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Methamphetamine-Induced Oxidative Stress and Inflammatory Markers as Indicators of Blood-Brain Barrier Disruption

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Abstract

Background: Methamphetamine (METH) abuse has been linked to neurotoxicity, oxidative stress, and dysfunction of the blood-brain barrier (BBB), potentially leading to cognitive impairments. This study aimed to evaluate the association between METH use, oxidative stress biomarkers, inflammation (NF-κB), endothelial permeability (MLCK), and memory impairment.
Methods: A total of 150 male participants, aged 18–50 years, were recruited, including 75 METH users and 75 age-matched healthy controls. Serum levels of myosin light chain kinase (MLCK, NCBI Gene ID: 4638), nuclear factor kappa B (NF-κB, NCBI Gene ID: 4790), total oxidant status (TOS), total antioxidant capacity (TAC), catalase activity (CAT), and oxidative stress index (OSI) were measured. Receiver operating characteristic (ROC) curves and logistic regression were used to analyze biomarker sensitivity and risk association.
Results: MLCK and NF-κB were significantly elevated in METH users compared to controls ($p< 0.001$*). TOS and OSI were higher, while TAC and CAT were lower in METH users ($p< 0.001$*). ROC analysis revealed MLCK (AUC = 0.978) and NF-κB (AUC = 0.959) as sensitive biomarkers for BBB dysfunction. Logistic regression indicated increased odds of memory impairment with elevated MLCK (OR = 1.246) and NF-κB (OR = 1.452), though these associations were not statistically significant ($p > 0.05$).
Conclusion: Chronic METH use is associated with oxidative stress, inflammation, and increased BBB permeability, implicating MLCK and NF-κB as potential biomarkers for neurovascular damage and cognitive decline. Larger studies are warranted to confirm these associations.

Keywords: Blood-Brain Barrier, Catalase, Cognitive Dysfunction, Inflammation, Methamphetamine, Myosins, NF-kappa B, Oxidative Stress, Protein Kinases.

Introduction

Methamphetamine (METH), also known as "ice" or "crystal," is an addictive drug and one of the most commonly abused stimulants worldwide. The use of high doses of METH or its abuse for extended periods may cause significant harm to human health, such as neurotoxicity (1-3). The World Narcotics Control Report (2024) indicated that the number of METH addicts is increasing, reaching about 30 million globally, as METH addiction has become an alternative to heroin and other drugs. People who abuse METH are likely to suffer from neuronal dysfunction and a higher risk of neurodegenerative diseases (4).

The blood-brain barrier (BBB) is a highly selective and dynamic interface that maintains central nervous system (CNS) homeostasis by regulating the transport of ions, molecules, and immune cells between the bloodstream and the brain. Disruption of the blood-brain barrier (BBB) is implicated in numerous neurodegenerative and inflammatory diseases (5). Abusing METH for a long time or in high doses leads to an impairment in the function of

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the BBB, as abuse of METH results in oxidative stress (OS), inflammation, and damage to the endothelial cells that make up the BBB. OS refers to the imbalance between the body's production of reactive oxygen species (ROS) and its ability to counteract or detoxify these reactive molecules (6). METH abuse enhances ROS production by activating NADPH oxidase (NOX) enzymes, impairing mitochondrial function, and depleting cellular antioxidants such as glutathione (7, 8). This oxidative imbalance leads to endothelial cell damage, tight junction disassembly, and increased paracellular permeability (9). Excessive ROS production, especially when induced by substances like METH, further contributes to oxidative stress and cellular damage (10).

Previous studies have shown that oxidative stress is not limited to stimulating inflammation or neuronal damage, but instead plays a pivotal role in histological and functional changes in various tissues of the body. In a study conducted by Obydah et al. (11). increased levels of oxidative markers such as malondialdehyde (MDA) and decreased antioxidant defenses, including total antioxidant capacity (TAC) and catalase (CAT), were associated with significant structural impairments in the brain, confirming the close relationship between oxidative imbalance and neurodegeneration (11).

Myosin light chain kinase (MLCK), encoded by the MYLK gene (NCBI Gene ID: 4638), is a cytoskeletal regulator that mediates tight junction protein phosphorylation, cytoskeletal contraction, and endothelial barrier breakdown. MLCK activation is closely linked to oxidative signaling and has been identified as a central mediator in METH-induced BBB dysfunction. Similarly, nuclear factor kappa B (NF-κB), encoded by the NFKB1 gene (NCBI Gene ID: 4790), is a transcription factor activated by ROS and proinflammatory cytokines. Its sustained activation has been associated with neuroinflammation and BBB impairment in both *in vitro* and *in vivo* models (12, 13). Reactive oxygen species (ROS) are among the main factors that can activate MLCK (14, 15). Activation of MLCK leads to endothelial hyperpermeability through the phosphorylation and reduced expression of endothelial cell-associated proteins, making the endothelial barrier more porous and allowing greater passage of molecules and cells between the bloodstream and the surrounding tissues (12).

Neuroinflammation is characterized by the activation of microglia and astrocytes, the upregulation of cytokines and chemokines, and the infiltration of immune cells from the periphery into the CNS (16). Both *in vitro* and *in vivo* studies demonstrate that METH can stimulate astrocytes and enhance microglial activity and expansion, thereby inducing a neuroinflammatory response (17, 18). Nuclear factor-κB (NF-κB) is a transcription factor that controls the expression of genes responsible for regulating cell growth, cell death, and responses to inflammation and immune activation (19). NF-κB is a vital pro-inflammatory transcription factor that contributes to the onset and progression of the inflammatory response, leading to neuroinflammation in key components of the blood-brain barrier (BBB), such as endothelial cells (ECs) and glial cells (19, 20).

In recent years, there has been growing evidence that methamphetamine use not only leads to short-term changes in behavior and cognition but may also cause long-term neurological changes at the molecular and tissue levels. Recent studies have shown that methamphetamine may contribute to the acceleration of degenerative processes in the brain by affecting proteins associated with Alzheimer's disease, such as amyloid beta 40 (Aβ40) and phosphorylated tau protein 217 (p-tau217), which are early indicators of neuronal damage and memory loss (21). These findings reveal a potential new mechanism for methamphetamine-associated cognitive impairment and underscore the importance of assessing relevant biomarkers in understanding the extent of brain damage caused by methamphetamine chronic use.

Although several studies have described the general neurotoxic effects of METH, few have directly investigated the simultaneous involvement of oxidative stress, MLCK, NF-κB, and memory impairment as markers of BBB dysfunction in human subjects. Therefore, this study aims to explore the levels of oxidative stress markers and inflammatory proteins in individuals with chronic METH use, as well as to assess their potential as predictive indicators of BBB disruption and cognitive decline.

Materials and Methods

Study Design and Participants

This case-control study was conducted between November 2023 and May 2024 at the Drug Rehabilitation Center and Ibn Rushed Teaching Hospital for Psychiatry in Baghdad, Iraq. A total of 150 male participants aged between 18 -50 years were enrolled. The study group consisted of 75 individuals with a confirmed history of methamphetamine (METH) use for at least 6 months, while the control group included 75 age-matched healthy non-users with no history of drug abuse.

Participants with diabetes mellitus, neurological diseases, chronic kidney disease, or malignancies were excluded. METH use was confirmed through structured interviews and urine toxicology screening.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the College of Science, Mustansiriyah University (Approval Code: BCSMU/0224/0002C). Written informed consent was obtained from all participants before their inclusion.

Blood Sample Collection and Preparation

Five milliliters (5 mL) of venous blood were collected from each participant under aseptic conditions. Blood was allowed to clot at room temperature before being centrifuged at 1500 g for 10 minutes to separate the serum. The serum was aliquoted into Eppendorf tubes and stored at –20 °C until further analysis.

Biochemical Analysis

Inflammatory and Endothelial Biomarkers

Serum levels of Myosin Light Chain Kinase (MLCK) and Nuclear Factor Kappa B (NF-κB) were quantified using commercial ELISA kits (Sunlong Biotech Co., Ltd., China; Cat. No. SL2624Hu and SL1514Hu, respectively). Absorbance was read at 450 nm using a Stat Fax 4200 ELISA microplate reader (Awareness Technology Inc., USA).

Oxidative Stress Markers

The total oxidant status (TOS) and total antioxidant capacity (TAC) were measured according to Erel's method (22, 23). The activity of catalase (CAT) in serum samples was determined using a spectrophotometric method based on ammonium molybdate oxidation (24).

Assessment of Cognitive Impairment

Memory impairment (hypomnesia) was evaluated by assessing cognitive function using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). Among the METH group, 44% exhibited cognitive impairment based on these assessments.

Statistical Analysis

All data were analyzed using SPSS software version 26.0 (IBM Corp., USA) and Microsoft Excel 2021 (Microsoft Corp., USA). Continuous variables were presented as mean ± standard deviation (SD). Independent-sample t-tests were used to compare the groups. Pearson correlation was employed to evaluate associations between biochemical markers.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic utility of biomarkers. Binary logistic regression was used to assess the odds ratios (ORs) for hypomnesia in relation to biomarker levels. A p-value ≤ 0.05 was considered statistically significant. Values with $p < 0.05$ are marked with an asterisk (*).

Results

Participant Characteristics

The demographic and clinical characteristics of the study participants are summarized in Table 1. The mean age was comparable between methamphetamine (METH) users (26.60 ± 6.55 years) and the control group (27.52 ± 7.90 years; p = 0.439). Among METH users, 44% (n = 33) reported symptoms consistent with memory impairment (hypomnesia). The duration of METH use ranged from <1 year to over 3 years.

Oxidative Stress and Inflammatory Markers

Compared with the control group, METH users exhibited significantly elevated levels of Total Oxidant Status (TOS), Oxidative Stress Index (OSI), MLCK, and NF-κB, along with a significant decrease in Total Antioxidant Capacity (TAC) and Catalase (CAT) activity (Table 1).

Table 1. Biochemical and clinical characteristics of study participants.

Parameter		Control	Meth	*p*-value
Number		75	75	-
Age (year)		27.52±7.90	26.60±6.55	0.439
Duration	≤1 year		12	
	1-3 years		25	
	>3 years		38	
Hypomnesia N(%)		0(0%)	33(44%)	
TOS (μM H_2O_2 Eq)		10.88±3.95	15.98±8.84	<0.001*
TAC (mM ascorbic acid Eq)		5.78±2.94	2.91±1.79	<0.001*
OSI		3.52±5.88	7.05±4.88	<0.001*
CAT (mIU/mL)		31.38±6.72	23.29±9.98	<0.001*
NF-κB (ng/mL)		0.188±0.013	0.423±0.296	<0.001*
MLCK (ng/mL)		0.902±0.526	2.963±1.013	<0.001*

Significant p-values are marked with asterisk.

A grouped bar chart comparing MLCK and NF-κB concentrations between the control and METH groups shows a significant increase in both biomarkers in the METH group (p< 0.001), indicating blood-brain barrier dysfunction and inflammatory activation (Fig. 1).

Similarly, statistically significant differences in oxidative stress markers are observed between the control and METH groups, with TOS and OSI elevated, and TAC and CAT reduced in the METH group, indicating oxidative stress imbalance (Fig. 2).

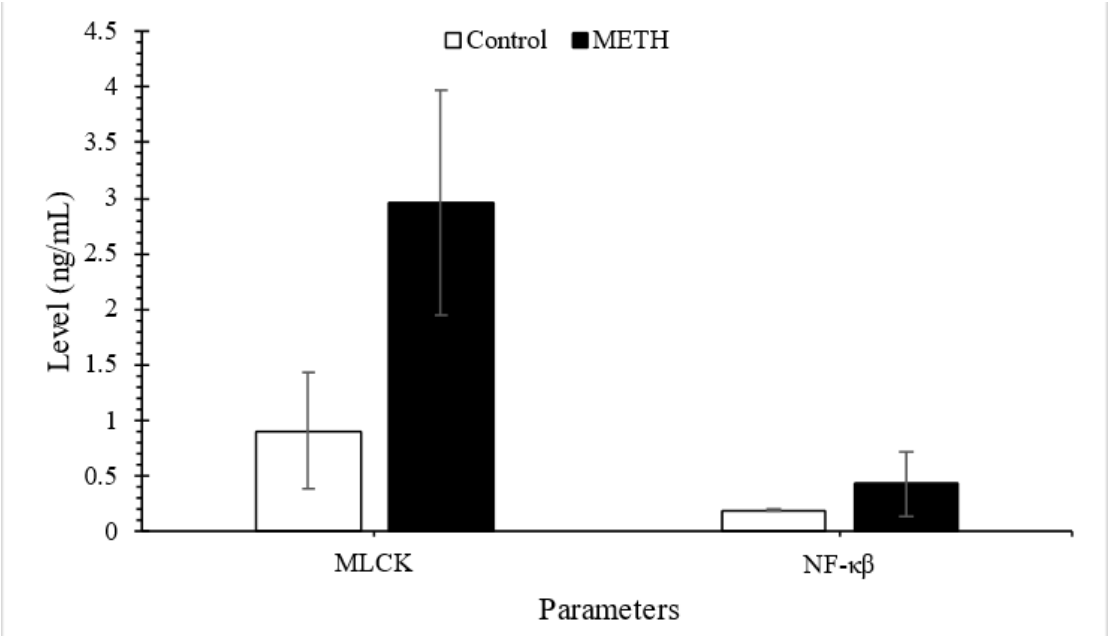

Fig. 1. Comparison of MLCK and NF-κB levels between Control and METH groups. A significant increase in both biomarkers is observed in the METH group (***p< 0.001), indicating blood-brain barrier dysfunction and inflammatory activation. White bars for control and black bars for METH users.

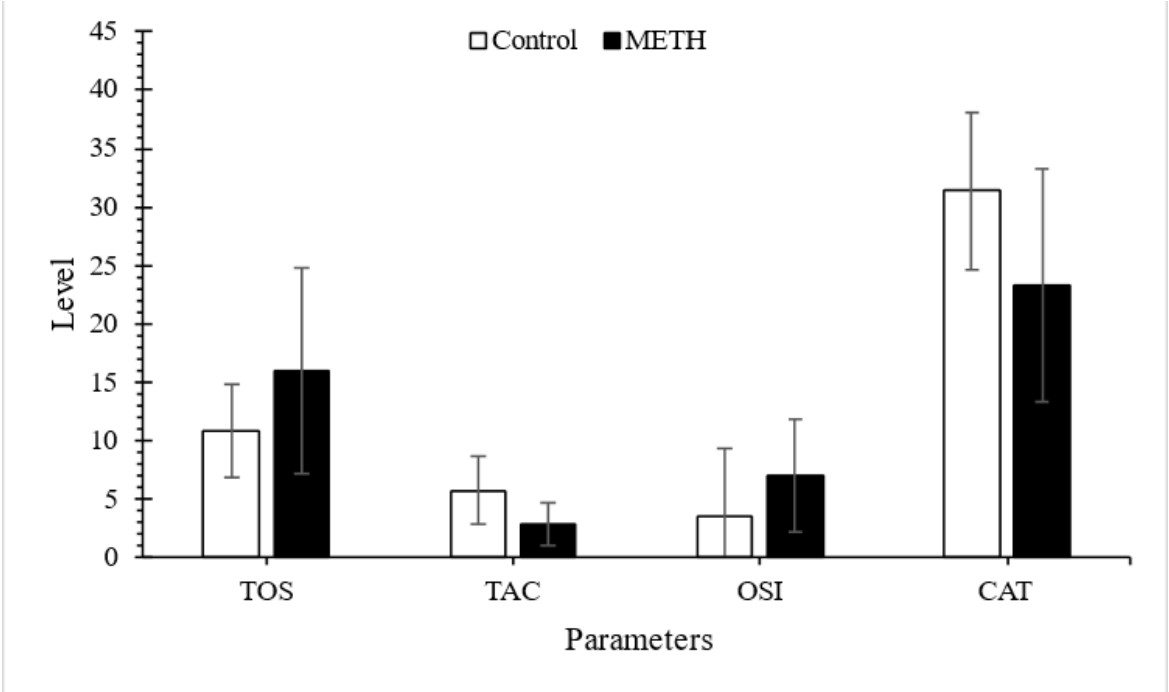

Fig. 2. Oxidative stress marker in control vs METH groups. TOS and OSI are elevated, while TAC and CAT are reduced in the METH group, indicating oxidative imbalance. White bars for control and black bars for METH users.

Correlation Between Biomarkers

Pearson correlation analysis revealed a significant negative correlation between TAC and MLCK ($r = –0.306$, $p= 0.008$), and a positive correlation between OSI and MLCK ($r = 0.431$, $p< 0.001$) (Table 2). NF-κB showed weak and non-significant correlations with oxidative stress markers.

Table 2. Correlation between MLCK and NF-κB with oxidative stress markers.

Parameters	NF-κβ		MLCK	
	r	***p***	**r**	***p***
TOS	0.114	0.330	0.226	0.051
TAC	-0.040	0.733	**-0.306***	**0.008**
OSI	0.192	0.098	**0.431***	**<0.001**
CAT	-0.129	0.269	-0.041	0.727
NF-κβ	-	-	0.013	0.914
MLCK	0.013	0.914	-	-

Diagnostic Performance of Biomarkers

Receiver Operating Characteristic (ROC) curve analysis showed that MLCK (AUC = 0.978) and NF-κB (AUC = 0.959) were highly sensitive and specific for distinguishing METH users from controls (Table 3).

Table 3. ROC analysis of biomarkers for BBB dysfunction.

Parameters	AUC	SE	*p*-value	Cut-off value	Sensitivity	Specificity
NF-κβ (ng/ml)	0.959	0.017	<0.001*	0.199	94.7%	82.7%
MLCK (ng/ml)	0.978	0.012	<0.001*	1.65	94.7%	92%
TOS	0.675	0.045	<0.001*	11.25	62%	52%
TAC	0.797	0.039	<0.001*	3.49	80%	80%
OSI	0.822	0.035	<0.001*	2.92	80%	78%
CAT	0.715	0.045	<0.001*	28.88	72%	69.7%

Risk Estimation for Cognitive Impairment

Binary logistic regression analysis showed that elevated MLCK and NF-κB levels were associated with increased odds for hypomnesia, although these associations were not statistically significant.

Table 4. Odds ratio of the studied biomarkers as risk factors for hypomnesia in Meth addicts.

Parameter	OR	CI (95%)	*p*-value
TOS	1.011	0.960-1.065	0.686
TAC	1.111	0.855-1.444	0.431
OSI	0.953	0.864-1.051	0.344
CAT	1.019	0.973-1.067	0.420
NF-κβ	1.452	0.310-6.809	0.636
MLCK	1.246	0.789-1.969	0.346

Discussion

This study demonstrates that chronic methamphetamine (METH) use is significantly associated with increased oxidative stress, elevated levels of myosin light chain kinase (MLCK) and nuclear factor kappa B (NF-κB), and reduced antioxidant capacity-changes that collectively point to blood-brain barrier (BBB) disruption and potential cognitive dysfunction (25, 26).

The observed elevation of MLCK among METH users supports previous reports indicating that oxidative stress-induced activation of MLCK contributes to endothelial hyperpermeability and tight junction dysfunction, primarily via phosphorylation of cytoskeletal proteins and disassembly of adherent's junctions. Activating MLCK leads to the phosphorylation of claudin-5 and occludin, which causes loss of their function and weakens the communication between endothelial cells, resulting in BBB dysfunction. In our cohort, MLCK showed a strong diagnostic performance (AUC = 0.978), confirming its potential as a sensitive biomarker of BBB compromise. This aligns with findings from Rigor et al. who reported that MLCK is a critical effector in ROS-mediated endothelial dysfunction (27-29)

NF-κB, a central transcription factor in the regulation of pro-inflammatory genes, was significantly elevated in individuals exposed to methamphetamine. Its activation, often initiated by reactive oxygen species (ROS), has been strongly implicated in promoting neuroinflammation and microglial activation processes that contribute to neuronal damage and compromise of the blood-brain barrier. The high AUC value of 0.959 observed in this study underscores the diagnostic potential of NF-κB in identifying METH-related neurovascular alterations. These findings are in agreement with prior research demonstrating that methamphetamine exposure leads to enhanced expression of inflammatory mediators, including NF-κB, which contribute to central nervous system toxicity (30).

Furthermore, this study demonstrated a marked elevation in total oxidant status (TOS) and oxidative stress index (OSI), alongside a significant reduction in total antioxidant capacity (TAC) and catalase (CAT) activity among methamphetamine users. This is consistent with the study by Altuhafi et al., in which diabetic patients with nephropathy showed decreased GPx enzyme activity, leading to an imbalance between pro- and antioxidant factors, and was associated with marked tissue damage in renal tissue (31). This reinforces our hypothesis that methamphetamine-induced oxidative stress may be a common mechanism underlying tissue damage, both in the brain and in other organs. This redox imbalance reflects an intensified state of oxidative stress, often associated with mitochondrial dysfunction and excessive production of reactive oxygen species (ROS). These findings are consistent with recent evidence by Jayanthi S. et al., who reported that methamphetamine exposure leads to significant oxidative dysregulation and neuronal injury via ROS-mediated mechanisms (32) .

Interestingly, while logistic regression showed that elevated MLCK and NF-κB levels increased the odds of cognitive impairment in METH users (OR = 1.246 and 1.452, respectively), the associations were not statistically significant. This ack of significance may be attributed to sample size limitations or the need for more sensitive neurocognitive assessment tools beyond self-reporting. Future studies using objective neuropsychological batteries or neuroimaging techniques may clarify these associations.

The moderate-to-strong correlations between MLCK and OSI (r = 0.431), and between MLCK and TAC (r = –0.306), suggest that MLCK elevation is closely linked to oxidative stress, reinforcing the hypothesis that ROS acts as a molecular trigger for cytoskeletal and endothelial changes. The absence of strong correlations with NF-κB may indicate differential regulatory pathways or temporal variation in biomarker expression.

Collectively, our results support a model in which METH induces oxidative stress, which in turn activates MLCK and NF-κB, leading to BBB breakdown and contributing to the observed memory impairments. These mechanisms represent important targets for potential therapeutic interventions aimed at preserving neurovascular integrity in substance use disorders.

In addition to the current study's demonstration of elevated levels of oxidative stress and inflammatory markers (such as NF-κB and MLCK) in methamphetamine users, recent evidence suggests that methamphetamine use-associated cognitive impairment also extends to neuronal tissue changes similar to those seen in neurodegenerative diseases such as Alzheimer's disease. A recent study by Abood and Mohammed demonstrated significantly elevated levels of Amyloid-β40 and p-tau217 in the serum of male methamphetamine users, which were significantly associated with cognitive impairment. These findings suggest that methamphetamine may not only disrupt the blood-brain barrier but may also contribute to the induction of toxic protein deposits associated with memory impairment, reinforcing the importance of monitoring these markers as potential biomarkers of drug-induced cognitive decline.

This study provides compelling evidence that chronic methamphetamine use disrupts blood-brain barrier integrity by increasing oxidative stress and activating inflammatory mediators such as MLCK and NF-κB. These molecular changes are closely linked to a reduction in antioxidant defenses and the emergence of cognitive dysfunction. The high sensitivity and specificity of MLCK and NF-κB as diagnostic biomarkers for BBB dysfunction support their potential role in early detection and monitoring of methamphetamine-induced neurovascular damage. Future longitudinal studies incorporating neuroimaging and cognitive testing are warranted to further explore these mechanisms and identify potential therapeutic targets.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author Contributions

Mushtaq T. Abood: Experimental work, statistical analysis, original draft writing; Mustafa Taha Mohammed: Project supervision, conceptualization, manuscript revision; both authors have read and approved the final manuscript.

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