Psychiatric Comorbidities and Liver Injury Are Associated With Unbalanced Plasma Bile Acid Profile During Methamphetamine Withdrawal

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Background: The pathogenesis of methamphetamine use disorders (MUDs) remains largely unknown; however, bile acids may play a role as potential mediators of liver injury and psychiatric comorbidities. The aim of this study was to characterize bile acid (BA) profiles in plasma of patients with MUDs undergoing withdrawal.

Methods: Liver functions and psychiatric symptoms were evaluated in a retrospective cohort (30 MUDs versus 30 control subjects) and an exploratory cohort (30 MUDs including 10 subjects each at the 7-day, 3-month, and 12-month withdrawal stages versus 10 control subjects). BAs compositions in plasma samples from MUD patients in the exploratory cohort were determined by gas-liquid chromatography.

Results: Both psychiatric comorbidities and methamphetamine-induced liver injury were observed in patients in both MUD cohorts. The plasma concentrations of the total BA, cholic acid (CA), and chenodeoxycholic acid (CDCA) were lower in MUD patients relative to controls. The maximum decline was observed at the 3-month stage, with gradual recovery at the 12-month stage. Notably, the ratios of deoxycholic acid (DCA)/CA and lithocholic acid (LCA)/CDCA were statistically significant at the 3-month stage compared with controls. Significant correlations were found between the LCA/CDCA ratio and the levels of alanine transaminase and aspartate aminotransferase, and between the LCA/CDCA ratio and the HAM-A score.

Conclusion: BA profile during METH withdrawal was remarkably altered, with these unbalanced BAs being associated with liver injury. The associations between BA profiles and psychiatric symptoms suggest an association between specific BAs and disease progression, possibly through the liver-brain axis.

Keywords: methamphetamine withdrawal, bile acid, psychiatric comorbidities, liver injury, crosstalk
INTRODUCTION

Methamphetamine (METH), a potent addictive psychostimulant, was initially developed from its parent drug amphetamine, but the prevalence of METH abuse has been significantly increasing (1). According to the 2019 State Council of China report, approximately 56.1% of registered drug abusers suffered from some form of METH dependence (The State Council China, 2018 China Drug Situation Report, 2019).

Anxiety and depression, the most common psychiatric symptoms of patients with methamphetamine use disorders (MUDs), may persist for 6 months or longer during its withdrawal (2), and may even recur and persist throughout life (1, 3). Our previous cross-sectional study revealed important serotonin and choline, and the severities of anxiety and depression symptoms in MUDs (4, 5). Despite studies showing that METH is neurotoxic, pharmacologic interventions focused on modulating monoaminergic pathways have largely failed and no medications to date have been approved by the U.S. Food and Drug Administration (FDA) for treating METH dependence (6).

In addition to the stimulating and psychotropic effects to the brain(7), METH damages multiple peripheral organs (8), including the liver, intestines, kidneys, and muscles, of which the liver is the most vulnerable organ (9, 10). For instance, patients with MUDs have shown serological evidence of METH-induced cataract liver injury and chronic liver diseases, and animal models of MUDs have shown histological evidence of acute hepatotoxicity and oxidative stress (10, 11). Furthermore, associations among METH-induced liver injury, increased peripheral and brain ammonia, and long-term depletions of dopamine and serotonin have been observed in METH-treated rat models (12–14), suggesting that liver injury may be associated with the process of neurological impairment in patients with MUDs (11, 15). Thus, these systematic impairments including acute or chronic liver injury may interfere with pharmacologic interventions targeting brain dysfunction, leading to poor outcome. To date, however, the underlying molecular mechanisms involving these associations among peripheral organs and the CNS have not been extensively investigated.

Bile acids (BAs) are a large group of structurally related molecules derived from cholesterol and synthesized exclusively in the liver (16). Although BAs were thought to primarily function to expedite the digestion and absorption of dietary lipids and lipophilic vitamins by forming micelles in the small intestine (17), they could function to signal through receptors on various cell types throughout the body, including the CNS and other organ systems (18). Abnormal circulating bile acid metabolite levels in the patients with Alzheimer’s disease predicted worse outcomes (19). Alterations in cholesterol and BAs metabolism have been shown to contribute to the development of neurodegenerative and neurological diseases, such as Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis (20–22). Recent reports of gut-based bariatric surgery suggest that chronically elevate systemic BA concentrations and attenuate cocaine-induced cumulative dopamine increase, and this surgery reduces reward-related behavior and psychomotor sensitization to cocaine in a mouse model (23). Moreover, fecal BA excretion levels have been shown to correlate with alcohol abuse and abstinence (24). Thus, we hypothesized that peripheral BA profiles may serve as a potential diagnostic biomarker or therapeutic target for substance use disorders (SUDs). However, the direct role of BAs in the context of METH dependence and withdrawal remains unclear.

The present study was designed to investigate the dynamic pattern of BAs in patients with MUDs currently undergoing METH withdrawal to analyze the correlations among anxiety and depression scales, neurotransmitters, laboratory parameters associated with liver and kidney function, glycolipid metabolism, and BAs. These findings might uncover the crosstalk between the liver and the central nervous system (CNS) and provide clues toward a better understanding of the role of BAs in MUDs.

MATERIALS AND METHODS

Participant Cohorts

The present study recruited two independent cohorts from a joint program of drug detoxification and rehabilitation in the First Affiliated Hospital of Kunming Medical University and the Kunming Drug Rehabilitation Center between July 2017 and October 2019. The retrospective cohort consisted of 30 male MUDs undergoing withdrawal and 30 male healthy control subjects (HCs). The exploratory cohort consisted of 30 male MUDs undergoing withdrawal, 10 each at the 7-day, 3-month, and 12-month withdrawal stages, and 10 age-matched HCs. Subjects were excluded if they had any other Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) axis I or II disorders, other than amphetamine dependence; were positive for anti-HIV or anti-HCV antibodies; had any neurological disorders or serious medical conditions; or were multi-substance abusers including abuse of an opioid containing acetaminophen, which can cause liver damage.

All protocols and recruitment procedures were approved by the Research Ethics Committee of the First Affiliated Hospital of Kunming Medical University (2018-L-42), and all participants provided written informed consent before enrollment.

Scale Administration

Interviews with a professionally trained interviewer were conducted simultaneously with the collection of biological samples. The HAM-A scale consists of 14 questions, seven elements examining psychological stress and seven examining physical stresses (25). Total scores of <17, 18–24, 25–30, and >30, indicated mild, mild to moderate, moderate to severe, and severe grades of stress severity, respectively. The HAM-D scale consists of a 24-item questionnaire that measures the severity of depressive symptoms, with total scores > 20 considered indicative of major depression (26).

Blood Tests

Fasting blood specimens were collected from study participants into 10 mL EDTA-2Na vacuum tubes, and the blood samples were centrifuged at 1,500 g for 15 min. The plasma was transferred to a new tube and centrifuged at 20,000 g at 4°C for
15 min. The supernatants were aliquoted and stored at -80°C until analysis. Biochemical parameters were measured using the Beckman Coulter Synchrone DxC800 Chemistry Analyzer (Beckman, USA). Concentrations of neurotransmitters were measured by ultrasensitive liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS; ACQUITY UPLC-Xevo TQ-S, Waters Corp., Milford, MA, USA).

Targeted Metabolomics Analysis of BAs

Samples were prepared and BA concentrations measured as described (27). Briefly, an internal standards solution containing six internal standards was added to each plasma sample or standard solution and centrifuged. The internal standard solution contained 100nM concentrations of d4-glycocholic acid (GCA), d4-taurocholic acid (TCA), d4-cholic acid (CA), d4-glycodeoxycholic acid (GDCA), and d4-deoxycholic acid (DCA) and a 200 nM concentration of d4-lithocholic acid (LCA).

BAs were analyzed using a Waters ACQUITY ultraperformance LC system coupled with a Waters XEVO TQ-S mass spectrometer with an ESI source controlled by Masslynx 4.1 software. Chromatographic separations were performed on an ACQUITY BEH C18 column (1.7 µM, 100 mm × 2.1 mm inter-dimensional) (Waters). Raw UPLC-MS data obtained in negative mode were analyzed using Target Lynx applications manager version 4.1 (Waters) to obtain calibration equations and determine the concentrations of each BA in these samples (28).

Statistical Analysis

Demographic, clinical, and biochemical parameters were compared using SPSS Statistics version 23.0 software (IBM Corp., Armonk, NY, USA). Categorical variables using Chi-squared tests. If each group of continuous variables satisfied both the normality test (Shapiro-Wilk normality test) and the homogeneity of variance test (Levene’s test), t-tests were used to conduct variance analysis between two groups whereas one-way ANOVA were used to conduct variance analysis among three groups. If any group of continuous variables could not satisfy the Shapiro-Wilk normality test or the Levene’s test, Wilcoxon rank-sum Test were used to conduct variance analysis between two groups whereas Kruskal-Wallis test were used to conduct variance analysis among three groups. All p values were corrected by Bonferroni method, an adjusted p value < 0.05 was considered statistically significant. Box plots and correlations analyses were performed and visualized using the usingpheatmap, ggplot2 and ggpubr packages in R (v 3.6.3).

RESULTS

Characteristics of the Study Participants

The clinical characteristics of the retrospective cohort (Research cohort 1) are shown in Table 1. Sixty men, 30 MUDs and 30 HCs, aged 25–50 years were enrolled. The duration of METH use in the 30 MUDs ranged from 61 to 107 months. The major routes of METH administration were smoking and nasal insufflation. There were no significant differences in age, body mass index (BMI), level of education, and self-reported annual income between these two groups (Table 1).

To determine the dynamic alterations in psychiatric symptoms and liver damage during METH withdrawal, a second, prospective cohort (Research cohort 2) was recruited. The demographic characteristics of this cohort have been described previously (4, 5) and are shown in Table S1. There were no significant differences in age, BMI, METH-use history, and education level among the three MUD subgroups and between the MUD and HC groups. Although self-reported annual income was not well balanced, this was corrected in the subsequent statistical analyses.

Co-Existence of Liver Injury and Psychiatric Symptoms in MUDs

Questionnaires assessing the HAM-A and HAM-D rating scales, which were developed to quantify the severity of anxiety and depression, respectively, were administered by experienced interviewers. Compared with the HCs, the MUDs in Research cohort 1 had significantly higher scores on both the HAM-A (p = 2.47x10^-6) and HAM-D (p = 4.91x10^-6) scales. In addition, measurements of liver injury-related blood parameters (Table 1) showed that plasma concentrations of alanine transaminase (ALT, p = 3.78x10^-2) and aspartate aminotransferase (AST, p = 2.85x10^-2) were significantly higher in the MUD than in the HC group. These findings indicate that the MUDs in Research cohort 1 had obvious psychiatric comorbidities and METH-induced liver damage.

The psychiatric symptoms and blood concentrations of peripheral neurotransmitters in Research cohort 2 have been reported (5). Blood parameters associated with glucose and lipid metabolism, as well as liver and kidney function, were also assessed. Both ALT and AST levels were significantly higher in the MUDs than in the HCs (Table S1), consistent with the findings in Research cohort 1. Interestingly, most of the parameters differing in these two groups, including AST, ALT, and triglyceride (TG) concentrations, as well as scores on the HAM-A and HAM-D scales, showed greatest significance in the 10 MUD patients at the 3-month withdrawal stage. HAM-A scores correlated significantly with the concentrations of ALT (p < 0.001, r = 0.73), AST (p = 0.006, r = 0.49), TG (p < 0.001, r = 0.58) and LDL-cholesterol (p = 0.01, r = 0.47), whereas HAM-D scores correlated significantly with the concentrations of AST (p < 0.001, r = 0.78), TG (p = 0.004, r = 0.51) and HDL-cholesterol (p = 0.004, r = 0.52) and the AST/ALT ratio (p = 0.002, r = 0.54). Taken together, these findings showed that liver and psychiatric symptoms were altered and correlated with each other in patients undergoing their first year of METH withdrawal (Figure 1 and Figure S1).

Dynamics of Plasma BA Concentrations During METH Withdrawal

BA has been reported to play critical roles in neurodegenerative and neurological diseases (5, 29). To determine the dynamic changes in BA concentrations at various stages of withdrawal, 42 BAs were simultaneously evaluated in
both MUDs and HCs from Research cohort 2 (Table S2). Intergroup differential analysis showed significant alterations in plasma BAs of all three MUD subgroups, with similar trends for BA profile and blood parameters associated with liver and psychiatric symptoms. These variations were greater at the 3-month withdrawal stage than at the 7-day and 12-month stages. For example, the total BA concentration in plasma was significantly lower in all 30 MUDs than in the HCs ($p = 8.66 \times 10^{-5}$). The maximum reduction occurred at the 3-month stage ($p = 7.44 \times 10^{-5}$), with the greatest reductions occurring at the 3-month withdrawal stage ($p = 9.79 \times 10^{-3}$), and the greatest reductions occurring at 3-months ($p = 1.08 \times 10^{-5}$ & $p_{\text{PCDCA}} = 4.27 \times 10^{-3}$). The concentrations of selected BAs such as $\text{GCDCA}$, $\text{UCB}$, and $\text{GCA}$, were significantly changed in all MUDs relative to the HCs, while the significance was only observed at the 3-month stage ($p_{\text{PCGCA}} = 0.03$, $p_{\text{PCDCA}} = 0.04$, $p_{\text{GCA}} = 0.04$).

Assessments showed that 11 BAs, including four secondary BAs (hyocholic acid (HCA), a-muricholic acid (aMCA), 23-norcholeic acid (NorCA), and andursodeoxycholic acid (UDCA)), and seven conjugated BAs (THCA, taurochenodeoxycholic acid (TCDC), ursodeoxycholic acid (UC), glycochenodeoxycholic acid (GCDCA), and GLCA-3S), were significantly altered only in MUD patients at the 3-month withdrawal stage (Table S2 and Figure 2), suggesting that alterations in key BAs in MUDs during withdrawal were stage specific.

In addition, the ratios of selected BAs were calculated to investigate the enzymatic activities involved in BA metabolism. The CA/CDCA ratio was used to determine the changes in enzymatic activity towards the secondary BAs; the ratios of secondary to primary BAs (DCA/CA and $\text{LCA}/\text{CDCA}$) were used to determine the changes in enzymatic activity towards the production of secondary BAs; and the $\text{GCDCA}/\text{UDCA}$ and $\text{UCB}$/glycoconjugated BAs were used to determine the changes in enzymatic activity towards the production of secondary BAs. The changes in BA metabolism, particularly in the production of secondary BAs, were stage specific in patients undergoing METH withdrawal.

To further determine the associations between plasma BAs and liver injury in MUDs, the Spearman correlations between BA profiles and plasma concentrations of ALT and AST were calculated and analyzed. The LCA/CDCA ratio correlated significantly with both ALT ($r = 0.93, p = 5.03 \times 10^{-4}$) and AST ($r = 0.93, p = 1.37 \times 10^{-4}$) concentrations (Figure 3). Similarly, the TLCA/CDCA ratio correlated significantly with...
ALT ($r = 0.91$, $p = 2.26 \times 10^{-4}$) and AST ($r = 0.90$, $p = 4.33 \times 10^{-4}$) concentrations. These results indicate that BA profiles during withdrawal are markedly altered, and that these unbalanced BAs are associated with liver injury in patients with MUDs.

**Unbalanced Plasma BAs Were Associated With Psychiatric Comorbidities and Neurotransmitters During METH Withdrawal**

We also investigated the correlations among BA concentrations, psychiatric comorbidities and neurotransmitter concentrations. The concentrations of total BAs, bCA, CA, CDCA, UCA, THCA, GHCA, HCA, UDCA, 7_ketoLCA and 3-DHCA were negatively correlated with HAM-A score in MUDs (Figure 4), of which the CDCA and HAM-A score showing the strongest negative correlation ($r = -0.57$, $p = 0.001$). In contrast, the LCA/CDCA ratios ($r = 0.46$, $p = 0.01$) and TaMCA ($r = 0.42$, $p = 0.02$) correlated positively with HAM-A scores.

In addition, CA/CDCA ratios, as well as the concentrations of CA, GCDCA, NorCA, and THCA, were positively correlated with choline concentrations, whereas the concentrations of total BAs, CA, CDCA, GCDCA, GHDC, HCA, THCA, HDCA, NorCA, TCDCA, THDCA, and UCA were positively correlated with GABA concentrations (Figure 4). Interestingly, serotonin concentration correlated only with HCA concentration. Altogether, these results indicated that unbalanced BA profiles were associated with psychiatric symptoms and altered neurotransmitters in MUD patients during METH withdrawal.

**DISCUSSION**

This study recruited two cohorts of patients with MUDs and age-matched HCs and assessed the concentrations of their circulating BAs, neurotransmitters, and blood parameters related to liver and kidney function and glycolipid metabolism. To our knowledge, this study is the first to show that BA profiles were significantly altered in patients with MUDs, and that these unbalanced BAs were associated with both liver injury and psychiatric comorbidities in patients during the first year of METH withdrawal.
Mood problems (depression and anxiety) and cognitive impairments have been associated with liver damage, although these associations were investigated primarily in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (30). More recently, epidemiological studies have shown that patients with psychosis are at greater risk of presenting with damaged liver function (31), and are at increased risk of chronic liver diseases (32), even during early stages of psychosis (33). Studies using animal models suggested that liver dysfunction could reduce METH clearance, increase brain drug concentrations, and therefore enhance its psychotropic effects on locomotor activity in a dose-dependent manner (34). Hyperthermia-dependent liver damage has been observed in mice after acute administration of METH, accompanied by increased plasma aspartate, ALT, and plasma ammonia concentrations (12). The co-occurrence of liver injury and psychiatric comorbidities was validated in two independent cohorts, with ALT and AST concentrations being associated with the severity of symptoms of anxiety and depression. Although it is unclear whether liver injury persists along with long-lasting psychiatric comorbidities in MUDs years after withdrawal, this study provides evidence supporting the critical role of crosstalk between dysregulation of the liver-brain axis and psychiatric symptoms during the first year of METH withdrawal.

BAs are the end-products of cholesterol metabolism and are mainly involved in liver, biliary, and intestinal diseases (35, 36). Most primary BAs are produced in the liver, and can be modified, by conjugation with glycine or taurine, and stored in the gallbladder. The concentrations of BAs have been shown to be altered in patients undergoing METH withdrawal compared to healthy controls (HCs) (Figure 2). Statistical significance was detected in three stages of METH withdrawal compared to HCs. *p < 0.05; **p < 0.01; ***p < 0.001 for between group comparisons. ns, no significance.
FIGURE 3 | Associations between plasma bile acid concentrations and liver damage after METH withdrawal, as determined by Spearman correlation analysis. Red indicates positive correlations and blue indicates negative correlations, with darker colors indicating stronger correlations. *p < 0.05; **p < 0.01; ***p < 0.001 for between group comparisons.
FIGURE 4 | Associations between plasma bile acid concentrations with psychiatric comorbidities and neurotransmitter concentrations after METH withdrawal, as determined by Spearman correlation analysis. Red indicates positive correlations and blue indicates negative correlations, with darker colors indicating stronger correlations. *p < 0.05; **p < 0.01; ***p < 0.001 for between group comparisons.
bladder until they are secreted into gut, where they are further modified by enzymes present in gut bacteria to produce secondary BAs (37). During this process, most BAs are reabsorbed and undergo enterohepatic recirculation through the portal venous system, with only a small fraction reaching the systemic circulation. Even though, the selection of plasma BAs could be used as diagnostic biomarkers to distinguish patients with schizophrenia (38) or diabetes (39) from healthy controls. To elucidate the role of BAs in the liver-brain axis in MUDs, this study profiled plasma BAs, finding that the concentrations of several key BAs were significantly lower in MUD patients than in HCs. These BA deficiencies during METH withdrawal were consistent with psychiatric comorbidities observed in MUDs, providing further evidence that BAs have neuroprotective functions in neurodegenerative diseases (40). The total BA concentration was found to correlate negatively with both HAM-A and HAM-D scales, but positively correlated with the concentrations of the neurotransmitters, choline and GABA, in HCs. These BA deficiencies during METH withdrawal were associated with psychiatric comorbidities and liver injury in METH withdrawal.

Hyperlipidemia, especially excess TGs, has been reported to affect the development of neural cognition and mood disorders through putative mechanisms such as brain blood barrier dysfunction or an imbalance in amyloid metabolism (45–47). The present study showed that the plasma concentrations of TGs and LDL-cholesterol correlated positively with both HAM-A and HAM-D scores, whereas the plasma concentrations of HDL-cholesterol correlated negatively with HAM-D scores. These findings suggested that hyperlipidemia was associated with worse psychiatric comorbidities in patients undergoing METH withdrawal.

Altered production of secondary BAs in patients with MUDs may indicate a significant change in their gut microbiota. This hypothesis is supported by studies showing that alterations in gut microbiota play key roles in the regulation of host metabolism and therefore contribute to severe withdrawal symptoms (48, 49). In addition, altered circulating BAs may affect CNS function by activating FXR in neurons and TGR5 in glial cells, thereby modulating neuroinflammatory and neuropsychiatric behaviors (50). However, this hypothesis has not been experimentally confirmed in patients with MUDs.

This study had several strengths. First, the characteristics of patients with MUDs in both cohorts were systematically analyzed. Second, the exploratory cohort included patients at different stages of METH withdrawal, with findings in these subgroups showing that the critical importance of the time window for potential clinical intervention. Third, this study explored clues to peripheral systems other than the CNS, which are relatively easy to obtain and to be developed as biomarkers. Finally, this study provided in-human evidence that excessively low BA concentrations and imbalances are adverse factors for psychiatric comorbidities and liver injury in METH withdrawal.

This study, however, also had several limitations. First, the samplesizes were relatively small. A study with relative larger sample size should hypothetically obtain more accurate results. Second, this was an observational study showing statistical associations; therefore, causality could not be determined. Third, because the gut microbiota has been shown to affect the neuro psychiatric behaviors associated with substance withdrawal (49, 51), future studies should investigate the association between the composition of gut microbiota and the mechanisms of BA metabolism during METH withdrawal.

In conclusion, the present study evaluated the plasma BA profile in patients with MUDs, finding that deficiencies in overall BAs and the production of secondary BAs were associated with psychiatric symptoms as well as METH-induced liver injury. Additional studies are needed to determine the molecular mechanisms underlying the crosstalk between the liver and the CNS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the First Affiliated Hospital of Kunming Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JHY and KW designed the study and supervised the project. YM, HJW, HWW, FC, ZX, ZZ, QP, JQY, YZ, CC, MC, and YJZ...
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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.801686/full?supp-material

Supplementary Figure 1 | Associations of dyslipidemia parameters with psychiatric comorbidities (A–D) and bile acid concentrations (E–H) after METH withdrawal, as determined by Spearman correlation analysis.

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