13) and 6 patients with remission state (HDRS  $\leq$  7).

After procedures were fully explained, written informed consent was obtained from all subjects. The current study was approved by the Ethics Committee of NHOKMC (27-09) and the Ethics Committee of NCNP (A2014-141).

### Electroconvulsive Therapy (ECT) Procedures

ECT was performed according to previously described procedures (Shibasaki et al., 2016; Itagaki et al., 2017). Before undergoing ECT, each patient was screened for general health through laboratory tests such as blood test and urinalysis, and physical examination to exclude significant medical illness or clinical symptoms. Anesthesia was induced with i.v. thiamylal sodium (2–3 mg/kg) and suxamethonium chloride (0.5–1 mg/kg, i.v.). A Thymatron System IV brief pulse square wave apparatus (Somatics Inc., Lake Bluff, IL) was used to induce electroconvulsions. Bilateral frontal-temporal electrodes were used as all ECT patients presented as severe, life-threatening cases (American Psychiatric Association, 2001). Only one adequate seizure was required for each session, which was defined as an electroencephalographic seizure lasting more than 25 seconds with a high amplitude, slow wave, and postictal suppression. The initial stimulus dose was determined using the half-age method (Petrides and Fink, 1996). If an adequate electroencephalographic seizure occurred in one session, the same stimulus energy was used at the next session. The maximum number of stimulations for each treatment session was 2. Electroconvulsive therapy was administered a maximum of 3 times per week and continued until the patient became asymptomatic or the attending psychiatrist determined that the patient had obtained the maximum benefit within 3 to 15 sessions (mean:  $10.0 \pm 3.5$ ; Table 1). After the purpose and the ECT procedure were described in detail, written informed consent was obtained from patients or caregivers of patients prior to initiating ECT. During the ECT course, medications were permitted and titrated as needed.

### Collection of Serum and CSF Samples

After an overnight fast, venous blood (Set 1) was taken in the morning (between 7:00 and 8:00 AM) before (Pre-ECT) and after (Post-ECT) ECT at NHOKMC. Blood samples were drawn into anticoagulant-free tubes and kept at room temperature for 1 hour. Serum was separated by centrifugation at 3000 rpm for 15 minutes at 4°C and stored at –80°C until assay.

Cerebrospinal fluid (Set 2) was obtained by lumbar puncture between 10:00 AM and 4:00 PM. Following application of local anesthetic, CSF was obtained by lumbar puncture at either L3–4 or L4–5 using an atraumatic pencil point needle (Uniever 22G, 75 mm, Unisis Corp, Tokyo, Japan). Eight mL of CSF was collected and immediately chilled on ice. The CSF was centrifuged at 4000 g for 10 minutes at 4°C, and the supernatant was dispensed into 0.5-mL aliquots in tubes and stored at –80°C until assay. Selected CSF samples were thawed (in ice-cold water), dispensed, and refrozen. CSF samples contaminated with blood were excluded from further analysis. While more depressed patients could have been sampled for CSF, it is challenging to subject severely depressed patients to a spinal tap.

### Detection of ATX by Enzyme-Linked Immunosorbent Assay

All serum and CSF samples were brought to room temperature before use in an enzyme-linked immunosorbent assay. Serum and CSF ATX levels were determined with a Quantikine human ATX immunoassay (R&D Systems, Minneapolis, MN) following the manufacturer's procedure. Quantification was performed with a Multi-Spectrophotometer Viento Microplate Reader (Sumitomo Dainippon Pharma Co, Osaka, Japan). The person performing the ATX assays at NHOKMC was unaware of the treatment status of the patients from whom the samples were obtained.

### Statistical Analysis

Data are shown as mean  $\pm$  SD. Tests for normality were performed using the Shapiro-Wilk and the Kolmogorov-Smirnov tests, and data were analyzed with nonparametric tests (SPSS version 22.0 for Windows, IBM Japan Corporation, Tokyo, Japan). Comparisons of parameters between patients with MDD and nondepressed controls were evaluated using the Mann-Whitney U-test. A chi-square test was used for categorical variables. A linear regression analysis was performed to evaluate possible relationships between serum and CSF ATX levels and clinical parameters, diagnosis, and clinical symptoms, controlled for gender. Repeated-measures ANOVA was used to compare the parameters between Pre-ECT and Post-ECT, controlled for gender. Statistical significance was defined as a 2-tailed  $P < .05$ .

## RESULTS

### Clinical Data

Patient characteristics of MDD patients and nondepressed controls for Set 1 and Set 2 are presented in Table 1. Distribution by gender within and between Set 1 and Set 2 did not significantly differ. However, patients in Set 1 were significantly older, and their onset of illness was earlier compared with subjects in Set 2. Patients with MDD in Set 1 had significantly higher HDRS compared with MDD patients in Set 2. There was no statistically significant difference in IMI equivalence doses.

### Relationship Between Serum and CSF Levels of ATX and Gender in All Samples

The mean serum ATX level for females was significantly higher than that of males ( $213.4 \pm 51.7$  vs  $151.8 \pm 32.8$  ng/mL,  $P < .001$ ). The mean CSF ATX level for females was also significantly higher than that of males ( $281.1 \pm 33.5$  vs  $257.8 \pm 26.8$  ng/mL,  $P = .007$ ). These results indicate a gender-based difference in ATX levels in both serum and CSF, which was confirmed by linear regression analysis (Table 2; serum: nonstandardized coefficient  $\beta = -61.6$ ,  $P < .001$ ; CSF: nonstandardized coefficient  $\beta = -23.6$ ,  $P = .005$ ). Because of the gender-based difference, further analyses of ATX levels were performed adjusting for gender.

### Relationship Between Serum and CSF Levels of ATX and Other MDD Patient Characteristics

No significant correlations were observed between either serum or CSF ATX levels and clinical characteristics such as age, age of onset, duration of current episode, number of episodes, body weight, body mass index, smoking history, use of nonsteroidal antiinflammatory drugs, and IMI equivalence dose (Set 1 and 2; data not shown).

**Table 2.** Multivariate Linear Regression Analyses Between Serum and CSF ATX Levels, Diagnosis

	Serum ATX at Pre-ECT (Set 1)			CSF ATX (Set 2)		
	Nonstandardized Coefficient $\beta$	(95% CI)	P value	Nonstandardized Coefficient $\beta$	(95% CI)	P value
Constant	227.034	(212.535–241.534)	<.001*	289.670	(275.585–303.754)	<.001*
Diagnosis (control = 0/MDD = 1)	-30.998	(-49.598 –12.397)	.001*	-17.186	(-33.350–-1.022)	.038*
Gender (female = 0/male = 1)	-61.606	(-80.419–-42.793)	<.001*	-23.599	(-39.763–7.435)	.005*
	$R^2 = 0.398, P < .001$			$R^2 = 0.205, P = .003$		

Abbreviations: CSF, cerebrospinal fluid; ATX, autotaxin; MDD, major depressive disorder. Serum samples (Set 1) and CSF samples (Set 2) were collected from separate facilities. The horizontal bars represent the mean values adjusted for gender. \* $P < .05$ .

There was no significant association of serum ATX levels with hepatic enzyme, lipid, inflammatory indices, or nutritional status, such as GOT, GPT,  $\gamma$ -GTP, total bilirubin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, C-reactive protein, leukocyte count, total protein, or albumin in the MDD group (Set 1; data not shown).

### Serum and CSF Levels of ATX in the MDD Group Compared With the Control Group

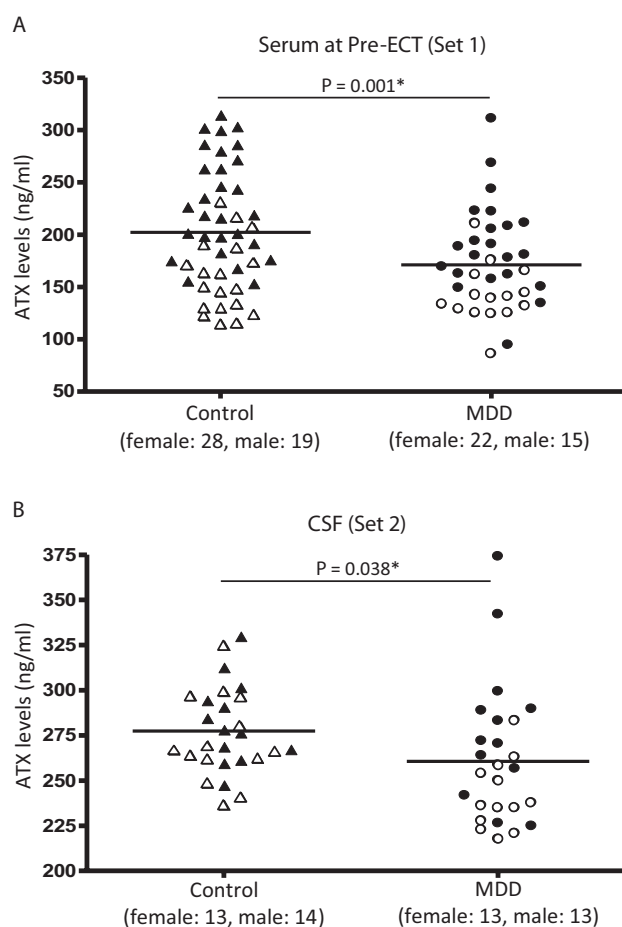
The mean serum levels of ATX in MDD patients at Pre-ECT and nondepressed controls in Set 1 were  $171.1 \pm 46.3$  and  $202.1 \pm 56.3$  ng/mL, respectively (Figure 1). The mean CSF levels of ATX in MDD patients and nondepressed controls in Set 2 were  $260.7 \pm 37.6$  ng/mL and  $277.4 \pm 24.0$  ng/mL, respectively (Figure 1). Serum ATX levels in patients with MDD were significantly lower than those of nondepressed controls as demonstrated by linear regression analysis adjusted for gender (Table 2; nonstandardized coefficient  $\beta = -30.998$ ,  $P = .001$ ). CSF ATX levels in MDD patients were also significantly lower than those of nondepressed controls (Table 2; nonstandardized coefficient  $\beta = -17.186$ ,  $P = .038$ ).

### Correlation Between Serum and CSF Levels of ATX and Clinical Symptomatic Scores in MDD Patients

Correlation coefficients were calculated between serum and CSF levels of ATX and HDRS for each MDD group using linear regression analysis, adjusting for gender and age (Figure 2). In the serum samples from MDD patients (Set 1) before undergoing ECT, there was a significant negative correlation between serum levels of ATX and total HDRS score (Figure 2; nonstandardized coefficient  $\beta = -1.714$ ,  $P = .032$ ). Furthermore, a negative correlation between serum levels of ATX and subscale HDRS scores (activity) was observed (nonstandardized coefficient  $\beta = -9.491$ ,  $P = .033$ ). Higher serum levels of ATX were associated with a trend in lower subscale HDRS scores (core symptom, somatic anxiety, delusion, nonstandardized coefficient  $\beta = -3.722$ ,  $-6.542$ , and  $-6.602$ ;  $P = .064$ ,  $.053$ , and  $.095$ , respectively). On the other hand, in Set 2, CSF levels of ATX did not correlate with total HDRS score (nonstandardized coefficient  $\beta = -1.341$ ,  $P = .186$ ) as well as subscale HDRS scores (data not shown).

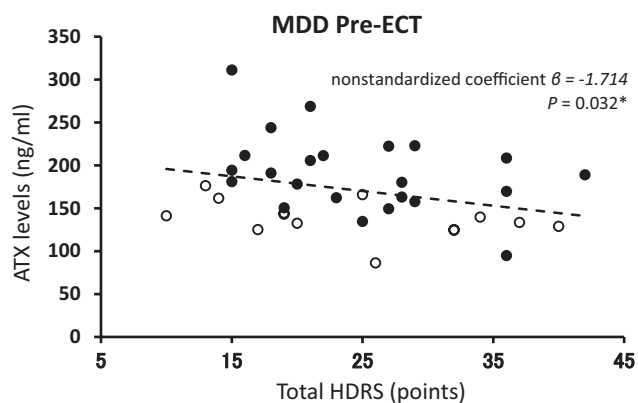
### Alterations of Serum Levels of ATX in the MDD Group Over the Course of ECT

In Set 1, 30 of 37 serum samples from MDD patients (female: 17, male: 13) were collected after ECT. A total of 7 serum samples were eliminated from analysis: 2 patients withdrew



**Figure 1.** Scatter plot of serum levels of autotaxin (ATX) (A) before a course of electroconvulsive therapy (ECT) and cerebrospinal fluid (CSF) levels of ATX (B) in control group (female:  $\blacktriangle$ ; male:  $\triangle$ ) and major depressive disorder (MDD) group (female:  $\bullet$ ; male:  $\circ$ ). Serum samples (Set 1) and CSF samples (Set 2) were collected from separate facilities. The horizontal bars represent the mean values adjusted for gender. \* $P < .05$ .

their consent, 4 patients were temporarily discharged, and 1 had a fever. Among the 30 patients, HDRS scores for depressive symptoms were significantly decreased following ECT (Pre-ECT:  $24.4 \pm 8.3$ , Post-ECT:  $5.0 \pm 2.9$ ;  $P < .001$ ). Twenty-eight of 30 patients with MDD (93.3%) responded to ECT with a 50% or more decrease in HDRS score. There was no significant difference in the IMI equivalence dose between Pre-ECT and Post-ECT (Pre-ECT:  $207.1 \pm 167.1$  mg/d and Post-ECT:



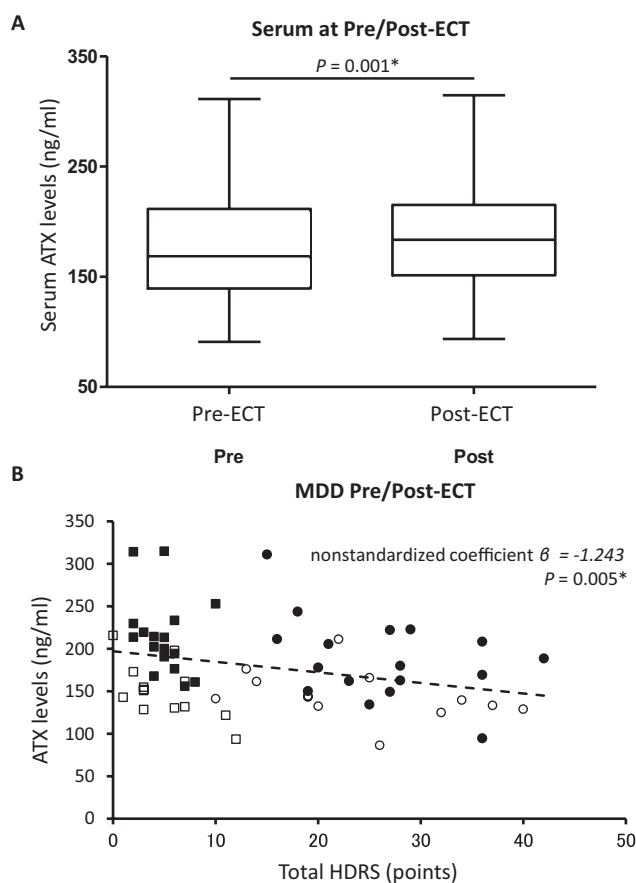
**Figure 2.** Correlation between serum levels of autotaxin (ATX) before a course of electroconvulsive therapy (ECT) and total Hamilton Depression Rating Scale-17 (HDRS) score in patients with major depressive disorder (MDD). The correlation coefficient was calculated by linear regression. Female values (●),  $n = 22$ ; male values (○),  $n = 15$ . The dashed line represents the approximate correlation curve adjusted for gender. \* $P < .05$ .

$184.2 \pm 97.1$  mg/d,  $P = .409$ ). Of the 37 patients that completed their course of ECT, serum samples from 30 patients were obtained. There were no statistically significant differences, including age, gender, HDRS score before and after ECT, and the number of ECT sessions received by each patient, between the 7 patients whose serum was not obtained and the 30 patients from whom serum was obtained (data not shown). Serum levels of ATX before ECT also did not differ between these 2 groups (data not shown).

The mean serum levels of ATX before and after ECT were  $169.6 \pm 46.3$  and  $186.9 \pm 51.4$  ng/mL, respectively. There was a statistically significant increase in serum levels of ATX in the MDD group over the course of ECT (Figure 3A;  $P = .001$ , repeated-measures ANOVA, adjusted for gender). Notably, 2 nonresponders to ECT showed slightly decreased rather than increased ATX levels after ECT. Correlation coefficients were calculated between serum levels of ATX and HDRS scores, combining results before and after ECT. There was a significant negative correlation between increased serum levels of ATX and decreased total HDRS score after ECT (Figure 3B; nonstandardized coefficient  $\beta = -1.243$ ,  $P = .005$ ).

## Discussion

Both serum and CSF ATX were significantly reduced in MDD patients, and Pre-ECT ATX serum levels and depressive symptoms were negatively correlated. Furthermore, serum levels of ATX increased following ECT. In the current study, antidepressants did not appear to directly affect ATX levels as no correlations were observed between ATX levels and IMI dose equivalence (serum: nonstandardized coefficient  $\beta = 0.065$ ,  $P = .154$ ; CSF: nonstandardized coefficient  $\beta = -0.140$ ,  $P = .159$ ) and between IMI dose equivalence before and after ECT. Also, in rat brain, chronic antidepressant treatment did not affect either mRNA or protein expression of ATX (supplementary Figure 1). The current findings indicate that alterations of ATX, which produces LPA, in part, could underlie the pathophysiology and symptomatology of MDD. However, there was no significant correlation in ATX CSF levels with severity of depression (HDRS), and the reason for this might be due to the limited number of patients and the inclusion of patients with either mild depression or patients who were in remission.



**Figure 3.** (A) Serum levels of autotaxin (ATX) before and after a course of electroconvulsive therapy (ECT) in the major depressive disorder (MDD) group, Set 1. (B) Correlation between serum levels of ATX and total Hamilton Depression Rating Scale-17 (HDRS) score at Pre/Post-ECT in the MDD group, Set 1. The correlation coefficient was calculated by linear regression. Pre-ECT female values (●),  $n = 17$ ; male values (○),  $n = 13$ . Post-ECT female values (■),  $n = 17$ ; male values (□),  $n = 13$ . The horizontal bars represent mean values. The dashed line represents the approximate correlation curve adjusted for gender. \* $P < .05$ .

Autotaxin is abundantly expressed in brain glial cells, which play an important role in the pathophysiology of depression. Autotaxin mRNA is widely expressed in adult tissue, particularly in the brain (Fuss et al., 1997). In the adult brain, ATX is restricted to early and differentiating oligodendrocyte lineage cells and reactive astrocytes and choroid plexus epithelial and leptomeningeal cells (Savaskan et al., 2007). Brain glial cells such as oligodendrocyte and astrocytes are suggested as important sources of ATX (Savaskan et al., 2007; Zhang et al., 2014). Brain imaging and postmortem evaluation of the brain from MDD patients showed robust glial abnormalities such as decreased oligodendrocyte and astrocyte density and reduced expression of genes related to oligodendrocyte and astrocyte function (Tham et al., 2011; Wang et al., 2017). In addition, preclinical animal models of depression exposed to chronic stress showed morphological and numerical decreases in cortical, hippocampal, and amygdalar oligodendrocytes (Banar et al., 2007; Czeh et al., 2007) and astrocytes (Banar et al., 2010; Gong et al., 2012; Rajkowska and Stockmeier, 2013; Sanacora and Banar, 2013), which support findings from brains of MDD patients (Rajkowska and Stockmeier, 2013; Rajkowska et al., 2015). These results suggest a potential linkage between MDD and a reduction of glia, which is a key source of ATX and could explain the reason for

the decreased levels of ATX in MDD patients. By contrast, electroconvulsive seizure treatment in rats increased the number of newly divided cells expressing oligodendrocyte markers in the frontal cortex (Madsen et al., 2005). Electroconvulsive seizure also significantly increased the expression of glial fibrillary acidic protein, a marker of reactive astrocytes, in the rat frontal limbic system (Kragh et al., 1993). These preclinical findings in combination with the current clinical findings suggest that amelioration of MDD by ECT could be mediated by an induction of the proliferation of oligodendrocyte and reactive astrocytes, thereby increasing ATX levels.

Another possibility is that chronic stress could be involved in the regulation of ATX expression. MDD is characterized by abnormal physiological responses to chronic stress. One likely source of serum ATX is adipose tissue (Ferry et al., 2003). Hypercortisolemia has been attributed to hypothalamic–pituitary–adrenal (HPA) axis dysregulation, a consistent biological response to chronic stress in MDD (Kunugi et al., 2006). Chronic treatment with prednisolone, which induces hypercortisolemia and changes in the HPA axis, decreases serum levels of ATX in humans by changing adipose tissue ATX expression (Sumida et al., 2013). This finding suggests reduced expression of ATX levels in MDD could be mediated through and a dysfunctional HPA axis. It is possible that a dysfunctional HPA axis could have mediated the decreased ATX observed in MDD patients in the current study, but measurement of serum or CSF cortisol will be needed to show a relationship between these parameters and alteration of ATX levels in MDD patients.

To place the current findings into perspective, there are a few limitations that should be mentioned. While the total sample size of the current study was not very large, significant correlations were nonetheless observed. It is possible that some of the changes in serum ATX levels following ECT could be due in part to a placebo response, but there were only 2 patients who did not respond to ECT, so this possibility could not be tested in the current study. While withholding treatment in the current study would have been unethical, examination of more patients in which ECT failed to alleviate symptoms would determine the extent, if any, of a placebo effect on ATX expression. Secondly, ATX, but not LPA, was measured. Measurement of LPA levels and its species requires the use of an enzymatic cycling assay and liquid chromatography/mass spectrometry, respectively (Kurano et al., 2015). Furthermore, the currently obtained samples, both serum and CSF, may not be used to measure LPA since sampling conditions were not under stringent conditions needed to ensure LPA stability (Hosogaya et al., 2008). Although there is a strong association between peripherally expressed ATX and LPA in humans (Watanabe et al., 2007; Masuda et al., 2008), the correlation between ATX and LPA levels in MDD patients is unclear. The correlation between peripheral blood and CSF ATX levels is not clear, though there could be a linkage between CSF and peripheral ATX levels as the current study showed decreased levels of ATX in both serum and CSF. An exact correlation may be difficult to obtain as there are technical difficulties with measuring LPA levels and there are a number of LPA species (Kurano et al., 2015). Further confirming the suitability of ATX levels as a surrogate to LPA activity could also be performed in preclinical models of depression by demonstrating a relationship between ATX and LPA levels in the periphery and in the CSF from the same MDD patient. Finally, only one factor in a biological cascade was measured without exploring a possible relationship between ATX levels and inflammation/immunological indices, such as cytokines. If inflammation, via the ATX/LPA axis mediates MDD, then future studies will need to demonstrate a relationship

between ATX levels and inflammation/immunological indices, perhaps by utilizing fluids from the same patient.

The current study confirmed previous findings that the serum concentration of ATX in women is significantly higher than that of men (Nakamura et al., 2008). Since ATX is essential for stabilization of blood vessels and angiogenesis (Tanaka et al., 2006; van Meeteren et al., 2006) and is produced in adipocytes, higher levels in females could reflect basic biological differences or the higher body fat ratio found in women compared with men (Blaak, 2001). On the other hand, no significant difference was observed in CSF ATX concentrations between nondepressed males and females using a 2-site immunoenzymetric assay (Nakamura et al., 2009). In the current study, not only serum but also CSF ATX levels in women were significantly higher than those in men. This discrepancy could be due to a limited number of patients ( $n = 53$ ) and a difference in the quantification method used in the current study compared with previous studies. There was no correlation between age and either serum or CSF ATX levels in females (serum: nonstandardized coefficient  $\beta = -0.182$ ,  $P = .757$ ; CSF: nonstandardized coefficient  $\beta = -0.629$ ,  $P = .926$ ), and between postmenopausal and serum or CSF ATX levels in females (serum: nonstandardized coefficient  $\beta = 6.226$ ,  $P = .737$ ; CSF: nonstandardized coefficient  $\beta = 9.712$ ,  $P = .613$ ), suggesting that there is no correlation between ATX levels and menopausal status. However, a future study should address potential relationships between menstrual and menopausal status and ATX levels.

In conclusion, the current study found, for the first time, that both serum and CSF levels of ATX were significantly decreased in MDD patients compared with nondepressed controls matched for age and gender. Also, there were significant correlations between depressive symptoms and serum levels of ATX. A course of ECT in MDD patients significantly increased serum levels of ATX. The findings suggest that alteration of ATX levels indicate changes in levels of lysophospholipids such as LPA, which occurs as a cellular response to MDD and could reflect the severity of depressive symptoms, which are, in turn, sensitive to ECT. Thus, the current findings lend support to the possibility that a decline in ATX, leading to decreased LPA, could be associated with the pathophysiology of MDD, and serum and CSF ATX measurement could be used as a biomarker for evaluating the efficacy of treatments in some MDD patients. However, in the current study, LPA levels were not directly quantified, given current methodological limitations. Future studies, utilizing readily accessible quantification methods, should be able to demonstrate a direct relationship between levels of ATX and LPA in MDD patients.

## Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

## Funding

This work was supported by a Grants-in-Aid from the Japan Society for the Promotion of Science (15K09819 to M.T., 16K19796 to N.K., 16K18883 to M.O.-T., 15H02552 to Shigeto Y.); an Intramural Research Grant for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry (24-11, 27-1 to H.K.); Grant-in-Aid for Scientific Research (A) from the Ministry of Education, Science, Sports and Culture (25253075 to H.K.), and Health and Labour Sciences Research Grants for Comprehensive Research on Persons with Disabilities from

Japan Agency for Medical Research and Development (AMED) (15dk0310061h0001, 16dk0307062h0001 to H.K.); Integrated Research on Depression, Dementia and Development Disorders from AMED (18dm0107093h0003 to Shigeto Y).

## Acknowledgments

We are grateful to our colleagues for their tireless and expert assistance: Dr Hideo Kobayakawa, Dr Keigo Nakatsu, Dr Takashi Iwamoto, and Dr Motonobu Nakamura. We also thank Dr Yasutaka Fujita for establishing the patients' database, Professor Junko Tanaka and Tomoyuki Akita for advice on statistical analysis, and Dr Aldric Hama for editorial assistance.

## Interest Statement.

None.

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