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Plasma Ceramides Are Elevated in Depression

Patricia Gracia-Garcia, M.D., **Vani Rao, M.D.**, **Norman J. Haughey, Ph.D.**, **Veera Venkata Ratnam Bandaru, Ph.D.**, **Gwenn Smith, Ph.D.**, **Paul B. Rosenberg, Ph.D.**, **Antonio Lobo, M.D.**, **Constantine G. Lyketsos, M.D.**, and **Michelle M. Mielke, Ph.D.**
Drs. Gracia-Garcia and Lobo are affiliated with the Department of Psychiatry Hospital Clínico Universitario, University of Zaragoza, Instituto Aragonés de Ciencias de la Salud, Zaragoza and CIBERSAM, Spain; Drs. Rao, Smith, Rosenberg, Lyketsos, and Mielke are affiliated with the Department of Psychiatry, Johns Hopkins University School of Medicine; Drs. Haughey and Bandaru are affiliated with the Department of Neurology, Johns Hopkins University School of Medicine.

Abstract

This study preliminarily examined whether plasma ceramides were elevated in depression, and if the elevation was more pronounced in Alzheimer's compared to controls. Results suggest plasma ceramides are elevated in persons with a major depression diagnosis regardless of dementia status.

Keywords

ceramides; lipids; depression

INTRODUCTION

While monoamine dysfunction, particularly of the serotonin (5-HT) system, is the primary neurobiological hypothesis guiding research and treatment of major depressive disorders,[1] emerging evidence suggests perturbations in sphingolipid metabolism may also be involved. The sphingolipid ceramide is a bioactive signaling lipid that regulates cellular events ranging from proliferation to apoptosis.[2] Ceramides can be rapidly generated via hydrolysis of sphingomyelins by sphingomyelinases. Recent findings have implicated acidic sphingomyelinase (ASM), and its reaction product ceramide, in monoamine function as well as the pathology of depressive disorders. Further, ceramides may alter the function of the dopamine transporter, causing a reduction in dopamine and increase in 5-HT transport into rat striatal synaptosomes.[3] Further, increasing the ceramide content of cell membranes increases the affinity of the 5-HT-1A receptor.[4] In the one clinical study, peripheral blood mononuclear cell ASM activity was increased in subjects with major depression compared to healthy volunteers.[5]

Approximately 25-30% of people with Alzheimer's disease (AD) are diagnosed with major depression.[6] Multiple studies have shown that particular forms of ceramide are increased in the brains of people with AD[7] and predict memory impairment[8] while experimental studies have identified pathogenic links between increased ceramide and abberant amyloid-processing.[7,9] Together, these findings suggest that perturbed sphingolipid metabolism may

CORRESPONDING AUTHOR: Michelle M. Mielke, Ph.D., Assistant Professor, Johns Hopkins University School of Medicine, Department of Psychiatry, Division of Geriatric Psychiatry and Behavioral Sciences, Bayview – Alpha Commons Building, 4th floor – room 454, Baltimore, MD 21224, Phone: 443-326-5174, Fax: 410-550-1407, mmielke1@jhmi.edu.

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increase the vulnerability of AD patients to depressive symptoms. The present preliminary study examined whether current or past depression was associated with increased plasma ceramides, and whether the increase was greater in AD patients with depressive symptoms.

METHOD

Participants included 25 cognitively normal controls (NC) and 21 Alzheimer disease (AD) patients recruited from the Johns Hopkins Alzheimer's Disease Research Center and Memory clinics. Participants were ≥55 years of age, had no neurological disease other than AD, and were required to have an informant. NC had a Clinical Dementia Rating (CDR) of 0;[10] AD patients had a CDR=1 and met NINCDS/ADRDA criteria for probable AD.[11] The study was approved by the Johns Hopkins University Institutional Review Board.

Participant evaluation included a clinical assessment, medical history, medication inventory, neuropsychological examination, and blood draw. Major depression was assessed via self- and informant-report of clinically diagnosed recent-depression (major depression within 2 years), past-depression (last episode >2 years ago) and no major depression.

Non-fasting blood was drawn and plasma was isolated and frozen at −80°C until processing. Sphingolipids were extracted as previously described,[12] and detected and quantified by LC/MS/MS using multiple reaction monitoring (MRM).

Ceramide measurements were log-transformed and examined as continuous variables in units of counts per second (cps), a quantification of area under the curve, commonly used for sphingolipid assays. Group differences in plasma lipids were first examined with ANOVAs, and subsequent pairwise associations with t-tests. Effect size was examined using Cohen's d. The *a priori* p-value was set at $p<0.05$. All analyses were conducted using SPSS version 16.0.

RESULTS

Fifteen participants (5 NC and 10 AD) reported Recent-Depression, eight (4 NC and 4 AD) reported Past-Depression, and twenty-three (16 NC and 7 AD) had no current or past history of depression (No-Depression). As results between plasma ceramides and depression were the same, and there were no differences in mean ceramide levels between NC and AD, the two groups were combined.

The mean age of the sample was 74.6 (SD=6.9) and mean education was 15.8 (SD=3.2) years; 20 (43.5%) were women. Based on the General Health Medical Rating (GHMR) Scale, the majority of participants (80.0%) had "Excellent" health while the others (20.0%) had "Good" health. Half (50.0%) of the sample was diagnosed with hypertension, 6.5% with angina, and 10.9% with diabetes mellitus. There were no differences between NC and AD patients with regards to age, education or other health-related characteristics ($p<0.05$). The mean MMSE for the NC group was 28.8 (SD=1.2) and for the AD group was 22.2 (SD=3.1). Nineteen of the 21 AD patients (90.4%) were taking cholinesterase inhibitors or Namenda at baseline. Fourteen (93.3%) participants with Recent-Depression, 5 (62.5%) with Past-Depression group and 0 with No-Depression were taking anti-depressants; all but one were taking selective serotonin re-uptake inhibitors (SSRIs). There were no differences in age, gender, education or health-related characteristics including hypertension, hypercholesterolemia, or diabetes by depression status ($p<0.05$).

Plasma ceramides C16:0, C18:0, C20:0, C24:1 and C26:1, but *not* C22:0 or C24:0 varied by depression group ($p<0.05$; Table 1). Examining pairwise associations, participants with Recent-Depression had higher mean log ceramide levels of C16:0, C18:0, C20:0, C24:1 and

C26:1 compared to those with No-Depression or Past-Depression ($p < 0.05$) (Table 1). Effect sizes for significant pairwise associations were large, ranging from 0.73 to 2.39. Mean ceramide levels did not differ between the No-Depression and Past-Depression groups. There was also not a correlation between plasma ceramide levels and Geriatric Depression Scale (GDS) score across or within each depression group. Plasma ceramides did not differ by current anti-depressant use ($p>0.10$).

DISCUSSION

Participants with recent major depression (within the previous 2 years), had higher plasma levels of ceramide C16:0, C18:0, C20:0, C24:1 and C26:1 compared to subjects with a past- (last episode >2 years ago) or no-history of major depression. This increase was observed both in individuals with normal cognition and those with AD. Effect sizes were large.

These results are consistent with a previous clinical study that examined ceramide metabolism in depression and found higher ASM activity (which leads to higher ceramide levels) in peripheral blood mononuclear cells of patients with major depression versus controls.[5] In combination with our current findings, these data suggest that peripheral measures of sphingolipid metabolism may be useful indicators of current depression. While the role of ceramides in the pathogenesis of depression remains to be elucidated, an increase in the ceramide content of cell membranes can perturb monoaminergic transport across the cell membrane and alter 5HT1A affinity for 5-HT.[3,4] It has been suggested that ceramides may be responsible for the therapeutic latency of anti-depressants.[13] Additionally, ceramides increase the activity of phospholipaseA2,[14] which has been reported to be elevated in major depression.[15]

Findings from cellular and animal studies suggest that anti-depressant drugs may regulate ceramide levels. Treatment with imipramine and amitriptiline decreased ASM activity in cultured cells,[5] suggesting that these antidepressants may decrease ceramide levels. The effects of anti-depressants on plasma ceramides were not directly measured in the present study as all but one participant in the Recent-Depression group were taking anti-depressants. Plasma ceramide levels in the Past-Depression group did not differ between the five subjects taking an anti-depressant and the three subjects who were not, but the sample sizes are too small to draw a conclusion.

The major limitation of this study is that the diagnosis of depression was by self- and informant-report of a physician’s diagnosis rather than with validated diagnostic instruments. Additionally, limitation is the small sample size, although effect sizes were statistically significant and quite large regardless of the sample size. Lastly, Recent-Depression included those diagnosed within two years, some of whom may have remitted. Despite this limitation, however, there were still significant differences in plasma ceramides between those with Recent-Depression and those with Past-Depression. One explanation for these findings is that subjects in the Recent-Depression group are still in a “depressive state” and once the depression has completely remitted, as in the Past-depression group, plasma ceramide levels return to normal. Future research will need to examine plasma ceramide levels or ASM activity over the course of major depression. Such an approach will allow us to understand the relationship between plasma ceramide levels or ASM activity to affective symptoms and cognitive dysfunction .

In summary, these findings support a potential role for dysregulated ceramide metabolism in the pathogenesis of depressive disorders. Additional research to identify the mechanisms by which ceramide metabolism contributes to pathogenesis may lead to the identification of new therapeutic targets to treat depressive disorders.

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TABLE 1

Comparison of mean plasma log ceramide values (in counts per second) between depression groups and effect sizes.

	No-Dep	Recent-Dep	Past-Dep			Recent-Dep		Recent-Dep		Past-Dep	
Log	**n=23**	**n=15**	**n=8**			**vs. No-Dep**		**Past-Dep**		**vs. No-Dep**	
Ceramide	***mean (sd)***	***mean (sd)***	***mean (sd)***	$F_{2,43}$	**p-value**	***p-value***	***cohen's d***	***p-value***	***cohen's d***	***p-value***	***cohen's d***
C16:0	12.88 (0.22)	13.08 (0.20)	12.78 (0.25)	6.13	**0.005**	**0.007**	0.95	**0.004**	1.33	0.283	0.42
C18:0	12.45 (0.37)	12.97 (0.19)	12.37 (0.30)	15.59	**<0.0001**	**<0.0001**	1.77	**<0.0001**	2.39	0.618	0.24
C20:0	13.89 (0.27)	14.23 (0.21)	13.77 (0.35)	9.77	**<0.001**	**<0.001**	1.41	**<0.001**	1.59	0.350	0.38
C22:0	16.23 (0.55)	16.27 (0.54)	16.22 (0.32)	0.04	0.962						
C24:0	17.96 (0.37)	17.95 (0.33)	17.85 (0.20)	0.35	0.708						
C24:1	16.78 (0.30)	16.97 (0.24)	16.69 (0.20)	3.44	**0.041**	**0.048**	0.70	**0.013**	1.27	0.466	0.35
C26:0	14.55 (0.33)	14.63 (0.31)	14.36 (0.16)	2.14	0.130						
C26:1	13.50 (0.31)	13.69 (0.20)	13.38 (0.29)	3.79	**0.031**	**0.042**	0.73	**0.006**	1.24	0.368	0.40

No-Dep = Non-depressed; Recent-Dep = Recent major depressive episode withing the past 2 years; Past-Dep = Past depression (>2 years)

Bold indicates $p<0.05$

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