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ORIGINAL ARTICLE

Observational Study

Disrupted leptin-fatty acid biosynthesis is an early manifestation of metabolic abnormalities in schizophrenia

Mohammad M Khan

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Abstract

BACKGROUND

Insulin resistance (IR) and impaired energy expenditure (IEE) are irreparable metabolic comorbidities in schizophrenia. Although mechanism(s) underlying IR and IEE remains unclear, leptin and fatty acid signaling, which has profound influence on insulin secretion/sensitivity, glucose metabolism and energy expenditure, could be disrupted. However, no association of plasma leptin with erythrocyte membrane fatty acids, body mass index (BMI), and psychotic symptoms in the same cohort of untreated patients with first-episode psychosis (FEP) or medicated patients with chronic schizophrenia (CSZ) is presented before. These studies are crucial for deciphering the role of leptin and fatty acids in the development of IR and IEE in schizophrenia.

AIM

To determine the association between plasma leptin, erythrocyte membrane fatty acids, particularly, saturated fatty acids (SFAs), BMI and psychotic symptoms in patients with FEP and CSZ.

METHODS

In this study, twenty-two drug naive patients with FEP, twenty-one CSZ patients treated with atypical antipsychotic drugs, and fourteen healthy control (CNT) subjects were analyzed. Plasma leptin was measured using sandwich mode enzyme-linked immunosorbent assay. Erythrocyte membrane SFAs were measured using ultrathin capillary gas chromatography. BMI was calculated by using the formula: weight (kg)/height (m^2). Psychiatric symptoms were evaluated at baseline using brief psychiatric rating scale (BPRS), and positive and negative

syndrome scale (PANSS). The total BPRS scores, positive and negative symptom scores (PANSS-PSS and PANSS-NSS, respectively) were recorded. Pearson correlation coefficient (r) analyses were performed to find the nature and strength of association between plasma leptin, PANSS scores, BMI and SFAs, particularly, palmitic acid (PA).

RESULTS

In patients with FEP, plasma leptin not BMI was significantly lower (P = 0.034), whereas, erythrocyte membrane SFAs were significantly higher (P < 0.005) compared to the CNT subjects. Further, plasma leptin showed negative correlation with erythrocyte membrane SFAs-PA (r = −0.4972, P = 0.001), PANSS-PSS (r = −0.4034, P = 0.028), and PANSS-NSS (r = −0.3487, P = 0.048). However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS-PSS (r = 0.5844, P = 0.0034) and PANSS-NSS (r = 0.5380, P = 0.008). In CSZ patients, plasma leptin, BMI, and erythrocyte membrane SFAs, all were significantly higher (P < 0.05) compared to the CNT subjects. Plasma leptin showed positive correlation with BMI (r = 0.312, P = 0.032) but not with PANSS scores or erythrocyte membrane SFAs-PA. However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS-NSS only (r = 0.4729, P = 0.031). Similar changes in the plasma leptin and erythrocyte membrane SFAs have also been reported in individuals at ultra-high risk of developing psychosis; therefore, the above findings suggest that leptin-fatty acid biosynthesis could be disrupted before the onset of psychosis in schizophrenia.

CONCLUSION

Disrupted leptin-fatty acid biosynthesis/signaling could be an early manifestation of metabolic comorbidities in schizophrenia. Large-scale studies are warranted to validate the above findings.

Key Words: Schizophrenia; Leptin; Fatty acids; Insulin resistance; Impaired energy expenditure

Core Tip: Insulin resistance (IR) and impaired energy expenditure (IEE) are untreatable metabolic comorbidities in schizophrenia. Leptin and fatty acids have profound influence on insulin synthesis, secretion and energy metabolism. Although previous studies have measured plasma leptin and membrane fatty acids in schizophrenia, findings are very heterogeneous, and moreover, no single study has ever measured both plasma leptin and membrane fatty acids together in the same cohort of schizophrenia patients. These studies are crucial not only for analyzing the relationship between leptin and fatty acids in the same cohort of schizophrenia patients, but also for deciphering their role in the development of IR and IEE.

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INTRODUCTION

Schizophrenia is a complex multisystem disorder, which apart from displaying psychotic symptoms and cognitive deficit also manifests a range of metabolic abnormalities including insulin resistance (IR) and impaired energy expenditure (IEE)[1-4]. Evidence suggests that IR and IEE may develop before the onset of psychosis and deteriorate further following antipsychotic intervention, prompting premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia[5-9]. Deciphering the underlying mechanism(s) may help in developing appropriate therapies for minimizing IR and IEE and increasing treatment adherence and outcome in schizophrenia.

While several mechanisms may contribute in the development of IR and IEE, disrupted adipokine and fatty acid (FA) signaling could play a central role. Leptin is an important adipokine, which at physiologically elevated condition strongly inhibits insulin synthesis and secretion and causes weight gain by stimulating lipogenesis and adipogenesis while concurrently inhibiting fatty acid oxidation[10-12]. Removing leptin from blood circulation has been shown to normalize body weight and hyperglycemia in obese animals[13].

FAs, specially, saturated FAs (SFAs) stimulate insulin secretion from pancreatic β-cells[14], but inhibit both leptin synthesis and secretion from adipose tissue[15,16]. Since adipose tissue (adipocytes), like

erythrocytes, contain high percentage of SFAs; consequently, SFAs could be the main regulators of leptin synthesis and secretion from adipose tissue. Evidence suggests that elevated SFAs can impair glucose and FA metabolism by inducing endoplasmic reticulum stress and mitochondrial dysfunction [17]. Moreover, while intracellular accumulation of all FAs can provoke IR, effect of SFAs could be more detrimental and persistent due to the development of various inflammatory cues[18].

Although previous studies have measured plasma leptin and membrane SFAs in schizophrenia, findings are very conflicting and association between leptin, SFAs and body mass index (BMI) has not been studied. Moreover, no study has ever measured plasma leptin, membrane SFAs and BMI together in the same cohort of patients with schizophrenia. These studies are crucial not only for analyzing the relationship between leptin, SFAs, and BMI in schizophrenia, but also for deciphering their role in the development of IR, IEE, and other metabolic comorbidities.

In this study, association between plasma leptin, erythrocyte membrane SFAs, and BMI was determined in the drug-naive patients with first-episode psychosis (FEP), medicated patients with chronic schizophrenia (CSZ), and healthy control (CNT) subjects. While our group has published earlier preliminary data on the membrane FAs including SFAs, monounsaturated FAs and polyunsaturated FAs[19], data on the plasma leptin and BMI and its association with erythrocyte membrane SFAs, BMI and clinical symptoms in patients with FEP and CSZ is naive and is presented here. In addition, possible mechanisms delineating the role of leptin and SFAs in the development of IR and IEE are discussed.

MATERIALS AND METHODS

Patients and control subjects

A total of twenty-two (n = 22) drug-naïve FEP patients, twenty-one (n = 21) medicated patients with CSZ, and fourteen (n = 14) male control (CNT) subjects were analyzed in this study. Patients with FEP were enrolled from consecutive admissions at the Department of Psychiatry, Dwight David Eisenhower Army Medical Center (DDEAMC), Fort Gordon, GA. The patients were mostly active duty army personal diagnosed with schizophrenia or schizophreniform disorder using DSM IV criteria, and after six months follow-up period during subsequent hospitalization. The BMI was calculated according to the formula BMI = kg/m^2, where kg is body weight in kilogram and m is the height in meters[20]. Clinical symptoms of the patients were evaluated at baseline using brief psychiatric rating scale (BPRS) and the positive and negative syndrome scale (PANSS)[21,22]. The total BPRS scores, positive symptoms scores (PANSS-PSS: sum of scores on conceptual disorganization, hallucination, delusions, unusual thoughts, contents, and suspiciousness), and negative symptom scores (PANSS-NSS: sum of scores on emotional withdrawal, blunted effect and motor retardation) were examined in this study. The mean age at the onset of psychosis was 22.40 ± 4.08 years. Patients with CSZ were enrolled at the outpatient clinic of Mental Health Service, VA Medical Center (VAMC), Augusta, GA. The clinical symptoms of these patients were analyzed using the same methodologies as used for patients with FEP. The CSZ patients were on treatment with various atypical antipsychotic drugs (AAD) including clozapine (n = 14), olanzapine (n = 4), or risperidone (n = 3) for the past 1-5 years. It is important to point out that FEP patients after discharge from Army Medical Centers such as DDEAMC are admitted to the Psychiatry Services at the VA Medical Centers. Therefore, both patient groups in this study represent unique populations with demographic similarities except, the years of illness and treatment. The CNT subjects (n = 14) consisted of healthy volunteers recruited *via* advertisements at the Medical College of Georgia (MCG), VAMC, and DDEAMC. The CNT subjects were matched for age and gender with the patients with FEP. The demographic and clinical characteristics of the patients are presented in the Table 1. Institutional Review Boards of DDEAMC and MCG, Augusta, GA approved the research protocol, and a signed consent was taken from all the patients and CNT subjects.

Regarding inclusion and exclusion criteria, all patients with FEP and CSZ were included in this study on the basis of the following criteria; they were medically healthy except psychosis, and none had a history of seizures or severe head injury with loss of consciousness or a history of substance abuse within the last one year. Patients with any of these complications were excluded from the study. Moreover, during the six months follow up period of patients with FEP, those patients who did not meet DSM IV criteria for diagnosis or who turned out to have primary bipolar or major depression were also excluded from the study. A total of 38 patients with FEP were followed up for six months, 29 patients (23 male and 6 female) were found to be eligible. Out of 29 patients, 6 female patients were excluded and 1 male patient plasma sample was not used due to turbidity, so only only 22 male patients with FEP were analyzed.

Analysis of erythrocyte membrane FAs and plasma leptin

The procedures for measuring erythrocyte membrane FAs has been published earlier by our group, it is not discussed here for brevity[19,23]. For measuring plasma leptin, fasting blood was drawn in Lavender vaccutainer containing EDTA. The blood was centrifuged at 2500 rpm for 10 min at 5C. Plasma was carefully separated and stored at -20C before use. Sandwich mode enzyme-linked immunosorbent assay (ELISA) was used to measure plasma leptin using a commercially available Kit

Table 1 Demographic and clinical characteristics of the study subjects

Characteristics	CNT	FEP	CSZ
Age (yr)	25 ± 7.6	23.54 ± 4.65	42.23 ± 5.12
Gender (M:F)	14:0	22:0	21:0
Age at onset of psychosis		22.80 ± 4.78	23.15 ± 6.35
Years of Illness		≤ 5.0 d	22.77 ± 7.21
Total BPRS Total		45.18 ± 12.53	38.17 ± 6.96
Total PANSS-PSS		21.03 ± 4.81	12.88 ± 4.10
Total PANSS-NSS		20.91 ± 5.10	07.82 ± 2.31
Plasma leptin (ng/mL)	5.79 ± 0.80	4.77 ± 1.35	08.33 ± 1.25
BMI (kg/m^2)	25.1 ± 2.61	23.2 ± 2.14	29.86 ± 3.60
Smoking		2/23	3/21
Antipsychotic use			+++
Tobacco			
Cannabis			

CNT: Control subjects; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BPRS: Brief psychiatric rating scale; PANSS-PSS: Positive symptom scores; PANSS-NSS: Negative symptom scores; BMI: Body mass index.

from Signet Laboratories (Dedham, MA). The ELISA procedure was performed in accordance with the directions of the manufacturer in a sandwich mode using two monoclonal antibodies to leptin: a coating antibody and an HRP-conjugated antibody. The ELISA plates were supplied pre-coated with the coating antibody. All samples were diluted to 1:3000 (in PAT buffer provided with kits) before use. The plates were incubated in duplicates with 100 L of diluted samples overnight at 4C in dark. The wells were washed three times with 250 L of PT buffer (PBS-Tween 20 buffer provided with kit). Plates were then incubated with 100 L of diluted conjugate (HRP-conjugated leptin antibody) for 2 h at room temperature in the dark. The plates were then extensively (3-4 times) washed with 250 L of PT buffer followed by incubation with 150 L O-Phenylenediamine substrate for 20 min at room temperature in the dark to allow color formation. Reaction was stopped by the addition of 50 L of 5.0 M sulfuric acid and the color intensity was read at dual wavelengths using 492 nm as the test wavelength and 620 nm for the reference wavelength. All samples were analyzed twice simultaneously.

Statistical analysis

All statistical analyses were performed using Prism software and the values are expressed as mean ± SE. The values of slope and intercept for the standard samples were calculated by the linear regression method. The data was further analyzed for significance between groups using Student's *t*-test (two-tailed variance) or One-Way ANOVA, and a P value < 0.05 was considered significant. Pearson correlation coefficient (r) analysis was performed to find the nature and strength of association between different variables including SFAs, plasma leptin, BMI, and clinical symptoms including PANSS-PSS and PANSS-NSS.

RESULTS

Table 1 shows the demographic and clinical characteristics of the patients and CNT subjects. Figure 1 shows statistical analyses of plasma leptin, BMI, erythrocyte membrane SFAs including palmitic acid (PA) and stearic acid (SA) in CNT subjects, FEP and CSZ patients. Average plasma leptin (Figure 1A) in FEP patients (4.77 ± 1.35 ng/mL) was significantly (P = 0.028) lower than CNT subjects (5.79 ± 0.80 ng/mL), whereas, in CSZ patients, plasma leptin (8.33 ± 1.25 ng/mL) was significantly higher than FEP patients (P = 0.006). The average BMI value (Figure 1B) of FEP patients (23.21 ± 2.14) was statistically similar to the BMI value of CNT subjects (25.10 ± 2.61, P = 0.144). However, the average BMI value (Figure 1B) of AAD treated CSZ patients (29.86 ± 3.60) was significantly (P = 0.012) higher than FEP patients, and the increase was in parallel with the increase in plasma leptin (Figure 1A). Regarding erythrocyte membrane SFAs, both PA (Figure 1C) and SA (Figure 1D) were significantly (P < 0.005) higher in both FEP and CSZ patients compared to the CNT subjects suggesting that membrane SFA abnormalities in schizophrenia are untreatable.

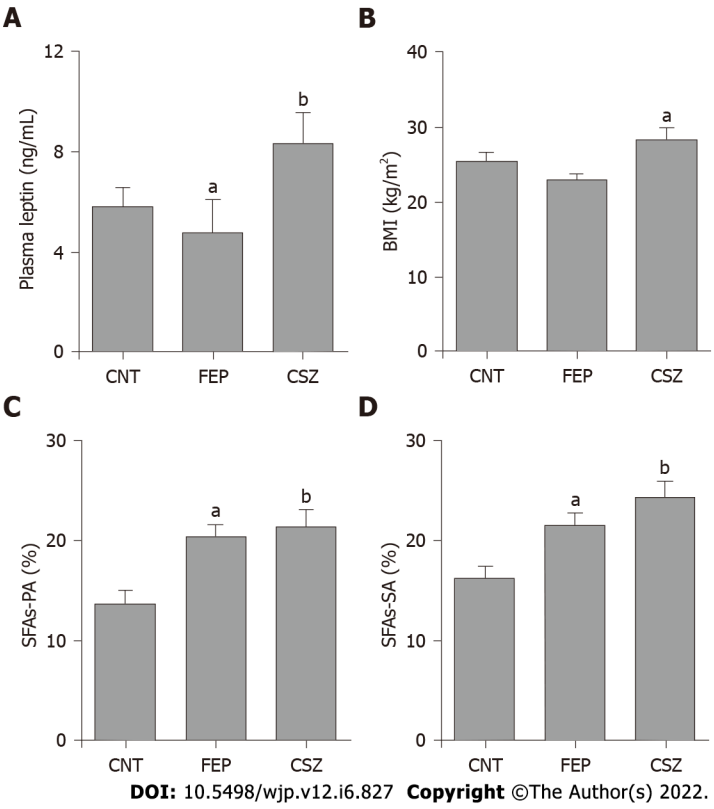

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Figure 1 Statistical analyses of plasma leptin, body mass index, erythrocyte membrane saturated fatty acids in healthy control subjects, first-episode psychosis and chronic schizophrenia patients. A: Average plasma leptin (Figure 1A) in first-episode psychosis (FEP) patients (4.77 ± 1.35 ng/mL) was significantly (P = 0.028) lower than healthy control (CNT) subjects (5.79 ± 0.80 ng/mL). In chronic schizophrenia (CSZ) patients, plasma leptin (8.33 ± 1.25 ng/mL) was significantly higher than FEP patients (P = 0.006); B: The average body mass index (BMI) value of FEP patients (23.21 ± 2.14) was statistically similar to the BMI value of CNT subjects (25.10 ± 2.61, P = 0.144). The average BMI value of clozapine treated CSZ patients (29.86 ± 3.60) was significantly (P = 0.012) higher than FEP patients; C and D: Erythrocyte membrane palmitic acid and stearic acid, respectively were significantly (P < 0.005) higher in both FEP and CSZ patients compared to the CNT subjects. CNT: Healthy control; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs: Saturated fatty acids; PA: Palmitic acid; SA: Stearic acid. ^{a}P < 0.05 and ^{b}P < 0.01.

Figure 2 shows the association of plasma leptin with clinical symptom scores. In patients with FEP, plasma leptin showed negative association with both PANSS-PSS (Figure 2A, r = −0.4034, P = 0.028) and PANSS-NSS (Figure 2B, r = −0.3487, P = 0.05). In CSZ patients, although negative association was observed between plasma leptin and either PANSS-PSS (Figure 2C, r = −0.3055, P = 0.18) or PANSS-NSS (Figure 2D, r = −0.3001; P = 0.13), it did not return significance. This could be due to treatment-induced alterations in both plasma leptin and PANSS scores compared to the drug-naive patients with FEP.

Figure 3 shows the association of erythrocyte membrane SFAs-PA with the clinical symptom scores. In patients with FEP, erythrocyte SFAs-PA showed positive correlation with both PANSS-PSS (Figure 3A, r = 0.5844, P = 0.0034) and PANSS-NSS (Figure 3B, r = 0.5381, P = 0.008). In AAD treated CSZ patients, erythrocyte SFAs-PA showed significant positive correlation with PANSS-NSS (Figure 3D, r = 0.4729; P = 0.031), but it was not significant in case of PANSS-PSS (Figure 3C, r = 0.2485, P = 0.28). These findings suggest that elevated erythrocyte SFAs could be associated more strongly with the negative symptoms in patients with both FEP and CSZ.

Since SFAs strongly inhibit leptin synthesis and secretion, therefore, association of leptin with erythrocyte SFAs-PA and BMI was also determined. In FEP patients, plasma leptin was negatively associated with SFAs-PA (Figure 4A, r = −0.4335, P = 0.0194) but not with BMI (Figure 4B, r = 0.2169, P = 0.3206), whereas, in patients with CSZ, plasma leptin showed positive association with BMI (Figure 4C, r = 0.4135, P = 0.0152) but not with erythrocyte SFAs-PA (Figure 4D, r = 0.3331, P = 0.1401). Moreover, SFAs-PA was elevated in both FEP and CSZ patients (Figure 1C and D), whereas, plasma leptin (Figure 1A) and BMI (Figure 1B) were elevated only in patients with CSZ suggesting that elevated plasma leptin could be involved in increasing BMI in CSZ patients.

DISCUSSION

In this study, significant changes in plasma leptin, BMI, and erythrocyte membrane SFAs were observed in patients with FEP and CSZ compared to the CNT subjects. These changes were also significantly

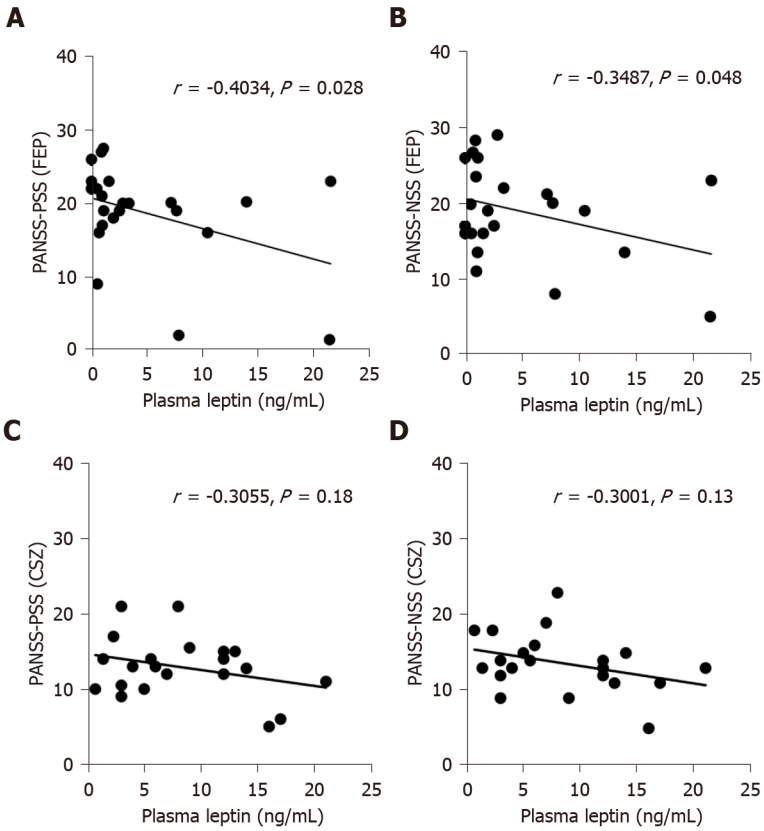

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Figure 2 Association of plasma leptin with clinical symptom (positive and negative syndrome scale) scores. A and B: In first-episode psychosis patients, plasma leptin showed negative correlation with both positive symptom score (PANSS-PSS) (r = −0.4034, P = 0.028) and negative symptom score (PANSS-NSS) (r = −0.3487, P = 0.05); C and D: In chronic schizophrenia patients, no significant negative correlation was observed between plasma leptin and either PANSS-PSS (r = −0.3055, P = 0.18) or PANSS-NSS (r = −0.3001; P = 0.13). PANSS-PSS: Positive and negative syndrome scale-positive symptom score; PANSS-NSS: Positive and negative syndrome scale-negative symptom score; FEP: First-episode psychosis; CSZ: Chronic schizophrenia.

associated with clinical symptoms in both groups of patients. The central message is that in patients with FEP, plasma leptin was significantly low and showed negative association with PANSS scores, whereas, SFAs were significantly higher and showed positive association with PANSS scores. Additionally, plasma leptin showed negative association with SFAs, which is in line with the negative effects of SFAs on leptin synthesis and secretion[15]. In AAD treated CSZ patients, plasma leptin, SFAs and BMI all were significantly higher, which is also in agreement with previous studies showing increased leptin synthesis, and weight gain after AAD treatment[24-26].

This is the first report that shows disrupted leptin and erythrocyte membrane SFA biosynthesis in the same cohort of drug-naive patients with FEP and ADD treated patients with CSZ. In addition, negative association between plasma leptin and erythrocyte SFAs has not been reported before. These findings together with the literature discussed below, suggest that leptin-fatty acid signaling, which plays a central role in insulin secretion, sensitivity, food-intake and energy metabolism, could be disrupted in schizophrenia.

Before discussing the role of leptin and SFAs in the development of IR and IEE, it can be argued that how elevated erythrocyte SFAs could relate to the changes in adipose tissue where leptin and other adipokines are synthesized[27]. Since both erythrocytes and adipose tissue share developmental relationship, and contain high percentage of SFAs[28,29], reduced leptin production in patients with FEP could be a result of increased SFA contents in the adipose tissue. And this effect should to be mediated, specifically, by the cytosolic pool of SFAs, accumulated either due to reduced FA oxidation or increased *de novo* FA biosynthesis or both because, studies have shown that SFAs circulating in the plasma or present in the extracellular space have no significant effect on leptin synthesis and secretion [15,30]. Further, like erythrocytes, SFAs could also be elevated in other tissues of FEP patients as a result of increased oxidative stress and inflammation, as both these conditions strongly stimulate *de novo* SFA biosynthesis[31-35]. Moreover, excess SFAs can be transported from intracellular space to the membrane and outside the cells by specific fatty acid transporter proteins[36].

Elevated SFAs in schizophrenia, and their role in the development of IR and IEE

Over the past thirty years, extensive efforts have been made to understand the role of membrane FAs in the pathophysiology and psychopathology of schizophrenia and other psychiatric disorders. Regarding

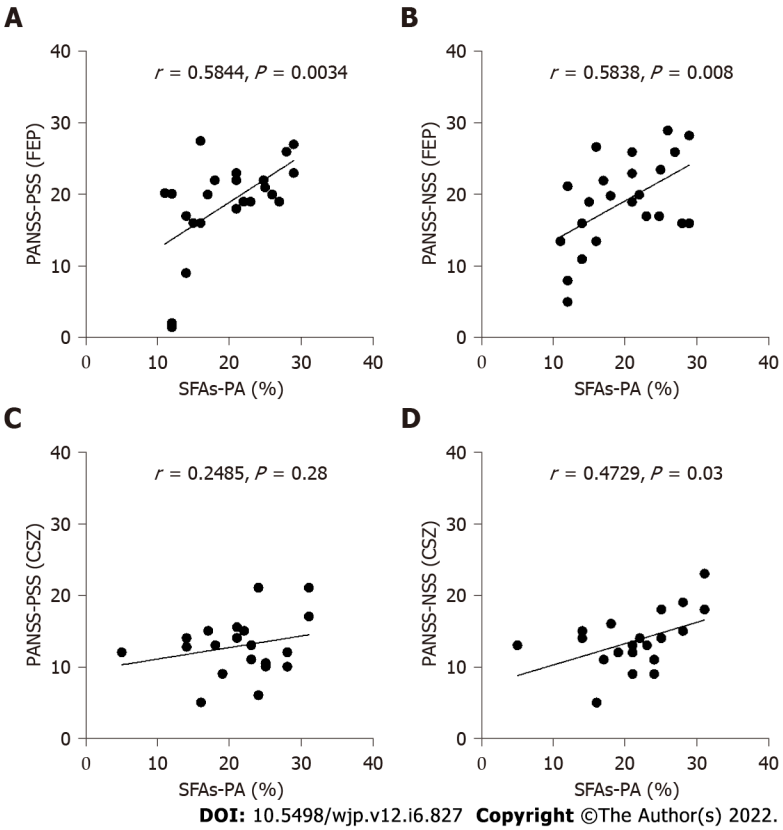

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Figure 3 Association of erythrocyte membrane saturated fatty acids-palmitic acid with clinical symptoms (positive and negative syndrome scale) scores. A and B: In first-episode psychosis patients, erythrocyte saturated fatty acids (SFAs)-palmitic acid (PA) showed positive correlation with both positive symptom score (PANSS-PSS) (A, r = 0.5844, P = 0.0034) and negative symptom score (PANSS-NSS) (B, r = 0.5381, P = 0.008); C and D: In chronic schizophrenia patients, erythrocyte SFAs-PA showed positive correlation with PANSS-NSS (D, r = 0.4729; P = 0.031), but it was not significant in case of PANSS-PSS (C, r = 0.2485, P = 0.28). Similar results were obtained with erythrocyte membrane stearic acid (data not shown). PANSS-PSS: Positive and negative syndrome scale-positive symptom score; PANSS-NSS: Positive and negative syndrome scale-negative symptom score; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; SFAs: Saturated fatty acids; PA: Palmitic acid.

membrane FAs compositions, although there may be some contradictory findings, most studies including our own have shown that erythrocyte membrane PUFAs are reduced, whereas, SFAs are increased in drug-naive patients with FEP[19,37-39]. Similar alterations in PUFAs and SFAs have also been observed in the brain tissue from the patients with FEP[40]. Specially, prefrontal cortex regions have been shown to have deficit in various PUFAs, whereas, proportion of SFAs (particularly, PA) was increased in the specific phospholipid moieties[40]. Likewise, skin fibroblasts from patients with FEP have been shown to have abnormal membrane FA compositions[41].

Intriguingly, erythrocyte FA abnormalities have also been reported in individuals at ultra-high risk of developing psychosis. In a recent study, significant reduction in various PUFAs and increase in SFAs including PA in the erythrocyte membrane has been reported in individuals at ultra-high risk of developing psychosis[42]. These findings strongly support the observations that we reported nearly 20 years ago in FEP patients, and also corroborate findings published by other groups in recent years[15,40]. In conclusion, disrupted FA biosynthesis comprising of reduced PUFAs and increased SFAs could be an early manifestation of schizophrenia pathophysiology.

Regarding the cause of SFA elevation, hypoxia-induced oxidative stress, and inflammation appear to be the potential causative factors in schizophrenia. Hypoxia has been shown to induce *de novo* FA biosynthesis in embryonic neurons and potentiate pro-inflammatory effects of SFAs in macrophages[32,43]. In addition, recent studies have shown that elevated SFAs under hypoxic conditions may serve as hydrogen acceptors, an effect that favors a shift towards anaerobic glycolysis leading to increased lactate production, an indication of IEE[32,33]. Since glutamate/glutamine are required for the *de novo* SFA biosynthesis in neurons under hypoxia[32], increased SFA biosynthesis therefore also support the findings that have shown impaired glutamate/glutamine ratio in patients with FEP and CSZ[44].

Concerning the role of FAs in schizophrenia pathophysiology, although reduced membrane PUFAs have been linked with cognitive deficit and psychotic symptoms[19,38,45,46], consensuses have not reached on the role of elevated SFAs. Since SFAs are the major fuel for energy production and utilization during resting state, increased SFA levels in patients with FEP could be an indication of impaired resting state energy expenditure. Indeed, several recent studies have shown that FEP patients and their first-degree relatives display IEE[47-52]. Also, several lines of evidence suggest that elevated

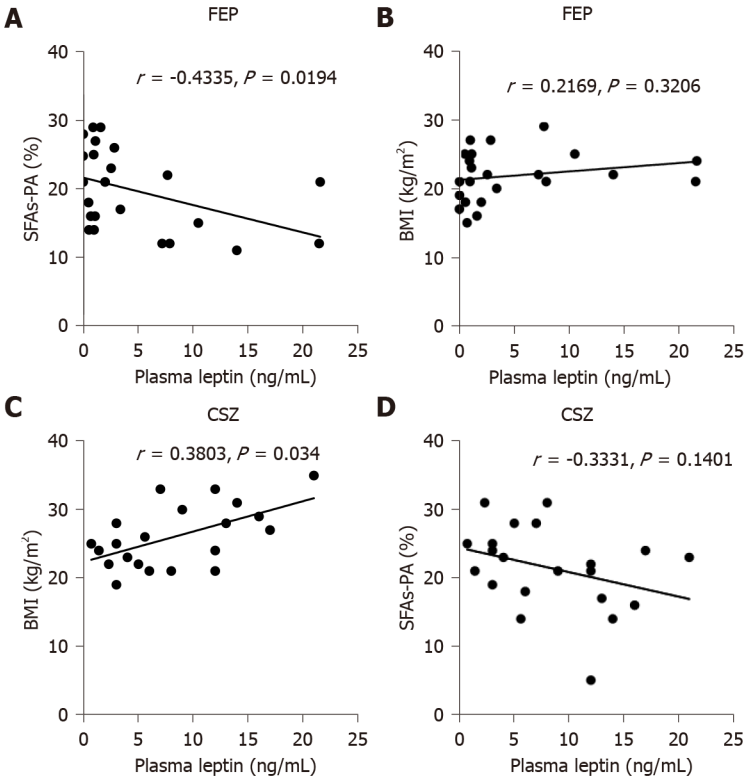

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Figure 4 Association of plasma leptin with erythrocyte saturated fatty acids and body mass index. A-D: In first-episode psychosis patients, plasma leptin showed negative correlation with saturated fatty acids (SFAs)-palmitic acid (PA) (A, r = −0.4335, P = 0.0194) but not with body mass index (BMI) (B, r = 0.2169, P = 0.3206), whereas, in chronic schizophrenia patients, plasma leptin showed positive correlation with BMI (C, r = 0.4135, P = 0.0152) but not with erythrocyte SFAs-PA (D, r = 0.3331, P = 0.1401). FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs: Saturated fatty acids; PA: Palmitic acid.

SFAs, particularly, PA could be a major risk factor for IR and IEE[53,54].

An overwhelming body of evidence suggests that most of the adverse effects including IR, IEE and increased lactate formation induced by SFAs occur as a result of increased oxidative stress and inflammation (see Figure 5 for detail mechanisms). It has been shown that SFAs, particularly, PA can cause abrupt release of Ca^{2+} from endoplasmic reticulum (ER) thereby depleting ER Ca^{2+} store, which in turn leads to a drastic increase in cytosolic and mitochondrial Ca^{2+} concentration *via* entry through store-operated Ca^{2+} channels[55-57]. This process stimulates reactive oxygen species (ROS) formation causing ER stress and mitochondrial dysfunctions (Figure 5). Evidence suggests that PA can induce ER stress in almost all the cellular systems including pancreas, cardiomyocytes, vascular smooth muscle cells, endothelial cells, skeletal muscle cells, glomerular podocytes, hepatocytes, adipose tissue, and brain by disrupting intracellular Ca^{2+} homeostasis[58].

Additional toxicity of SFAs can be produced by their ceramide derivatives because; elevated SFAs have also been shown to stimulate ceramide synthesis[59,60]. Indeed, while studies analyzing skin fibroblasts from patient with schizophrenia have found reduced total ceramide concentration, SFAs (PA) based ceramide concentration was increased compared to the CNT subjects[61-63]. Similarly, altered production of ceramides, containing PA and other SFA, has also been reported in other tissues from patients with FEP and CSZ[61-63]. Although ceramides have many important functions, their increased production can be detrimental as they can induce inflammation, obesity-associated insulin resistance, abnormal FA oxidation and other toxic effects in various tissues by inducing ER stress, mitochondrial dysfunction, and ROS formation (Figure 5)[59,60,64].

Regarding pro-inflammatory effects, SFA accumulation has been shown to induce pro-inflammatory response in adipose tissue, skeletal muscle, and liver[34,57,65]. In these events, PA activated adipocytes as well as intercalated macrophages, particularly inflammatory type (M1 type) have been shown to play a major role by secreting several pro-inflammatory cytokines including IL-1b, IL-6, IL-8, and TNF-α[57-59,65]. These and other inflammatory cytokines have been found elevated in the brain and plasma of patients with FEP and CSZ[66]. Although treatment with AAD has been shown to reduce various cytokines, IL-1b, IL-6, IL-8 and TNF-α remained elevated despite years of treatment[66,67]. Since we observed that like drug-naive patients with FEP, erythrocyte PA and other SFAs were also elevated in AAD treated CSZ patients, therefore, accumulation of SFAs could be the major contributing factor to the elevated pro-inflammatory response throughout the course of schizophrenia illness.

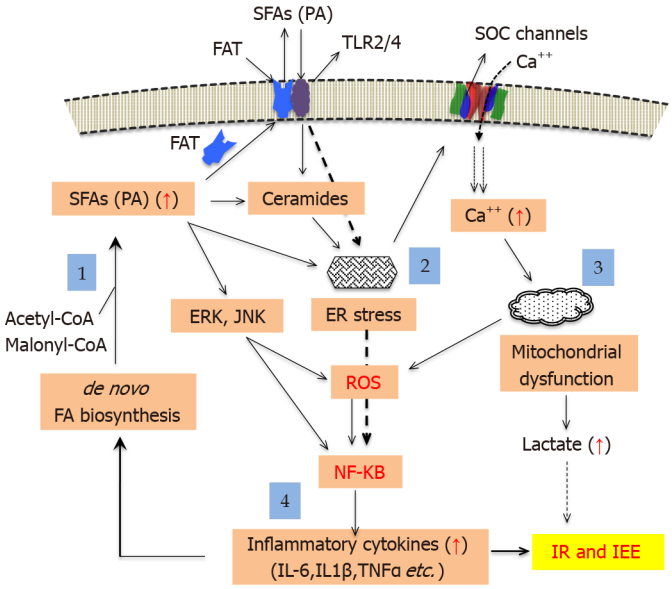

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Figure 5 Mechanisms underlying saturated fatty acids-(palmitic acid)-induced insulin resistance and impaired energy expenditure. Saturated fatty acids (SFAs) are synthesized *de novo* in the cytoplasm from acetyl-CoA and malonyl-CoA (light blue box 1), and are transported by fatty acid transporter proteins from intracellular space to the membrane and to the extra cellular space. Excess SFAs-palmitic acid (PA) can also be converted into ceramides, which together with PA can induce endoplasmic reticulum (ER) stress *via* depletion of stored calcium (light blue box 2). ER stress leads to increased calcium influx *via* plasma membrane-bound store operated calcium channels, resulting into the elevation of cytoplasmic and mitochondrial calcium and production of reactive oxygen species (ROS) as a result of mitochondrial dysfunction (light blue box 3). Both PA and ceramides can also activate plasma membrane TLR2/4 receptor resulting in the activation of MAPK/ERK and JNK pathways. Activation of these pathways leads to the production of ROS and NF-κB activation (light blue box 4), which enhances expression of inflammatory cytokine genes resulting into generation of inflammatory response and development of insulin resistance (IR) and impaired energy expenditure (IEE). SFA-induced mitochondrial dysfunction also stimulates anaerobic glycolysis leading to enhanced production of lactate, which also contributes in the development of IR and IEE. SFAs: Saturated fatty acids; PA: Palmitic acid; SOC: Store operated calcium; ROS: Reactive oxygen species; ER: Endoplasmic reticulum; IR: Insulin resistance; IEE: Impaired energy expenditure.

Altered leptin synthesis in schizophrenia and its role in the development of IR and IEE

Although adipose tissue secretes several adipokines[68], leptin and adiponectin have generated huge interest in schizophrenia. However, here the discussion is limited only to leptin for two reasons. First, several studies have shown that leptin but not adiponectin production is reduced in patients with FEP [69]. Second, if elevated above the normal physiological concentration for longer duration, leptin inhibits insulin secretion, increases fat mass accumulation, and obesity *via* its pro-inflammatory and pro-adipogenic actions[11,13].

In schizophrenia, while previous studies have measured plasma leptin in patients with FEP, findings are very conflicting. For instance, a recent meta-analysis and clinical studies found that plasma leptin production was significantly reduced in antipsychotic-naïve FEP patients compared to the CNT subjects [69-71], whereas other studies found opposite results[72-74]. The reasons for these discrepancies are not clear; however, a number of factors including gender, sex hormones, age, eating behavior, duration of illness, smoking, and other medications may affect leptin production. For instance, plasma leptin levels have been found higher in women than men of the same age, and are also affected by smoking[72-75].

Regarding the role of leptin in the development of IR and IEE, animal studies have shown that leptin deficiency can lead to IR and hyperglycemia, whereas, leptin administration can reverse these abnormalities[76]. Thus, normal leptin concentration is required for maintaining glucose homeostasis. Although leptin is a potent regulator/inhibitor of insulin secretion from pancreatic β-cells under physiological condition[11], it can normalize blood glucose level both by insulin dependent and insulin independent mechanisms and with or without involving central nervous system (CNS). For instance, in a rat model of insulin deficiency diabetes, leptin infusion directly into the brain reversed hyperglycemia, suggesting involvement of CNS dependent mechanism[77,78]. Leptin administration in these model animals also normalized plasma levels of glucagon and corticosterone, which are potent hyperglycemic factors. Likewise in mouse model of type-2 diabetes with normal leptin but defect in insulin like growth factor-1 and leptin receptor signaling, leptin administration significantly prevented insulin resistance and hyperglycemia[79].

Leptin also has profound influence on FA metabolism and energy homeostasis both in adipose and non-adipose tissues. It stimulates FA oxidation and glucose uptake in skeletal and cardiac muscles, inhibits glucose output and lipogenesis in liver[80,81]. In white adipose tissue also, leptin has been shown to directly inhibit *de novo* FA biosynthesis, and increase the release and oxidation of FA[82]. Thus, low plasma leptin in patients with FEP that is observed in this study, could be one of the

contributing factors in the increased membrane SFA levels in patients with FEP.

In the present study, although leptin was significantly low in drug-naive patients with FEP, it was significantly elevated in AAD treated CSZ patients, which is in agreement with previous reports showing increased leptin production by AAD treatment[24,25,69]. Leptin elevation by AAD could be a result of their direct antagonistic action at various calcium channels leading to reduce calcium influx, as optimum intracellular calcium is crucial for optimal leptin synthesis and secretion[16,83]. Several lines of evidence suggest that elevated leptin can cause obesity by inducing pro-inflammatory, pro-lipogenic, and pro-adipogenic response[12,13,24]. Leptin has been shown to increase the production of pro-inflammatory cytokines including TNF-α, IL-10, and IL-6 from adipocytes[12]. Along with TNF-α, leptin can also activate macrophages, intercalated within the adipose tissue, to secrete pro-inflammatory cytokines leading to further amplification of inflammatory response[84-86]. It has been suggested that pro-inflammatory effects of leptin, directly or through TNF-α or both, may lead to the inflammation of the pancreas causing βb-cell dysfunction and reduced insulin secretion[10,11,84], which are typically seen in patients with schizophrenia after long-term treatment with AAD.

Pro-adipogenic effect of leptin is further potentiated by its pro-lipogenic and pro-inflammatory responses[12]. Leptin has been shown to increase the production of PLIN1, CAV-1, PPARγ, SREBP1C, and/or adiponectin during differentiation[12]. Together, these proteins orchestrate signaling mechanisms that increase transcription of various genes required for adipocyte differentiation. Further, leptin has been shown to induce lipid accumulation in adipocytes *via* an mTOR-dependent signaling[12], even in the absence of insulin, which plays a crucial role in pre-adipocyte differentiation. This suggests that leptin may induce adipocyte differentiation and lipogenesis even in the absence of insulin signaling. In support of this, a recent study has shown that removing circulating plasma leptin reduced body weight and normalized hyperglycemia in obese animals[13]. This is an important finding, which may help in designing leptin-based therapies for treating obesity and diabetes in schizophrenia and other psychiatric disorders.

This study has some strengths and limitations. Regarding the strengths: (1) The patients and CNT subjects had comparable socioeconomic and demographic characteristics; (2) FEP patients had shortest reported duration of illness (≤ 5 d); (3) no drug abuse; (4) no prior antipsychotic exposure; (5) minimum smoking (2/21); (6) no sedentary life style of FEP patients as all were active duty army personals; (7) no female hormone (estrogens) influence on plasma leptin and membrane FAs as all patients were male; and (8) restricted food diet. Regarding the limitations: (1) The sample size/number of patients were modest and therefore larger studies are needed to validate the above findings; (2) plasma insulin and IR were not measured in these patients; although, several studies have reported IR in drug-naive patients with FEP, and CSZ; and (3) first visit BMI data of CSZ patients was not available; however, these patients were included mainly for comparison purpose, and similar demographic characteristics of patients and CNT subjects.

CONCLUSION

Over the years it has become increasingly clear that IR and IEE are irreparable metabolic comorbidities in schizophrenia. Although evidence suggests that IR and IEE may appear long before the onset of psychosis, antipsychotic intervention further deteriorates IR and IEE, prompting premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia.

Although various signaling mechanisms could be involved in the development of IR and IEE, in schizophrenia these mechanisms seem to stimulate *de novo* FA biosynthesis leading to increased intracellular concentration of SFAs and their subsequent incorporation into the membrane. Elevated levels of erythrocyte SFAs have also been reported in individuals at ultra-high risk of developing psychosis, therefore, disrupted *de novo* FA biosynthesis could be an early manifestation and underlying cause of IR, IEE and other metabolic comorbidities in schizophrenia.

Antipsychotic drugs have been shown to further aggravate the severity of IR and IEE, which could be related to their ineffectiveness in reducing *de novo* SFA biosynthesis. In addition, all AAD have been shown to increase synthesis of leptin, which if elevated above physiological concentration, stimulates *de novo* FA biosynthesis and lipogenesis while concurrently suppressing lipolysis and FA oxidation. Consequently, leptin elevation by AAD may coincide with the onset of weight gain in schizophrenia. Further, as leptin has been shown to directly inhibit insulin secretion from pancreatic β-cells, its elevation could be a major risk factor associated with the reduced insulin secretion and hyperglycemia, which is typically observed in patients with CSZ during extended treatment with AAD.

One of the strongest evidence for the role of elevated SFAs in the development of IR and IEE is provided by a recent study, which showed that adipocytes overloaded with both SFAs and PUFAs provoked IR irrespective of the inflammatory response suggesting that intracellular accumulation of FAs is sufficient to induce IR whether it increases inflammatory cytokine secretion or not. However, unlike PUFAs, the effect of SFAs could be more detrimental and persistent due to the development of various inflammatory cues. Since oxidative stress and inflammation are potential stimulators of *de novo* FA biosynthesis, therapies aimed at reducing oxidative stress and inflammation or *de novo* FA biosyn-

thesis could be highly effective in reducing IR, IEE and other metabolic comorbidities in patients with schizophrenia and other psychiatric conditions. Additionally, therapies aimed at normalizing leptin level could also be highly effective in increasing insulin level and controlling weight gain during long-term treatment. Since calcium is a potential regulator of leptin synthesis and secretion in adipose tissue, use of calcium supplementation could normalize the plasma levels of both inulin and leptin during schizophrenia treatment.

ARTICLE HIGHLIGHTS

Research background

Apart from classical symptoms of psychosis, patients with first-episode psychosis and their first-degree relatives display a range of metabolic comorbidities including insulin resistance and impaired energy expenditure. One of the major hurdles in treating schizophrenia psychosis is that intervention with antipsychotic drugs further exacerbates the severity of metabolic comorbidities, which leads to premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia. Finding the underlying mechanism(s) is crucial for designing effective therapies for minimizing the development or exacerbation of metabolic comorbidities during antipsychotic treatment in schizophrenia.

Research motivation

Finding the mechanism(s) underlying metabolic comorbidities is crucial for enhancing treatment adherence and outcome in schizophrenia. Finding such mechanism(s) will also help in designing effective therapies for minimizing the development or exacerbation of metabolic comorbidities during antipsychotic treatment in schizophrenia.

Research objectives

Since leptin and fatty acids together have profound influence on insulin secretion/sensitivity, and energy homeostasis, this study is directed to determine the association between plasma leptin, body mass index, and erythrocyte membrane fatty acids, particularly, saturated fatty acids (SFAs) in patients with first-episode psychosis (FEP).

Research methods

Plasma leptin was measured using sandwich mode enzyme-linked immunosorbent assay; whereas, erythrocyte membrane SFAs were measured using ultrathin capillary gas chromatography. Body mass index was calculated by using the formula: weight (kg)/height (m^2). Psychiatric symptoms were evaluated at baseline using brief psychiatric rating scale, and positive and negative syndrome scale (PANSS). Pearson correlation coefficient (r) analyses were performed to find the nature and strength of association between plasma leptin, PANSS scores, body mass index (BMI) and SFAs, particularly, palmitic acid (PA).

Research results

Plasma leptin not BMI was significantly lower, whereas, erythrocyte membrane SFAs were significantly higher in patients with FEP compared to the healthy control subjects. Further, plasma leptin showed negative correlation with erythrocyte membrane SFAs-PA, and PANSS scores. However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS scores. Since, similar changes in the plasma leptin and erythrocyte membrane SFAs have also been reported in individuals at ultra-high risk of developing psychosis, the above findings suggest that leptin-fatty acid biosynthesis could be disrupted from the early stage of the illness in schizophrenia.

Research conclusions

Disrupted leptin-fatty acid biosynthesis/signaling could be an early manifestation and underlying cause of metabolic comorbidities in patients with FEP.

Research perspectives

Although large-scale studies are needed for validation of the above results, the data presented above will help in developing appropriate therapies for minimizing the development of insulin resistance and other metabolic comorbidities and increasing treatment adherence and outcome in schizophrenia. Since oxidative stress and inflammation are the major risk factors for the disrupted leptin-fatty acid biosynthesis/signaling, supplementation with calcium, anti-oxidant and/or anti-inflammatory agents will be highly effective in reducing the development or exacerbation of preexisting metabolic comorbidities in schizophrenia.

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FOOTNOTES

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