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Evaluating the Protective Potentials of Melatonin on Methamphetamine-induced Kidney Function Deficits through the Oxidative Stress Pathway in Male Rats

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ABSTRACT

Methamphetamine abuse is recognized as a significant global health problem. In this study, the protective effects of melatonin on methamphetamine-induced nephrotoxicity were investigated in adult male Wistar rats. 32 adult male rats were divided into four groups of 8 rats per group as follows; group I was administered 0.5 ml/kg of Phosphate buffered saline (PBS), group II was given 20 g/kg of Methamphetamine (METH); group III was administered 10 mg/kg of melatonin (MLT); and group IV took 20 mg/kg of methamphetamine followed by 10 mg/kg of melatonin. The treatment was administered over 21 days via an oral cannula. After the experiment, the animals were euthanized with 20 mg/kg of intramuscular ketamine, and then perfusion fixation was carried out for rats that were used for histological analysis. Cervical dislocation was used for rats that were used for biochemical assay for oxidative stress markers analysis, and blood serum was used for kidney function tests. The results showed that METH decreased SOD and GPx activities but increased MDA concentration. Also, there was an increased level of creatinine, urea, sodium, and potassium concentrations following METH exposure. Severe kidney damage was revealed by histological analysis. Melatonin enhanced SOD and GPx activities, decreased MDA concentration, and improved kidney function, and kidney cytoarchitecture was restored. Conclusion: Melatonin showed an antioxidant effect against methamphetamine-induced nephrotoxicity and improved kidney functions in rats.

Keywords: Methamphetamine, Nephrotoxicity, Melatonin, Creatinine, Urea

INTRODUCTION

Methamphetamine (METH), known colloquially as “ice” or “crystal,” is a potent and highly addictive psychostimulant that exerts widespread effects on the central nervous system and various peripheral organ systems[1, 2] The global rise in METH consumption has precipitated major public health crises, characterized by physical and psychological dependency, profound neurotoxicity, and systemic complications such as cardiovascular disease and multi-organ damage[3, 4]. METH is distributed in several physical states, including powders, pastes, and crystals, and is typically administered via insufflation, ingestion, inhalation, or intravenous injection[5]. Chronic abuse of METH is associated with a myriad of physiological risks, including cardiovascular & cerebrovascular systems, hypertension, pulmonary hypertension, circulatory collapse, stroke, and impairment of kidney function[6]. Experimental data from the Centre for Neuroscience Research at Mahidol University, Thailand, confirms that METH administration in Wistar rats induces severe nephrotoxicity. This is characterized by histopathological lesions, such as glomerular injury and tubular necrosis, alongside a marked increase in renal biomarker findings that align with clinical reports of METH-related kidney damage in human populations[7-9].

As the primary organs for homeostatic regulation, filtration, and detoxification, the kidneys are uniquely susceptible to drug-induced injury due to their high metabolic demands and constant exposure to circulating xenobiotics [10, 11]. METH-induced tissue damage is largely driven by NF-κB signaling pathways, which trigger inflammatory responses and subsequent apoptosis, resulting in the depletion of functional renal cells [12]. When renal failure ensues—whether acute or chronic, the kidneys lose their capacity to clear metabolic waste, resulting in systemic toxicity [13]. The clearance of METH itself is

contingent upon a combination of hepatic metabolism and renal excretion [14, 15].

Creatinine is a metabolic byproduct of creatine phosphate derived from muscle catabolism. Under normal physiology, it is filtered by the glomerulus and secreted by the proximal tubules with minimal reabsorption [13]. Elevated serum creatinine is a critical indicator of diminished glomerular filtration and may also suggest muscular ischemia [16, 17].

Urea forms the primary nitrogenous end-product of protein metabolism. Synthesized in the liver from ammonia and amino groups, urea is typically eliminated by the kidneys [18]. Consequently, rising levels of blood urea and creatinine are hallmark clinical signs of reduced renal clearance [19-20].

Melatonin is an indoleamine hormone synthesized from tryptophan within the pineal gland, primarily secreted during the dark phase to regulate circadian rhythms [21]. Its biological actions are mediated through MT1 and MT2 G-protein coupled receptors, which influence intracellular signaling pathways involving cyclic nucleotides such as cAMP and cGMP [22, 23]. Beyond its chronobiotic role, melatonin's unique chemical structure allows it to function as a powerful antioxidant. It serves both as a direct scavenger of free radicals and as an enhancer of endogenous antioxidant enzymes during periods of oxidative stress [24, 25]. Research has highlighted melatonin's ability to neutralize oxidative stress induced by various pharmacological agents and chemical toxins [26-30]. Given its pleiotropic benefits and its established link to healthy aging [31], melatonin represents a significant therapeutic candidate for addressing drug-induced organ damage. It provides cytoprotection through its anti-inflammatory and anti-apoptotic properties, which have been extensively documented in models of ischemia-reperfusion injury, cardiovascular disease, and neurodegeneration 31-36, and preserves mitochondrial integrity. MLT maintains cellular energy production and limits toxin-induced damage [37].

This study aims to evaluate the protective efficacy of melatonin against METH-induced nephrotoxicity in adult male Wistar rats.

MATERIALS AND METHODS

Experimental animals

Thirty-two (32) adult male Wistar rats (Rattus norvegicus), weighing 100–120 g, were used for this study. The rats were housed in the Animal House of the Faculty of Basic Medical Sciences, University of Ilorin, Nigeria. The animals were allowed to acclimatize for two weeks before the commencement of the study. The animals were maintained under normal day-night cycles and allowed free access to a standard chow diet and water.

Ethical approval

This research was approved by the University of Ilorin ethical review committee (UERC) (UERC/ASN/2024/2978)

Animal treatment

Methamphetamine crystal was donated for the study by the Nigerian Drug Law Enforcement Agency (NDLEA) through the Kwara State Command. Melatonin was obtained from a local pharmacy in Ilorin, Kwara State, Nigeria.

The animals were randomly assigned into four (4) groups of 8 animals each. Group 1 was given 0.5 ml of phosphate-buffered saline (PBS); group 2 received 20 mg/kg of methamphetamine; group 3 was administered 10 mg/kg of melatonin; and group 4 was given 20 mg/kg of methamphetamine plus 10 mg/kg of melatonin. All administration was conducted orally and lasted 21 days.

Animal sacrifice and tissue collection

On the 22nd day of the experiment, the rats were euthanized using 20 mg/ kg ketamine hydrochloride intramuscularly [38] to make the rats unconscious. The right kidneys of rats were removed, weighed, immersed in cold sucrose solution, homogenized, and used for biochemical assessment. The left kidneys were fixed in 10% buffered formalin, then processed for hematoxylin and eosin staining.

Biochemical assays

To evaluate the impact of methamphetamine and the potential protective role of melatonin on renal function, the oxidative status and serum biochemistry were analyzed using standardized laboratory protocols.

Oxidative stress marker assays

Renal oxidative stress markers were quantified using specific assay kits for Superoxide Dismutase (SOD; KT-60703), Glutathione Peroxidase (GPx; MBS744364), and Malondialdehyde (MDA; MBS9389391). The excised kidney tissues were homogenized in an ice-cold 30% sucrose solution using an automated homogenizer maintained at 4°C. The resulting homogenate was transferred to specimen bottles and centrifuged at 3,000 rpm for 15 minutes. The supernatants were carefully aspirated into ice-cold, labeled glass bottles. These samples were then utilized to determine SOD, GPx, and MDA levels, strictly following the manufacturer's instructions provided with each assay kit.

Serum biochemical and electrolyte analysis

Systemic markers of renal function and electrolyte balance were assessed via blood serum analysis. Whole blood samples were centrifuged at 3,000 rpm for 15 minutes to isolate the serum. The following parameters were measured using Elabscience ELISA Microwells, adhering to the specific manufacturer protocols with Creatinine (Cr; CAT No: E-BC-K188-M) and Urea (CAT No: E-BC-K183-M); Sodium (Na; CAT No: E-BC-K207-M) and Potassium (K; CAT No: E-BC-K279-M).

Histological analysis

Kidney tissues were fixed in 10% buffered formalin solution, dehydrated in ascending graded alcohol, cleared in xylene, and embedded in paraffin. Then they were cut into 5 µm sections using a microtome and stained with hematoxylin and eosin (H&E) [39].

Statistical analysis

All quantitative data from this study were analyzed using analysis of variance ANOVA and Tukey post hoc test with the GraphPad Prism version 10.0.2 and expressed as mean±standard error of the mean (M±SEM). P <0.05 is considered statistically significant.

RESULTS

Effects of methamphetamine and melatonin on antioxidant capacity and oxidative damage in rats' kidney

There was a non-significant increase in MDA level of METH compared to PBS, METH + MLT groups, but significant compared to MLT at P<0.05 (Table 1). The SOD level of the METH group was lower compared to other experimental groups, but not significant at p< 0.05 (Table 1). There was a significant reduction in the level of GPx of the METH group at p< 0.05 compared to the PBS group, but non-significantly reduced compared to the MLT and METH + MLT groups (Table 1).

Effects of methamphetamine and melatonin on kidney function parameters in adult rats

The creatinine level of the METH group was higher than that of PBS, MLT, and METH + MLT groups, but not significantly so. The urea level of the PBS, MLT, and METH + MLT groups was non-significantly lower compared to the METH group. There was a significant increase in Sodium level in the METH group at p<0.05 compared to the METH + MLT, but not significantly higher when compared to the PBS and MLT groups (Table 2). The potassium level was significantly higher in the METH group compared to the PBS and MLT groups at p<0.05.

Table 1. Effect of methamphetamine and melatonin on kidney biochemical concentration activity in adult male Wistar rats.

N= 6	MDA (µM)	SOD (U/L)	GPx (U/L)
PBS	0.649 ±0.08	0.610 ±0.09	37.98 ±5.31
METH	0.880 ±0.01	0.477 ±0.06	19.97 ±3.54[a]
MEL	0.561 ±0.06[b]	0.511 ±0.03	42.48 ±3.20
METH+MEL	0.844 ±0.03	0.797 ±0.17	25.88 ±1.95

PBS (phosphate buffered saline; METH (Methamphetamine); MEL (Melatonin); [a, b] show statistically significant differences from PBS and METH, respectively, at p<0.05. MDA; malondialdehyde: SOD; superoxide dismutase: GPx: glutathione peroxidase. Data presented as Mean ± standard error of the mean (M±SEM).

Table 2. Effect of Methamphetamine and Melatonin on kidney function tests in adult male Wistar rats.

N= 6	Cr (µM)	Ur (mmol/L)	Na^+ (mmol/L)	K^+ (mmol/L)
PBS	37.93 ±8.16	10.83± 1.14	137.60 ±1.15	6.28±0.10
METH	63.92 ±31.29	11.10± 0.09	147.50 ±6.34	6.92±0.28[a]
MEL	39.51 ±13.25	8.53±1. 36	138.40 ±0.67	5.504±0.12[b]
METH+ MEL	44.25 ±10.62	9.49± 0.82	132.40 ±5.06[b]	5.761±0.37

PBS (phosphate-buffered saline; METH (Methamphetamine); MLT (Melatonin); METH + MLT (Methamphetamine followed by Melatonin). [a, b] show statistically significant differences from PBS and METH, respectively, at p<0.05. Cr = Creatinine; Ur = Urea; Na^+ = Sodium; K^+ = Potassium. Data presented as Mean ± standard error of the mean (M±SEM).

Histological observation

Photomicrograph of the kidney of rats exposed to methamphetamine and melatonin: PBS showing normal glomeruli (black arrow) and tubules (arrowhead). The METH group shows focal areas of necrosis (red arrow), shrunken and collapsed glomeruli (yellow arrow), and vacuolated tubules (red arrowhead). The MLT presented normal kidney tubules (arrowhead) and glomeruli (black arrow). The METH + MLT shows improved glomeruli (blue arrowhead), intact tubules (black arrowhead) compared to the METH (Figure 1).

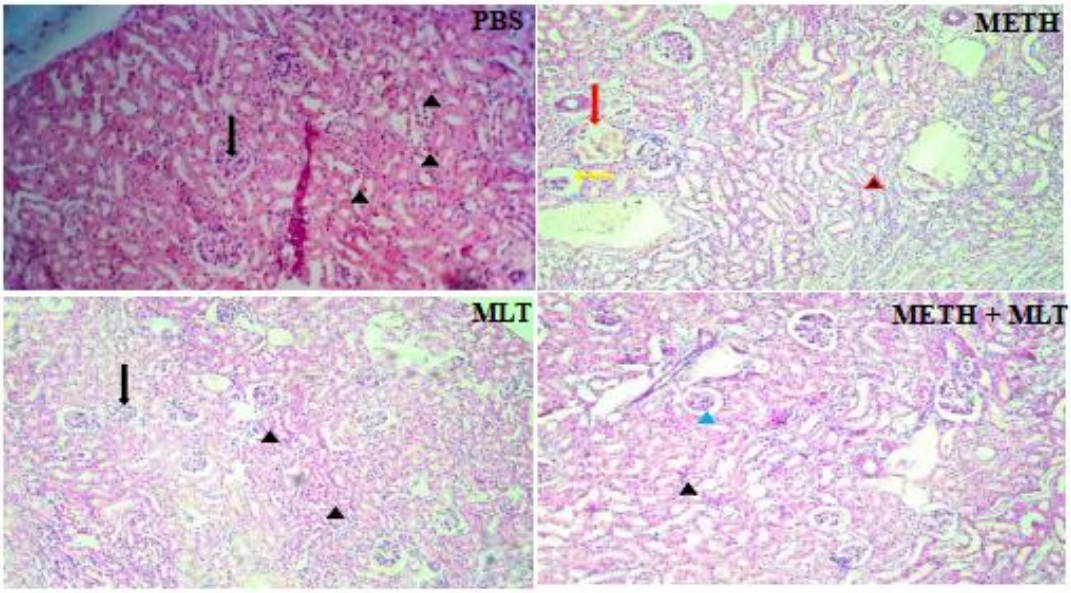

Figure 1: Representative photomicrograph of Rat kidney stained with Hematoxylin and eosin (H & E). PBS shows normal glomeruli (black arrow) and tubules (arrowhead). The METH group shows areas of necrosis (red arrow) and shrunken, collapsed glomeruli (yellow arrow). The MLT presented normal kidney tubules (arrowhead) and glomeruli (black arrow). The METH + MLT shows improved glomeruli (blue arrowhead) and intact tubules (black arrowhead). (mag. x100). PBS (Phosphate Buffered Saline), METH (Methamphetamine), MLT (Melatonin), METH + MLT (Methamphetamine + Melatonin).

DISCUSSION

The usage of illicit substances and various xenobiotics has been extensively documented to exert deleterious effects on the brain and peripheral vital organs, specifically the kidneys, resulting in significant architectural damage and functional loss [40-44]. As a powerful stimulant of the central nervous system, methamphetamine (METH) induces widespread systemic failure, affecting the hepatic, digestive, urogenital, and cardiovascular systems (45). The current investigation demonstrates that METH exposure significantly reduces the renal activity of key antioxidant enzymes, specifically superoxide dismutase (SOD) and glutathione peroxidase (GPx), while simultaneously elevating malondialdehyde (MDA) levels. This reduction in enzymatic capacity may be attributed to the pathological overproduction of reactive oxygen species (ROS), which intensifies oxidative stress and overwhelms the body's innate antioxidant defenses [46, 47]. The surge in MDA, a primary byproduct of lipid peroxidation, serves as a definitive marker of oxidative damage to cellular membranes. Research indicates that METH-driven ROS generation modifies essential cellular macromolecules, triggering dysfunction through pathways intricately linked to inflammatory activation[46-49]. The observed elevation in MDA within METH-treated groups highlights lipid peroxidation as a fundamental mechanism of renal tissue degradation [50]. Furthermore, the concurrent depletion of SOD and GPx activities validates the presence of oxidative stress-mediated injury, reflecting biochemical shifts commonly reported in experimental models of drug-induced nephrotoxicity[10, 11]. These results corroborate previous findings establishing that METH produces excessive ROS, which ultimately leads to inflammation, lipid peroxidation, and acute renal cell injury[5, 11]. These observations are further reinforced by the work of other researchers, who also reported significant reductions in SOD and GPx alongside increased MDA levels following METH exposure[10, 50].

Melatonin (MLT) intervention increased the activities of SOD and GPx. The antioxidant capacity of melatonin is linked to its amphiphilic nature, which facilitates its distribution throughout the cells,

allowing for protection of multiple organs from oxidative insults[47]. MLT not only increases the activity of antioxidant enzymes but also reduces the level of MDA, confirming its ability to protect cells and tissues from oxidative damage. This finding conforms with the previous studies reports[48-50] which demonstrated that melatonin administration significantly reduces MDA levels, indicating a potential restoration of redox homeostasis and a return to oxidative stability following chemical insult.

Renal function was markedly reduced, and the kidneys' electrolyte regulatory capacity was impaired; METH intake increased creatinine and urea levels, which are important biomarkers of renal function. An increase in the blood level of creatinine and urea signifies a decline in the glomerular filtration and proximal tubular secretion and general kidney functions [16, 18]. Similar to our findings, a study by [13] found a profound increase in the level of kidney function markers in individuals with METH abuse. Also, Richards et al. ([51] found an elevated level of Creatine phosphokinase in METH abusers. The kidney regulates electrolyte balance and ensures the healthy functioning of vital physiological processes in the body. METH increased the Na^+ and K^+ levels in the rats exposed to METH. An increase in Na+ accumulation in the blood is associated with conditions such as kidney disease, reduced filtration, heart failure, fluid retention, and proteinuria [52]. Similarly, elevated K^+ level, i.e., hyperkalemia, contributes to increasing vulnerability to cardiac arrhythmia, cardiac arrest, and death[21]. Changes in K+ and Na+ electrolyte levels may be accounted for by the psycho-stimulant effects of METH, which activate widespread physiological and biochemical changes [21].

The results of the present investigation align with previous literature documenting methamphetamine-induced cellular degradation, particularly within skeletal muscle tissues. Such damage frequently precipitates the efflux of intracellular potassium into the systemic circulation[53-55]. This phenomenon is often associated with rhabdomyolysis or ischemic muscle injury, common secondary complications of METH toxicity. Since the kidney is the site of potassium excretion, an increase in the blood level of potassium can be an indication of a reduction in renal function. The study by Umoren *et al*. (21) reported an increase in serum Na+ and K+ levels in rats following METH exposure, which further strengthens our findings.

Melatonin reduced the creatinine and urea levels and also brought down the level of electrolyte concentrations. The observed reductions in creatinine and urea levels may not be unrelated to the potent antioxidant capacity of MLT, which enhances the antioxidant activities of SOD and GPx, thereby lowering the MDA level (Table 1). The reduction in oxidative damage in the kidney undoubtedly improves renal function, as evidenced by lower creatinine and urea levels, confirming increased renal filtration and elimination capacity. Various studies have reported that melatonin reduced urea and creatinine levels in kidney tissue exposed to various toxins, thereby preventing oxidative stress [56, 57]. MLT enhanced the electrolyte regulatory capacity of the kidney, lowering the levels of Na+ and K+ against alcohol intoxication in a rat model of autoimmune nephritis 58, which further strengthens the findings of this study.

The renal cytoarchitecture of rats exposed to methamphetamine exhibited severe structural disorganization and a comprehensive loss of tissue integrity (Fig. 1). Microscopic examination revealed profound necrotic-like degeneration, characterized by collapsed glomeruli, dilated tubules featuring extensive vacuolation, the presence of proteinaceous casts, and significant inflammatory cell infiltration. These observations are consistent with existing literature, which documented similar histo-pathological manifestations following METH exposure, including glomerular atrophy, hyaline casts within the tubular lumen, and interstitial nephritis [59-60]. Clinical findings further support the pathological profile identified in this study; for instance, Mirza et al.61 observed comparable renal histological alterations in METH-dependent patients, reporting glomerulonephritis, hypertensive vascular changes, and interstitial fibrosis. The observed morphological deterioration serves as a physical manifestation of the oxidative stress induced by METH, specifically the elevation of malondialdehyde (MDA) and the concomitant depletion of superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities. Ultimately, the significant rise in creatinine and urea levels, classic indicators of impaired renal clearance, is supported by gross cytoarchitectural degeneration of the renal parenchyma.

Melatonin intervention reduced observable glomerular and tubular distortions and improved kidney cytoarchitectural integrity. The cytoprotective capacity of melatonin is associated with its potent antioxidant effects, whereby it enhances the antioxidant capacity of SOD and GPx, thereby protecting against kidney damage by lowering the lipid peroxidation marker MDA. A previous study has shown the potency of MLT in protecting liver cytoarchitecture against carbon tetrachloride toxicity[62]. Similarly, Sulaimon *et al*.[49] reported that melatonin exerted neuroprotective effects against sodium fluoride toxicity by increasing antioxidant enzyme activity and reducing MDA levels, thereby improving pontine cytoarchitectural integrity in rats.

CONCLUSION

The findings of this study demonstrate that melatonin is protective against methamphetamine-induced renal toxicity by suppressing oxidative stress, thereby preserving the structural and functional integrity of the kidneys.

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