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HISTOMORPHOLOGICAL AND BIOCHEMICAL EFFECT OF METHAMPHETAMINE (CRYSTAL ICE) ON THE HEART OF WISTAR RATS

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Abstract

Background: Methamphetamine (METH), commonly known as crystal ice, is a potent psychostimulant associated with oxidative stress–mediated organ toxicity. While its neurotoxic effects are well established, its structural and biochemical impact on the heart remains comparatively underexplored. METH induces excessive production of reactive oxygen species, contributing to cellular injury and tissue degeneration. This study evaluated the histomorphological and biochemical effects of graded doses of METH on the hearts of Wistar rats.

Methods: Adult Wistar rats were divided into five groups: a control group and four experimental groups administered 0.5 mg/kg, 1.0 mg/kg, 3.0 mg/kg, and 5.0 mg/kg of METH, respectively, for six weeks. Blood samples were analyzed for haematological and biochemical parameters, and cardiac tissues were processed for histopathological examination. Data were expressed as mean ± SD and analyzed using ANOVA with Scheffé post hoc testing. Statistical significance was set at $p < 0.05$.

Results: METH administration produced a significant reduction in body weight compared with control (202.7 ± 3.11 g vs 210.0 ± 5.30 g; $t = 5.987$; $p = 0.0001$). Haematological analysis showed significant decreases in haematocrit (41.0 ± 1.66 vs 45.6 ± 1.50; $t = 20.917$; $p = 0.0001$) and white blood cell count (2.3 ± 0.55 vs 7.4 ± 1.92; $t = 9.039$; $p = 0.004$), with a significant increase in monocyte count (17.2 ±

2.38 vs 7.4 ± 1.14; t = −8.684; p = 0.0001). Serum biochemical parameters demonstrated dose-dependent increases in AST (123.1 ± 3.85 to 140.2 ± 0.72 U/L), ALT (62.5 ± 2.48 to 82.0 ± 1.96 U/L), ALP (210.5 ± 6.81 to 241.2 ± 7.15 U/L), and total bilirubin (0.56 ± 0.08 to 0.75 ± 0.05 mg/dL), all statistically significant ($p < 0.05$). Histological examination revealed normal myocardial architecture in control and 0.5 mg/kg groups, whereas 1.0 mg/kg and 3.0 mg/kg groups exhibited myocyte fragmentation and karyolysis consistent with myolysis.

Conclusion: Chronic methamphetamine exposure induces significant biochemical alterations and histomorphological evidence of myocardial degeneration in Wistar rats, demonstrating its cardiotoxic potential.

Keywords: Methamphetamine, Crystal ice, Cardiotoxicity, Histomorphology, Wistar rats, Biochemical markers.

Introduction

Methamphetamine (METH), commonly referred to as “crystal,” “ice,” “speed,” or “crank,” is a highly addictive psychostimulant with an estimated 35 million users worldwide.[1] Its widespread abuse represents a significant global public health concern. Methamphetamine exerts its primary pharmacologic action through rapid and sustained release of dopamine within the central nervous system, leading to intense stimulation and reinforcing addictive behaviors.[2] Although much of the scientific literature has focused on its neuropsychiatric consequences,[3-5] accumulating clinical observations suggest that the cardiovascular system is also a major target of methamphetamine toxicity.[6-8]

Acute methamphetamine exposure provokes marked sympathetic activation characterized by hypertension, tachycardia, vasoconstriction, and hyperthermia.[9] These hemodynamic effects substantially increase myocardial oxygen demand while simultaneously compromising coronary perfusion.[10] Consequently, serious cardiovascular complications—including arrhythmias, myocardial ischemia, and cardiomyopathy—have been reported among users.[11,12] Despite such clinical evidence, the structural basis of methamphetamine-associated cardiac injury has not been comprehensively characterized. Indeed, while neurotoxicity has been extensively documented,[13] limited experimental data exist regarding its histomorphological effects on cardiac tissue.

Methamphetamine abuse has been implicated in up to 40% of cardiomyopathy cases among young patients in certain populations, according to Tobolski et al.[14] Cardiovascular manifestations reported in association with methamphetamine use include persistent hypertension, tachycardia, acute coronary syndrome, pulmonary arterial hypertension, cardiomyopathy, and overt heart failure.[15] Mechanistically, oxidative stress and excessive generation of reactive oxygen species (ROS) have been proposed as central mediators of methamphetamine-induced tissue injury.[16] Experimental investigations have highlight the role of ROS in promoting lipid peroxidation, mitochondrial dysfunction, and cellular degeneration.[17,18] Nevertheless, detailed experimental evidence describing myocardial structural alterations following controlled methamphetamine exposure remains sparse.

Most prior research has concentrated predominantly on central nervous system toxicity,[19,20] leaving a significant gap in understanding of cardiac histopathology. Human studies are inherently limited by ethical and methodological constraints,[21] particularly with respect to controlled dosing and systematic tissue examination. In contrast, animal models permit precise control of exposure parameters and allow direct histological assessment of myocardial architecture under experimental conditions.[22] The use of

Wistar rats provides a well-established and reproducible model for investigating toxicological effects on organ systems.

Accordingly, the present study was designed to investigate the histomorphological and biochemical effects of methamphetamine on the heart of adult Wistar rats. Specifically, the study sought to determine the effect of methamphetamine administration on body weight, evaluate its influence on haemoglobin concentration, assess alterations in serum biochemical parameters including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and examine histomorphological changes in cardiac tissue following graded exposure.

This investigation was guided by the null hypothesis that methamphetamine does not cause significant alterations in cardiac histomorphology or biochemical parameters, and the alternative hypothesis that methamphetamine induces significant structural and biochemical changes in the myocardium. By integrating biochemical analysis with histological evaluation, this study aims to provide experimental evidence clarifying the cardiotoxic potential of methamphetamine and contribute to a more comprehensive understanding of its systemic pathological effects.

Methods

Study Design and Experimental Animals

This experimental laboratory study was conducted to evaluate the histomorphological and biochemical effects of methamphetamine (crystal ice) on the heart of Wistar rats. Twenty-four adult Wistar rats weighing between 200 g and 220 g were used for the study. The animals were obtained and acclimatized under standard laboratory conditions with free access to water and commercial rat feed. They were maintained under controlled environmental conditions with a 12-hour light–dark cycle throughout the experimental period.

The rats were randomly assigned into five groups.[23] Group A served as the control and received no methamphetamine. Group B received 0.5 mg/kg body weight of methamphetamine, Group C received 1.0 mg/kg, Group D received 3.0 mg/kg, and Group E received 5.0 mg/kg. Methamphetamine was administered orally twice daily for a duration of six weeks. Body weights were recorded at baseline and at the end of the experimental period to assess treatment-related changes.

Ethical Approval

Ethical approval for the study was obtained from the Ambrose Alli University Health Research Ethics Committee prior to commencement of the experiment.[24] All procedures involving animals were conducted in accordance with institutional guidelines for the care and use of laboratory animals and adhered to internationally accepted standards for experimental animal research.

Sample Collection

At the end of the six-week treatment period, the animals were humanely sacrificed. Blood samples were collected for haematological and biochemical analyses. The thoracic cavity was carefully opened, and the heart was excised, rinsed in normal saline to remove blood residues, and prepared for histological processing.

Biochemical and Haematological Analysis

Serum biochemical parameters were evaluated to determine systemic effects associated with methamphetamine exposure. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activities were analyzed using the atomic absorption spectrophotometric

(AAS) method. These enzymes were selected as indicators of tissue injury and systemic biochemical alterations.

Haemoglobin concentration was estimated using a Sysmex KX-21N automated hematology analyzer according to the manufacturer's standard operating procedures. The analyzer provided quantitative measurements to assess possible hematologic changes associated with methamphetamine administration.

Histological Procedures

Cardiac tissues were fixed immediately in 10% neutral buffered formalin to preserve structural integrity. Following fixation, tissue samples were processed routinely, and 3-mm sections were prepared. The sections were embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E) for general histomorphological assessment.

Prepared slides were examined under light microscopy to evaluate myocardial architecture. Particular attention was paid to cellular arrangement, nuclear morphology, cytoplasmic characteristics, and evidence of degeneration such as myocyte fragmentation or karyolysis. Histological findings were documented and compared across control and treated groups to determine dose-related structural alterations.

Statistical Analysis

Data obtained from biochemical and haematological analyses were expressed as mean ± standard deviation. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 25. Comparisons among groups were conducted using analysis of variance (ANOVA), followed by Scheffé post hoc testing where appropriate. A p-value less than 0.05 was considered statistically significant.[25]

Results

Animal Characteristics

Twenty-five adult Wistar rats were randomized into 5 groups (n = 5 per group) and treated with graded doses of methamphetamine (0.5, 1.0, 3.0, and 5.0 mg/kg) or distilled water (control) for 6 weeks. No mortality was recorded during the experimental period.

Histomorphological Findings

Microscopic examination of myocardial tissue revealed dose-dependent structural alterations following methamphetamine administration (Table 1; Panels A - E).

Cardiac sections from the control group demonstrated normal myocardial architecture, with intact cardiac muscle fibers, peripherally located nuclei, and uniformly eosinophilic cytoplasm (Panel A). There was no evidence of cellular degeneration, fragmentation, or inflammatory infiltration. Similarly, myocardial sections from rats treated with 0.5 mg/kg methamphetamine showed preserved histological architecture comparable to the control group (Panel B). Myocyte alignment and nuclear morphology remained intact, and no structural abnormalities were observed.

In contrast, myocardial sections from the 1.0 mg/kg group demonstrated evident structural disruption. Fragmentation of cardiac myocytes and nuclear karyolysis were observed, consistent with features of myolysis (Panel C). The integrity of the myocardial fiber network appeared compromised relative to control animals. More pronounced degenerative changes were observed in the 3.0 mg/kg group. Sections revealed extensive myocyte fragmentation and marked nuclear dissolution (Panel D). The

degree of structural disruption in this group was greater than that observed in the 1.0 mg/kg group, indicating progressive myocardial injury at intermediate-to-high dosing.

Unexpectedly, myocardial sections from rats administered 5.0 mg/kg methamphetamine demonstrated near-normal morphology (Panel E). Cardiac fibers appeared largely preserved with intact nuclear positioning and cytoplasmic staining. The extent of histological injury in this group was less severe than that observed in the 1.0 mg/kg and 3.0 mg/kg groups.

Overall, these findings indicate a dose-related but non-linear pattern of methamphetamine-induced cardiotoxicity, with maximal structural disruption occurring at intermediate doses rather than at the highest dose tested (Table 1).**Serum Biochemical Findings**

Serum biochemical parameters demonstrated statistically significant differences across groups (Table 2). Mean aspartate aminotransferase (AST) levels increased from 123.1 ± 3.85 U/L in the control group to 135.4 ± 4.17 U/L in the 0.5 mg/kg group, 138.3 ± 3.94 U/L in the 1.0 mg/kg group, 139.6 ± 2.94 U/L in the 3.0 mg/kg group, and 140.2 ± 0.72 U/L in the 5.0 mg/kg group. Analysis of variance demonstrated a significant overall group effect ($P < 0.01$). Post hoc comparisons showed significant elevations in all treated groups compared with controls ($P < .05$ to $P < 0.01$).

Alanine aminotransferase (ALT) levels increased progressively from 62.5 ± 2.48 U/L in controls to 71.1 ± 2.9 U/L, 73.5 ± 2.87 U/L, 75.5 ± 2.58 U/L, and 82.0 ± 1.96 U/L in the 0.5, 1.0, 3.0, and 5.0 mg/kg groups, respectively. The overall between-group difference was statistically significant ($P < .01$). Pairwise comparisons demonstrated significant elevations in treated groups relative to control ($P < 0.05$ and $P < 0.01$).

Alkaline phosphatase (ALP) levels increased from 210.5 ± 6.81 U/L in the control group to 228.5 ± 6.59 U/L, 232.1 ± 4.86 U/L, 233.9 ± 6.18 U/L, and 241.2 ± 7.15 U/L in the respective treated groups. The overall group effect was statistically significant ($P < .01$), with treated groups demonstrating significant differences compared with control values ($P < 0.05$ to $P < 0.01$).

Total bilirubin levels increased from 0.56 ± 0.08 mg/dL in controls to 0.66 ± 0.04 mg/dL, 0.68 ± 0.07 mg/dL, 0.70 ± 0.05 mg/dL, and 0.75 ± 0.05 mg/dL in the 0.5, 1.0, 3.0, and 5.0 mg/kg groups, respectively. Analysis demonstrated statistically significant differences between groups ($P < 0.05$).

Although biochemical parameters showed a generally progressive dose-related increase (Table 2), histomorphological findings demonstrated maximal structural disruption at intermediate doses (Panels C and D), suggesting a partially discordant and non-linear cardiotoxic response.

Table 1. Histomorphological Findings of Myocardium Following Methamphetamine Administration

Group	Dose (mg/kg)	Histological Features
Control	0	Normal myocardial fibers with intact architecture
B	0.5	Preserved myocardial morphology comparable to control
C	1.0	Myocyte fragmentation and nuclear karyolysis
D	3.0	Extensive fragmentation and nuclear dissolution
E	5.0	Near-normal myocardial morphology

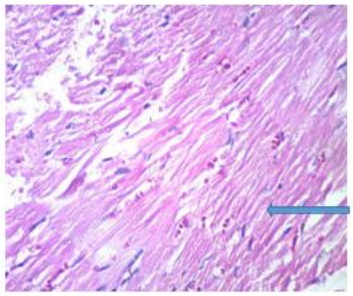
Table 2. Serum Biochemical Parameters After 6 Weeks of Methamphetamine Administration (n = 5 per Group)

Group	AST (U/L), Mean ± SE	ALT (U/L), Mean ± SE	ALP (U/L), Mean ± SE	Total Bilirubin (mg/dL), Mean ± SE
Control	123.1 ± 3.85	62.5 ± 2.48	210.5 ± 6.81	0.56 ± 0.08
0.5 mg/kg	135.4 ± 4.17*	71.1 ± 2.9†	228.5 ± 6.59†	0.66 ± 0.04†
1.0 mg/kg	138.3 ± 3.94*	73.5 ± 2.87†	232.1 ± 4.86*	0.68 ± 0.07*
3.0 mg/kg	139.6 ± 2.94*	75.5 ± 2.58†	233.9 ± 6.18*	0.70 ± 0.05*
5.0 mg/kg	140.2 ± 0.72‡	82.0 ± 1.96‡	241.2 ± 7.15‡	0.75 ± 0.05‡

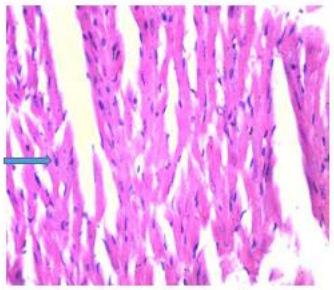
*P < .05 vs control
†P < .01 vs control
‡P < .01 vs control (highest magnitude difference)

Representative Photomicrographs of Myocardium After 6 Weeks of Methamphetamine Administration (Hematoxylin and Eosin Staining, Original Magnification ×400)

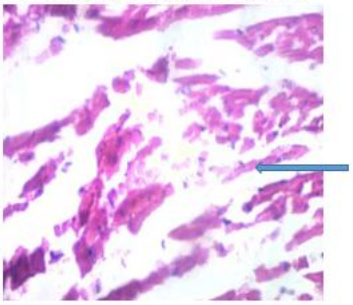
Panel A shows normal myocardial architecture in control rats. Panel B demonstrates preserved cardiac morphology in rats treated with 0.5 mg/kg methamphetamine. Panel C shows myocyte fragmentation and nuclear karyolysis in the 1.0 mg/kg group. Panel D demonstrates extensive myocyte fragmentation and nuclear dissolution in the 3.0 mg/kg group. Panel E shows near-normal myocardial architecture in rats treated with 5.0 mg/kg methamphetamine. Scale bar indicates 50 μm.



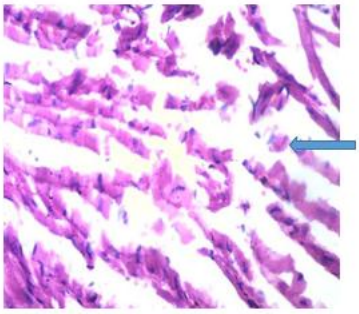
***Panel A**: Control Section (group A) of cardiac muscle shows myocytes with peripherally placed nuclei surrounded by eosinophilic cytoplasm. NORMAL HEART MUSCLE, H and E X400*



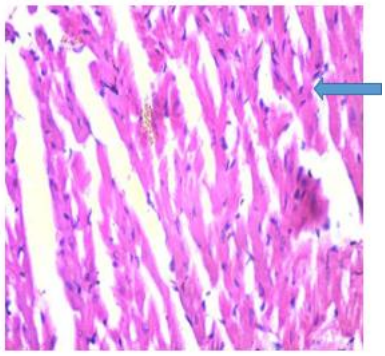
***Panel B**: Cardiac muscle section of group B rats administered 0.5mg/kg METH. Note myocytes with peripherally placed nuclei surrounded by eosinophilic cytoplasm. NORMAL HEART MUSCLE, H and E X400*



***Panel C**: Cardiac section of rat in group C administered 1.0mg/kg body weight of METH. Note fragmented myocytes with karyolysis of nuclei surrounded by eosinophilic cytoplasm. FEATURES OF MYOLYSISS, H and E X400*



***Panel D**: Cardiac section of rat (group D) administered 3.0mg/kg body weight of METH. Note fragmented myocytes with karyolysis of nuclei surrounded by eosinophilic cytoplasm. FEATURES OF MYOLYSIS, H and E X400.*



***Panel E**: Cardiac Section of rats in group E administered 5mg/kg body weight METH. Note myocytes with peripherally placed nuclei surrounded by eosinophilic cytoplasm. NORMAL HEART MUSCLE, H and E X400 FEATURES OF*

Discussion

This experimental study demonstrates that chronic methamphetamine exposure produces significant biochemical alterations and dose-dependent histomorphological changes in the myocardium of Wistar rats. The principal findings are threefold. First, methamphetamine administration resulted in progressive elevation of serum biochemical markers associated with tissue injury, including AST, ALT, ALP, and total bilirubin. Second, histological examination revealed myocardial degeneration characterized by myocyte fragmentation and nuclear karyolysis at intermediate doses (1.0 and 3.0 mg/kg). Third, the structural response exhibited a non-linear pattern, with relative preservation of myocardial architecture at the highest dose (5.0 mg/kg) despite sustained biochemical elevation. Collectively, these findings

provide experimental evidence supporting the cardiotoxic potential of methamphetamine and partially reject the null hypothesis of no structural or biochemical effect.

The observed myocyte fragmentation and nuclear karyolysis in the 1.0 mg/kg and 3.0 mg/kg groups are consistent with features of myolysis and cellular degeneration.[26] These structural alterations suggest direct myocardial injury, likely mediated through oxidative stress and catecholamine-induced cytotoxicity. Methamphetamine is known to provoke excessive sympathetic stimulation, resulting in sustained tachycardia, vasoconstriction, and increased myocardial oxygen demand.[27] Such hemodynamic stress may predispose to ischemic injury at the microvascular level, culminating in myocyte degeneration.

Experimental studies have implicated reactive oxygen species (ROS) in methamphetamine-induced organ damage,[28-30] demonstrating that oxidative stress can trigger lipid peroxidation, mitochondrial dysfunction, and nuclear dissolution. The nuclear karyolysis observed in this study aligns with these mechanisms and suggests that cardiomyocyte death may occur via oxidative and metabolic pathways. The dose-related increase in structural disruption between 1.0 mg/kg and 3.0 mg/kg supports a biologically plausible gradient of toxicity.

Unexpectedly, rats receiving 5.0 mg/kg methamphetamine demonstrated near-normal myocardial morphology. Several explanations may account for this non-linear response. High-dose exposure may have induced adaptive or compensatory mechanisms, such as upregulation of endogenous antioxidant systems, heat shock proteins, or cellular repair pathways. Alternatively, severe systemic toxicity at the highest dose may have altered drug metabolism, limiting sustained myocardial exposure. Another possibility is sampling variability inherent in small experimental groups (n = 5 per group). Similar non-monotonic dose–response patterns have been described in toxicological research,[31-33] and may reflect complex interactions between oxidative stress, inflammatory signaling, and compensatory cellular adaptation.

Serum AST, ALT, and ALP levels increased progressively across treatment groups, with statistically significant elevations compared with controls. Although these enzymes are commonly regarded as markers of hepatic injury, AST in particular is also present in cardiac muscle and is released during myocardial damage.[34,35] The concurrent elevation of AST with histological evidence of myocardial fragmentation supports the interpretation that methamphetamine exposure induces systemic and possibly cardiac-specific tissue injury.

The progressive rise in ALT and ALP further suggests generalized biochemical stress. Total bilirubin elevation may reflect impaired hepatic clearance or increased hemolysis secondary to oxidative stress.[36] While these biochemical markers are not exclusively cardiac-specific, their consistent dose-related elevation strengthens the evidence for systemic toxicity associated with chronic methamphetamine administration.

Interestingly, biochemical parameters demonstrated a more linear dose–response relationship than histomorphological findings. This partial discordance suggests that circulating enzyme levels may reflect cumulative systemic injury rather than localized myocardial structural change alone. It also underscores the importance of integrating biochemical and histological endpoints in toxicological investigations.

Methamphetamine-treated rats exhibited significant reduction in body weight compared with controls. This finding is consistent with the known anorectic and hypermetabolic effects of psychostimulants.[37]

Chronic sympathetic activation increases basal metabolic rate and suppresses appetite, contributing to weight loss.[38]

The observed reduction in hematocrit and white blood cell count, along with increased monocyte percentage, may indicate systemic inflammatory modulation or bone marrow suppression. Monocytosis could reflect a stress-induced inflammatory response secondary to tissue injury. These hematologic changes further support the systemic impact of chronic methamphetamine exposure beyond isolated cardiac effects.

Clinical observations have linked methamphetamine use to cardiomyopathy, arrhythmias, hypertension, and heart failure, particularly in younger populations.[39] Epidemiologic data suggest that methamphetamine abuse may account for a substantial proportion of non-ischemic cardiomyopathy cases in certain regions.[40] However, direct histopathological evidence from controlled experimental models has been limited.

The present findings contribute mechanistic insight by demonstrating structural myocardial disruption under controlled dosing conditions. Unlike many human studies, which are confounded by polysubstance use and comorbidities,[41-43] this experimental design isolates methamphetamine exposure as the principal variable. The demonstration of myolysis at intermediate doses strengthens the biological plausibility of clinical observations linking methamphetamine to cardiomyopathy.

Several interrelated mechanisms may underlie the cardiotoxic effects observed following methamphetamine exposure. Central to these is oxidative stress, as excessive dopamine metabolism and catecholamine autoxidation generate reactive oxygen species that promote lipid peroxidation, mitochondrial dysfunction, and cardiomyocyte injury. Sustained sympathomimetic stimulation further exacerbates damage by inducing persistent tachycardia and hypertension,[44] thereby increasing myocardial oxygen demand while reducing coronary perfusion and predisposing the myocardium to ischemic stress. In addition, disruption of intracellular calcium homeostasis may impair excitation–contraction coupling and activate calcium-dependent pathways that contribute to cellular dysfunction and death. The associated increase in monocyte counts also suggests inflammatory activation, which can amplify oxidative injury and accelerate tissue degeneration. Collectively, these overlapping oxidative, hemodynamic, metabolic, and inflammatory processes likely interact synergistically to produce cumulative myocardial damage.

A key strength of this study is the integration of biochemical assays with direct histological evaluation, providing complementary evidence of cardiotoxicity. The graded dosing design allows assessment of dose–response relationships under controlled conditions. However, several limitations warrant consideration. The small sample size (n = 5 per group) limits statistical power,[45,46] and may partly explain the non-linear histological findings at the highest dose. The study duration of six weeks, while sufficient to detect structural changes, may not reflect long-term exposure patterns seen in human users. Additionally, cardiac-specific biomarkers such as troponins or creatine kinase–MB were not assessed, which could have strengthened the specificity of biochemical interpretation. Future studies incorporating oxidative stress markers, inflammatory cytokines, and ultrastructural analysis would provide deeper mechanistic insight.

These findings underscore the cardiotoxic risk associated with chronic methamphetamine use. The demonstration of myocardial degeneration in an experimental model provides pathophysiological support for clinical reports of methamphetamine-associated cardiomyopathy. Given the global

prevalence of methamphetamine abuse, early cardiovascular screening and public health interventions targeting stimulant misuse are warranted.

Conclusion

Chronic methamphetamine exposure in Wistar rats induces significant biochemical alterations and histomorphological evidence of myocardial degeneration. Structural injury was most pronounced at intermediate doses, indicating a complex and partially non-linear cardiotoxic response. These findings contribute experimental evidence clarifying the myocardial consequences of methamphetamine exposure and reinforce concerns regarding its cardiovascular safety profile. Further mechanistic and longitudinal studies are necessary to elucidate the pathways underlying methamphetamine-induced cardiomyopathy and to inform preventive and therapeutic strategies.

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