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Original Research Article

Cardioprotective Role of Vitamin E against Methamphetamine-Induced Histological Changes in Male Rats

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Abstract: The aim of this study was to evaluate the toxic effects of methamphetamine on the histological structure of the heart muscle in adult male white rats, to assess the potential protective effects of vitamin E against the toxic effects of methamphetamine, and to evaluate the anti-oxidative effects of vitamin E. Three hundred and two white adult Sprague–Dawley rats were randomly allocated to four major groups, 8 rats per group. Each main group was then split into two subgroups according to length of treatment (15 or 30 days). The control group received daily doses for 15 days while the first group of experimental animals were given daily doses of methamphetamine (0.1 mg/kg, 1 mL/day) and the third group daily doses of vitamin E (0.1 mL/day) for 30 days. The animals were hyperactive and moved around more in the cages, were very agitated and eating and drinking less after being treated with methamphetamine. Heart samples were taken at the end of each experimental period and subjected to histopathology. Observed were coronary blood vessels, an infiltration of inflammatory cells, hemorrhage, and some muscle fiber atrophy, also with loss of the nuclei, and increase in the intramuscular connective tissue, the degree of the latter changing with the duration of the exposure. Some histological changes also were observed in the vitamin E group, which may be due to dose or time of administration. Group treated with methamphetamine and vitamin E had a lesser reduction in the severity of some histological lesions than the methamphetamine only group, but the pathological changes were not completely prevented. The study found that methamphetamine creates progressive tissue toxicity in the heart muscle, with the severity of the toxicity increasing as the amount of time the body was exposed to the drug, indicating a cumulative effect of the drug on cardiac tissue. The outcomes further suggest a partial protection of vitamin E against cardiac toxicity induced by chronic methamphetamine exposure, but not enough to prevent all histological changes, thus necessitating further research to determine the optimal dose and mechanism of protection during chronic methamphetamine exposure.

Keywords: Methamphetamine, Vitamin E, Cardioprotective, Methamphetamine Histopathology, Methamphetamine-Induced Cardiotxicity.

1- INTRODUCTION

Methamphetamine has the ability to cross the blood-brain barrier and to cause the release of large amounts of neurotransmitters, particularly dopamine and norepinephrine, which have widespread effects on the central nervous system and many other systems, it is considered to be one of the most potent psychostimulants. These characteristics have contributed to its global prevalence as one of the most commonly abused and addictive drugs, which has increased researchers' interest in studying its toxic effects on vital organs (UNODC, 2024; Cruickshank & Dyer, 2009; Darke *et al*., 2020). Recent studies indicate that methamphetamine is a toxic substance with multiple effects on the body's organs, and the heart is among the organs most vulnerable to its toxic effects, given the sensitivity of cardiac tissue to oxidative stress and the hemodynamic and metabolic disturbances caused by this drug, in addition to its direct effects on cardiac myocytes and coronary blood vessels (Somma *et al*., 2023; Kevil *et al*., 2019; Paratz *et al*., 2016). The heart plays a vital role in maintaining blood circulation and supplying the body's tissues with oxygen and nutrients by pumping blood regularly,

Therefore, any abnormality in the structure or function of the heart muscle may negatively affect the efficiency of the entire cardiovascular system and may lead to cardiac arrhythmias, reduced systolic efficiency, or the development of conditions such as cardiomyopathy and heart failure (Paratz *et al*., 2016; Schürer *et al*., 2017). Although there is clinical evidence linking methamphetamine use to an increased risk of cardiovascular disease, experimental studies examining its direct histological effects on the heart remain relatively limited (Paratz *et al*., 2020; Won *et al*., 2013), particularly with regard to describing pathological changes associated with dose and duration of use, as well as elucidating the molecular mechanisms responsible for cardiac damage. Numerous studies have indicated that oxidative stress is one of the most important pathological mechanisms responsible for methamphetamine-induced cardiac toxicity, as this drug leads to increased production of reactive oxygen species (ROS) and promotes lipid peroxidation, causing damage to cell membranes, mitochondrial dysfunction, and the activation of inflammatory and apoptotic pathways, all of which negatively impact the integrity and function of cardiac tissue (Ramli *et al*., 2025; Nazari *et al*., 2023). Given the pivotal role of oxidative stress in the development of these pathological changes, antioxidants have garnered increasing attention as potential protective agents for reducing methamphetamine-induced damage. Vitamin E (α-Tocopherol) is one of the most important fat-soluble antioxidants; it effectively inhibits lipid peroxidation reactions and protects cell membranes from oxidative damage, in addition to its role in reducing the inflammatory response and maintaining the integrity of cells and tissues. Numerous experimental studies have shown that vitamin E administration helps reduce markers of oxidative stress and improve histological changes in various models of drug toxicity, including cardiac toxicity, suggesting its potential as a protective agent against methamphetamine-induced cardiac damage (Shabani *et al*., 2023; Traber & Atkinson, 2007; Niki, 2014; Kumar *et al*., 2021). Therefore, the present study aimed to evaluate the protective effect of vitamin E against methamphetamine-induced cardiac histological changes in male white rats, and to verify its ability to reduce tissue damage associated with oxidative stress, thereby contributing to a better scientific understanding of the pathophysiological mechanisms associated with this toxicity and supporting the development of future preventive and therapeutic strategies to reduce its complications (Paratz *et al*., 2020; Kevil *et al*., 2019; Darke *et al*., 2020).

2- MATERIALS AND METHODS

2-1 Laboratory Animals

Thirty-two female Sprague-Dawley rats from 2-4 months of age and a weight of 150-200g were used for this investigation. The animals were kept in controlled environment under constant temperature 25ºC with water and nutrition.

2-2 Experimental Design

- Rats were randomly divided into four groups, three experimental and one control group, each group comprising four rats. Each of the three experimental groups (1, 2, and 3) was subdivided into two groups, one consisting of 4 rats that received treatment for 15 days and the other group of 4 rats that received treatment for 30 days. Weight of each group was noted at the beginning of the study as far as possible. The animals were split into 4 groups with 8 each, and treated as follows:
  - **Group 1** (G1, control): The rats were isolated for 30 days in order to get nutrients and water without treatment.
  - **Group 2** (G2) : The rats were orally administered with Methamphetamine (0.1mg/kg of body weight) in 1 ml of distilled water for 15 days in the first group consisted of rats (n = 4) and 30 days in the second group consisted of rats (n = 4).
  - **Group 3** (G3): This group was also subdivided into 2 sub-groups. The rats (n = 4) of the first subgroup were given Vitamin E at a dose of 0.1ml for 15 days and the second subgroup of rats (n = 4) was treated for 30 days.
  - **Group 4** (G4): This group was subdivided into two subgroups. To accomplish this, rats (4 rats/each) were assigned to the first subgroup, which was treated with methamphetamine at 0.1 mg/kg and Vitamin E at 0.1ml for 15 days, and the second subgroup, treated for 30 days.
- Food and water were provided in all experimental groups during the experimental periods.

2-3 Preparation of Histological Sections

Tissue slices were made in the histology lab. "Tikrit University college of science. The following steps were taken in accordance with Al-Hajj's (2015) approach to prepare microscopical sections:

In order to repair the removed heart segments, they were immediately submerged in 10% neutral buffered formalin for a whole day. The tissues were first dehydrated in a graded series of ethanol (70, 80, 90 and 100%) then cleared in xylene, embedded in paraffin wax at 60C and cut at 6 µ thick on a rotary microtome. The sections obtained were stained with hematoxylin and eosin (H&E) and mounted on slides with D.P.X. and covered by a cover slip. Finally, a light microscope was used to inspect the slides", and a digital camera that had been adapted to use a microscope was used to take pictures of them.

3- RESULTS

In the control group (G1), no pathological changes were found upon histological examination of the heart muscle, where the cardiac muscle fibers were seen to be arranged regularly with distinct central nuclei in the cardiomyocytes and fibroblasts in the endomysium and a small number of white blood cells were seen scattered in the tissues (Figure 1). In the methamphetamine group (G2) after 15 days of treatment, a clear disruption in the regularity of the cardiac muscle fibers was observed, along with their fragmentation, in addition to degeneration and rupture of some cardiac muscle fibers compared to the control group as illustrated in Figure (2). The severity of the histological changes increased after 30 days of treatment, and there was marked congestion of the coronary blood vessels, clear infiltration of inflammatory white blood cells and aggregation of cardiac muscle fibers "as shown in Figure (3). After 15 days, histological sections of the vitamin E (G3) group showed severe focal hemorrhage, surrounded by inflammatory cells and perinuclear vacuolar degeneration of the cytoplasm of cardiac myofibers as seen in Figure (4). After 30 days, atrophy of the cardiac muscle fibers was observed, along with loss of nuclei in some muscle cells, expansion of the intramuscular connective tissue, and infiltration of blood cells into it, in addition to fragmentation and disruption of the continuity of the cardiac muscle fibers as seen in Figure (5). As for the group treated with methamphetamine and vitamin E (G4), showed, after 15 days, compaction of the cardiac muscle fibers, with infiltration of white blood cells and macrophages into the intramuscular connective tissue, as well as cytoplasmic degeneration in many muscle fibers and the presence of intramuscular hemorrhage accompanied by hemolysis between the muscle fibers as depicted in Figure (6). Histological changes after 30 days showed cardiac muscle fibre atrophy, some muscle fibres were nucleus-free, there was an increase in intramural connective tissue, blood cells in the increased connective tissue and hemorrhage in the endocardium as seen in Figure" (7).

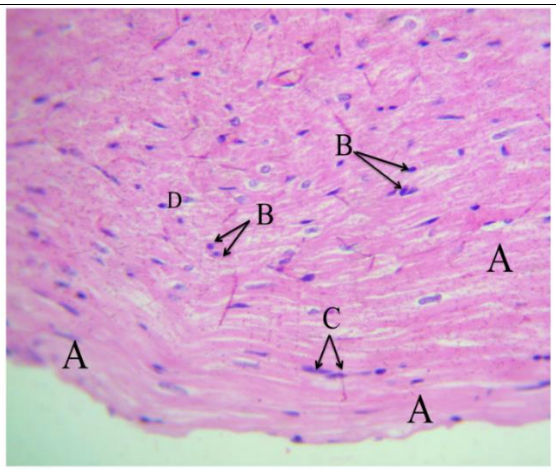

Fig. 1: Photomicrograph of a G1 showing normal cardiac tissue, regularly arranged myocardial fibers (A), centrally located nuclei of cardiac muscle cells (B), fibroblasts within the endomysial connective tissue (C), and a few scattered leukocytes (D). (H&E, 40×).

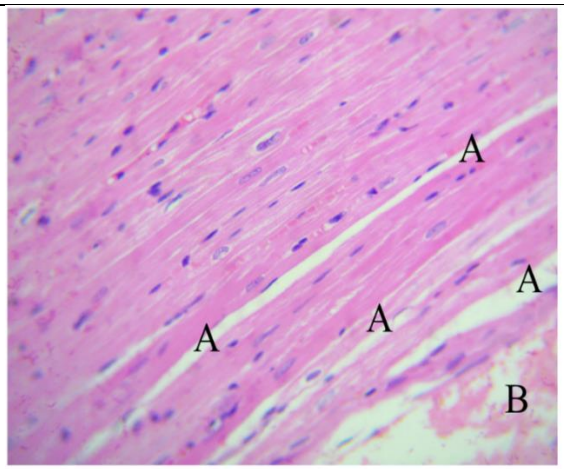

Fig. 2: Photomicrograph of a rat cardiac tissue from G2 showing disorganization and fragmentation of the cardiac muscle fibers (A), accompanied by degeneration and disruption of some myocardial fibers (B). (H&E, 40×).

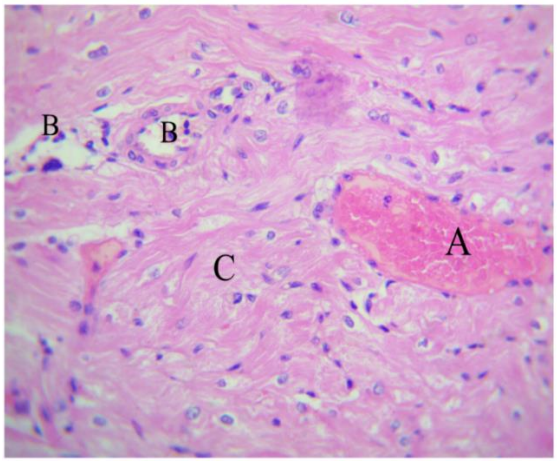

Fig. 3: Photomicrograph of a rat cardiac tissue from G2 demonstrating marked congestion of the coronary blood vessels (A), infiltration of inflammatory leukocytes (B), and closely packed myocardial fibers (C). (H&E, 40×).

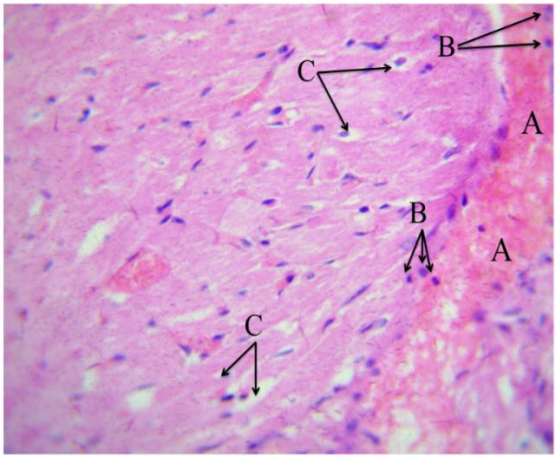

Fig. 4: Photomicrograph a rat cardiac tissue from G3 showing severe focal hemorrhage (A) surrounded by inflammatory leukocytes (B), together with perinuclear cytoplasmic vacuolar degeneration of the cardiac muscle fibers (C). (H&E, 40×).

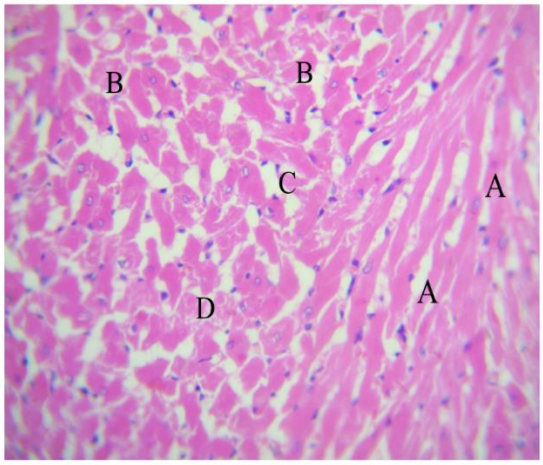

Fig. 5: Photomicrograph of a rat cardiac tissue from G3 demonstrating atrophy of the cardiac muscle fibers (A), loss of nuclei in some myocardial fibers (B), expansion of the endomysial connective tissue containing infiltrating blood cells (C), and fragmentation with discontinuity of myocardial fibers (D). (H&E, 40×).

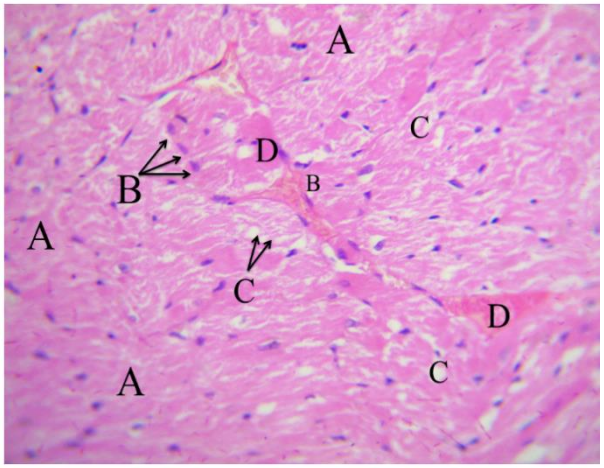

Fig. 6: Photomicrograph of a rat cardiac tissue from G4 and Vitamin E (0.1 mL/day) for 15 days), showing closely packed myocardial fibers (A), infiltration of scattered leukocytes and macrophages within the endomysial connective tissue (B), cytoplasmic degeneration of numerous cardiac muscle fibers (C), and interstitial hemorrhage with erythrocyte degradation between the myocardial fibers (D). (H&E, 40×)

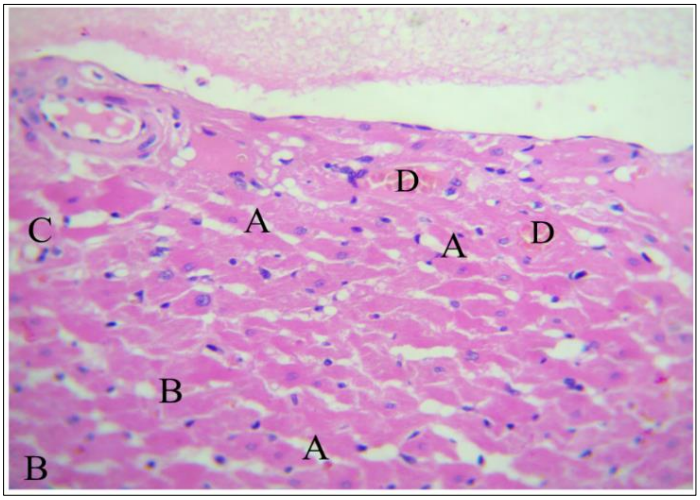

Fig. 7: Photomicrograph of a rat cardiac tissue from G4 illustrating atrophy of the cardiac muscle fibers (A), loss of nuclei in some myocardial fibers (B), expansion of the endomysial connective tissue with infiltration of blood cells (C), and hemorrhage in the endocardial region (D). (H&E, 40×).

4-DISCUSSION

The control group exhibited the normal histological structure of the heart muscle, characterized by the regular arrangement of cardiac muscle fibers and the presence of central nuclei and fibroblasts within the intramuscular connective tissue, with no pathological changes observed. This confirms the integrity of the animal model used and that it was not exposed to any factors that might affect the histological structure of the heart. These results are consistent with the normal histological description of the rat heart muscle reported in the reference studies (Bancroft & Gamble, 2019; Treuting *et al*., 2018)., making them a suitable basis for comparison with the pathological changes observed in the treated groups. The cardiac structural changes caused by methamphetamine can be explained by its stimulation of catecholamine release—particularly norepinephrine and dopamine—which leads to coronary vasoconstriction and increased oxygen consumption in the heart muscle (Kevil *et al*., 2019; Paratz *et al*., 2016; Darke *et al*., 2020)., resulting in ischemia and oxidative stress. This leads to increased production of reactive oxygen species (ROS), lipid peroxidation, and damage to proteins and DNA, as well as impaired mitochondrial function, ultimately resulting in cardiomyocyte degeneration and loss of cellular membrane integrity (Ramli *et al*., 2025; Nazari *et al*., 2023; Somma *et al*., 2023). Oxidative stress also is a trigger for activation of inflammatory pathways and release of pro-inflammatory cytokines, accounting for the presence of vascular congestion and inflammatory cell infiltration into cardiac tissue. These results are similar to the ones reported by Ramli *et*

al., (2025) showing that methamphetamine causes oxidative stress, mitochondrial dysfunction and activation of inflammatory pathway, leading to the obvious tissue damage in the myocardium. They are also similar to the study conducted by Shabani *et al*., (2023) which revealed methamphetamine induced increase in the production of free radicals and dysfunction of mitochondria, causing evident damage to the tissue of the myocardium. Moreover, longer exposure has been shown to lead to greater severity of lesions, suggesting that methamphetamine may accumulate, causing sustained production of free radicals, disturbances in calcium metabolism, activation of apoptosis pathways, and higher collagen deposits, all of which contribute to more severe damage to the heart muscle. The histological changes observed in the vitamin E group may be attributed to the effects of dose and duration of exposure, as some studies suggest that vitamin E may exhibit a pro-oxidant effect (pro-oxidant effect) (Traber & Atkinson, 2007; Niki, 2014), when used in high doses or in cases of an imbalance between antioxidants and oxidizing agents, which may lead to disruption of cell membrane integrity and the occurrence of certain degenerative and hemorrhagic changes. However, these findings differ from those reported in numerous studies that have confirmed the protective role of vitamin E in reducing oxidative stress and maintaining cardiac tissue integrity, including a study by Garg and Lee (2022), this discrepancy may be attributed to differences in the dose used, duration of treatment, animal model, and experimental conditions across the studies. In the group treated with both methamphetamine and vitamin E, vitamin E did not appear to be able to completely prevent the histological changes (Nazari *et al*., 2023; Paratz *et al*., 2020)., suggesting that the severity of methamphetamine-induced cardiac toxicity exceeded the protective capacity of the administered dose of the antioxidant. It is possible that persistent oxidative stress, inflammation, and mitochondrial dysfunction limited the effectiveness of vitamin E, leading to the persistence of some manifestations of tissue damage. These observations are partially consistent with a study by Shabani *et al*., (2023), which demonstrated that the efficacy of antioxidants in reducing methamphetamine-induced cardiac toxicity depends on their type, dose, and duration of administration. Recent studies have also indicated that antioxidants may mitigate the severity of tissue damage without completely preventing it, particularly in cases of chronic exposure, suggesting that vitamin E provided partial protection (Shabani *et al*., 2023; Kevil *et al*., 2019; Ramli *et al*., 2025).; however, this was insufficient to prevent all the pathological effects caused by methamphetamine in cardiac tissue.

5-CONCLUSION

Exposure to methamphetamine led to clear pathological histological changes in the myocardium, manifested as disruption of the normal structure of cardiac muscle fibers, degeneration, vascular congestion, inflammatory exudation, and hemorrhage, the severity of these changes increased with longer duration of exposure, indicating a cumulative effect of methamphetamine on cardiac tissue. The results of the vitamin E group also showed that administration of vitamin E alone did not fully preserve the normal histological structure of the heart muscle under the conditions of this study. Conversely, combined treatment with methamphetamine and vitamin E provided partial protection by reducing the severity of some tissue lesions; however, it was not sufficient to prevent all of the pathological effects caused by methamphetamine. The cardiac toxicity of methamphetamine is believed to result from several pathological mechanisms and the cardiac protective effect of vitamin E is dependent on the dose and duration of treatment, indicating the need for additional studies to more accurately define the dose and mechanism of action of vitamin E.

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