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Research Article

Nephroprotective effect of low dose of vitamin A on the kidney in toxic dose of methamphetamine induced adult male Wistar rats

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Methamphetamine (METH), a potent psychostimulant, is widely recognized for its neurotoxic and systemic toxic effects, including oxidative and inflammatory damage to peripheral organs such as the kidney. Excessive METH exposure induces nephrotoxicity characterized by oxidative stress, tubular degeneration, and impaired renal function. Vitamin A, in its active metabolite form (retinoic acid), exhibits strong antioxidant and cytoprotective properties that may counteract drug-induced organ injury. This study investigated the potential protective effect of low-dose of vitamin A on the kidneys of adult male Wistar rats exposed to toxic doses of methamphetamine. Twenty rats were randomly divided into four groups (n = 5): group A (control) feed and water, group B (METH-only; 20g/kg at 3-hour intervals within 12 hours in a day), group C (vitamin A-only; 0.7 mg/kg) while group D (combined METH + vitamin A). All the experimental groups were fed with feed and water. All treatments were administered orally via intubation for 28 consecutive days. After the final administration, animals were anesthetized and sacrificed; kidneys were harvested, fixed in 10% neutral formal-saline and processed for histological examination using Hematoxylin and Eosin (H&E) staining. Results of methamphetamine exposure group showed weight loss, oxidative stress, and notable renal architectural disruptions, including tubular necrosis, glomerular shrinkage, and inflammatory infiltration. However, co-administration of low-dose of vitamin A preserved renal morphology, reduced cellular degeneration, and stabilized biochemical markers of kidney function. The

findings of this study suggest that vitamin A confers a nephroprotective effect against methamphetamine-induced renal toxicity, likely mediated through its antioxidant and anti-inflammatory mechanism.

Keywords: Toxic dose, Vitamin A, Wistar rat, Nephroprotective, Methamphetamine

Introduction

Methamphetamine (METH) is a potent psychostimulant and a drug of global abuse, notorious for causing multi-organ toxicity, including significant damage to the kidneys (Smith *et al.,* 2022). Experimental studies in rodents have demonstrated that chronic or high-dose METH exposure leads to renal dysfunction, histopathological changes, inflammation, and oxidative stress (Cui *et al.,* 2016; Hassan *et al.,* 2020). These effects are primarily mediated by the overproduction of reactive oxygen species (ROS), mitochondrial dysfunction, and the activation of apoptotic pathways, which compromise the structural and functional integrity of nephrons. Vitamin A, a fat-soluble vitamin, plays a critical role in immune function, growth, and cellular integrity. At controlled doses, it may enhance antioxidant enzyme activity and mitigate oxidative damage caused by toxic substances, including METH (Ross, 2012; Zhang *et al.,* 2019). However, deficiency of vitamin A can be harmful, particularly to the liver and kidneys (Penniston & Tanumihardjo, 2006). Therefore, evaluating the effect of a low, therapeutic dose is essential for understanding its potential protective role without inducing toxicity. Despite growing evidence of METH-induced renal damage, limited studies have explored the use of antioxidants like vitamin A to mitigate this injury. The specific impact of low-dose vitamin A on the kidney under METH-induced toxicity conditions remains understudied. This study, using the well-characterized Wistar rat model, aims to investigate the potential nephroprotective effects of low-dose vitamin A, which may provide important insights into therapeutic interventions for drug-induced renal toxicity.

Methods

Location of the Study

This study was carried out at the Animal House of the College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Anambra State Nigeria.

Ethical Approval

Ethical approval was obtained from the Ethical Committee, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University.

Materials of the Study

During this investigation, the following materials were utilized. Twenty-four adult Wistar rats, Iron cages with iron nettings, sawdust (litters), Animal feed (grower and finisher mash), laboratory coat and gloves, dissecting kit, one stopwatch, digital video recorder, measuring cylinder, weighing balance, water bath, sample bottle, 10% Neutral Buffered Formalin (Sodium Phosphate Monobasic 4.0gm, Sodium Phosphate Dibasic 6.5gm, Formaldehyde 37% 100.0ml, Distilled Water 900.0ml), Cotton and anesthesia (chloroform), Graded Alcohol (50%,70%,95% and absolute alcohol), Glass slides and slide rack, Hot plate, Xylene, Paraffin wax, Embedding plate, and pot, Deepex (DPX) Mountant, Hematoxylin and eosin, Coverslips, Light Microscope, Orbit shake, Diamond pencil, Rotatory microtome, Ethanol for tissue processing, Micropipette, Specimen labels, and bottles, Trays, Paraffin dispenser, Cassette and slide storage, Pipette tips (various sizes), Knife sharpener, Notebook, and biro.

Procurement and Housing of Experimental Animals

Twenty-four (24) adult Wistar rats weighing 180-250kg were procured from Research Enterprise Farm, University of Ibadan, Oyo State. Perspex cages were used to house four (4) groups of six (6) animals each for routine experiments. Each cage had a wire gauze top for cross-ventilation. The animals were allowed for two weeks for acclimatization under normal temperatures ($27\text{-}30^0$) at the Animal House of the Basic Medical Sciences. Nnamdi Azikiwe University, Nnewi Campus. They were fed ad libitum with water and Grower mesh.

Experimental Design and Protocols

Twenty-four male adult rats were randomly grouped into Four groups (n=6)

Group A, Group B, Group C and Group D
Group A was control group which received feed and water only
Group B were administered 20mg/kgbw of Methamphetamine
Group C were administered 0.7mg/kgbw of Vitamin A (high dose)
Group D were administered 20mg/kgbw of Methamphetamine + 0.7mg/kgbw of Vitamin A (high dose)
Administration was done orally using oral gavage method. All experimental protocols were observed under strict supervision, the experiment lasted for 28 days and methamphetamine administration was done daily.

Termination of Treatment

Twenty-four hours (24) after the last administration, the animal were weighed first using a-weighing balance to get the final weight before the animals were sacrificed. The animals were anesthetized with chloroform, blunt scissors were used to make a midline incision along the abdomino-pelvic region in each rat to avoid damage to the visceral organs. The rats were dissected lying on their back, abdomen facing upwards and limbs pinned laterally to the board for easy dissection. The kidney was traced, harvested and examined macroscopically for any lesions or abnormalities. The kidney was weighed and then fixed in 10% formalin to maintain normal physiological conditions and for the interest of histological investigations in the histology laboratory of Anatomy Department, Nnamdi Azikiwe University, Nnewi campus.

Tissue Processing

For easy study of sections under a microscope, the tissues were passed through several processes of fixation, dehydration, clearing, infiltration, embedding, sectioning, and staining.

Fixation

The essence of fixation is to preserve the various constituents of the cells in a life-like state and to prevent autolytic changes and putrefaction. Fixation was carried out in 10% Neutral Buffered Formalin (Sodium Phosphate Monobasic 4.0gm, Sodium Phosphate Dibasic 6.5gm, Formaldehyde 37% 100.0ml, Distilled Water 900.0ml). The tissues remained in the fluid for 48 hours. After fixation, the tissues were washed overnight under stream tap water to remove any surplus fixatives.

Dehydration

Dehydration of the fixed tissues was done to remove water and other substances. This was carried out in different percentages of alcohol 50%, 70%, and 95% absolute. In each grade of alcohol, tissues were changed twice for two (2) hours and one (1) hour for each change.

Clearing

The tissues were then cleared in two changes of xylene for two hours to remove the absolute alcohol that was used to dehydrate the tissues thereby replacing the absolute alcohol in the tissues with xylene. Xylene is usually miscible with absolute alcohol and paraffin wax; therefore, xylene was used as the clearing agent. After clearing, infiltration was carried out.

Infiltration

The tissues were transferred to two changes of molten paraffin wax for 2 hours each. I ensured that the amount of wax was 25-50 times the volume of the tissue. Infiltration was carried out to replace xylene in the tissue spaces with molten paraffin wax. The temperature of the paraffin was kept at 60^{o}C.

Embedding

The tissues were embedded by submerging them in two changes of molten paraffin wax contained in cassette metal molds at a constant temperature of 52-60C in an oven of paraffin wax for 2 hours each time. The tissues were well-oriented in the molds to ensure the presentation of the desired parts of the tissues to be examined in the tissue sections.

Sectioning

This is the process by which a thin slice of the tissue of about 4µm thick is made using a rotatory microtome (Leica RM 2125 RST).

Staining

Hematoxylin & Eosin Staining (H&E): Sections were dewaxed using xylene for one (1) minute and then rehydrated by alcohol through descending grades of ethyl alcohol and thereafter washed in distilled water. The sections were stained with Hematoxylin for twenty (20) minutes and differentiated with 2% acid alcohol for two (2) seconds. The acid alcohol was washed off with tap water and the sections passed through running tap water for ten (10) minutes to regain the blue colour. The sections were counterstained in 1% aqueous eosin for thirty (30) seconds and were dehydrated through ascending grades of ethyl alcohol, cleared in xylene, and mounted using DPX. After which, the sections were viewed under a light microscope.

Data Analysis

Data was analyzed using the SPSS version 27.0.1 software package. Mean and standard deviation were obtained, and one-way analysis of variance (ANOVA) was used to compare values between groups. Data was expressed as Mean + Standard Deviation (SD) and then considered statistically significant when $P < 0.05$.

Results

Physical and Behavioral Changes

Prior to the commencement of the experiment, all the animals appeared healthy, active, and exhibited normal behavioural patterns. During the one-week acclimatization period, the animals maintained normal stool consistency and showed no signs of illness or distress. Following the administration of methamphetamine, varying degrees of toxicity were observed, with the severity of clinical signs increasing progressively with continued exposure to the drug. The toxic manifestations included tremors, heightened agitation and aggressive behaviour, impaired balance and coordination, and a staggering gait, all of which are indicative of methamphetamine-induced neurobehavioral toxicity.

Table 1. Comparison of mean initial and final body weight and weight change in all the groups (A, B, C, &D)

GROUPS	WEIGHT (g)	MEAN± SEM	p-value
GROUP A	Initial	130.40±2.03	0.007
	Final	145.96±0.02	
GROUP B	Initial	136.20±4.83	0.001
	Final	121.04±6.01	
GROUP C	Initial	135.94±3.92	0.000
	Final	160.00±1.09	
GROUP D	Initial	135.90±0.50	0.001
	Final	147.80±0.92	

Data was analyzed using Student dependent T-test and values were considered significant at $P<0.05$.

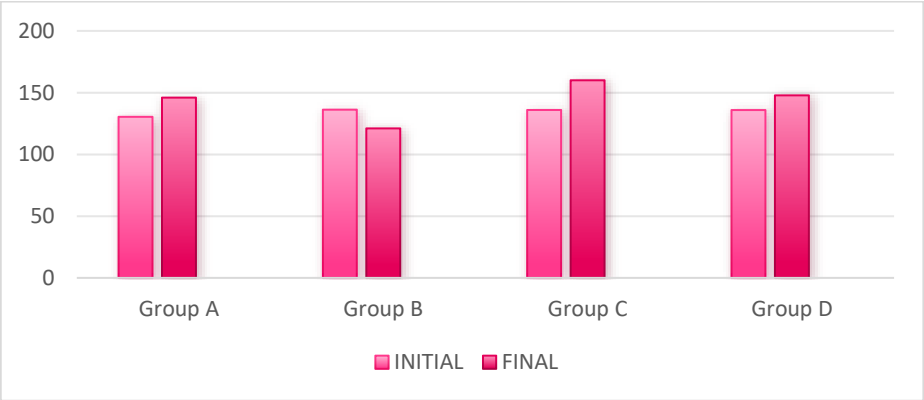

Figure 1. bar chart showing Comparison of mean body weight for group A(control) and experimental groups (B, C, and D)

The control group (Group A) exhibited a significant increase in body weight from 130.40 ± 2.03 g to 145.96 ± 0.02 g (p = 0.007), indicative of normal physiological growth. Methamphetamine administration in Group B resulted in a significant decline in body weight from 136.20 ± 4.83 g to 121.04 ± 6.01 g (p = 0.001), suggesting that the drug adversely affected normal growth and nutritional status. In the low-dose vitamin A group (Group C), body weight increased significantly from 135.94 ± 3.92 g to 160.00 ± 1.09 g (p < 0.001), demonstrating that vitamin A alone supported healthy weight gain. Furthermore, animals that received both methamphetamine and low-dose vitamin A (Group D) showed a significant increase in body weight from 135.90 ± 0.50 g to 147.80 ± 0.92 g (p = 0.001). The improved weight gain observed in this group, compared with the methamphetamine-only group, indicates that low-dose vitamin A partially counteracted the detrimental effects of methamphetamine on body weight, suggesting a protective effect against methamphetamine-induced systemic toxicity. The bar chart illustrates the changes in body weight of the experimental groups before and after treatment. The control group (Group A) and the low-dose vitamin A group (Group C) exhibited significant increases in body weight, with Group C showing the greatest weight gain. The methamphetamine-treated group (Group B) showed a marked reduction in body weight, indicating the toxic effect of methamphetamine. The methamphetamine plus low-dose vitamin A group (Group D) also demonstrated a significant increase in body weight compared with the methamphetamine-only group, suggesting that low-dose vitamin A attenuated methamphetamine-induced weight loss and supported normal growth.

Table 2. Comparison of mean relative kidney weight for group A(control) and experimental groups (B, C, and D)

	GROUPS	MEAN±SEM	P-VALUE	F-VALUE
Kidney Weight	**Group A**	**0.55±0.08**		
	Group B	**0.63±0.03**	**0.000**	**23.928**
	Group C	**0.55±0.01**	**0.001**	
	Group D	**0.58±0.11**	**0.030**	

Data was analyzed using One-way ANOVA followed by multiple comparison using LSD and data were considered significant at P<0.05.

The relative kidney weight results showed significant differences among the experimental groups (F = 23.928). The control group (Group A) had a mean relative kidney weight of 0.55 ± 0.08 g, representing normal renal morphology. Rats treated with methamphetamine alone (Group B) exhibited the highest relative kidney weight (0.63 ± 0.03 g, p < 0.001), suggesting renal enlargement associated with methamphetamine-induced nephrotoxicity. The low-dose vitamin A group (Group C) had a relative kidney weight (0.55 ± 0.01 g, p = 0.001) comparable to the control, indicating that vitamin A alone did not adversely affect the kidneys. Methamphetamine plus low-dose vitamin A group (Group D) showed a lower relative kidney weight (0.58 ± 0.11 g, p = 0.030) than the methamphetamine-only group, suggesting that low-dose vitamin A reduced methamphetamine-induced renal enlargement and exerted a nephroprotective effect.

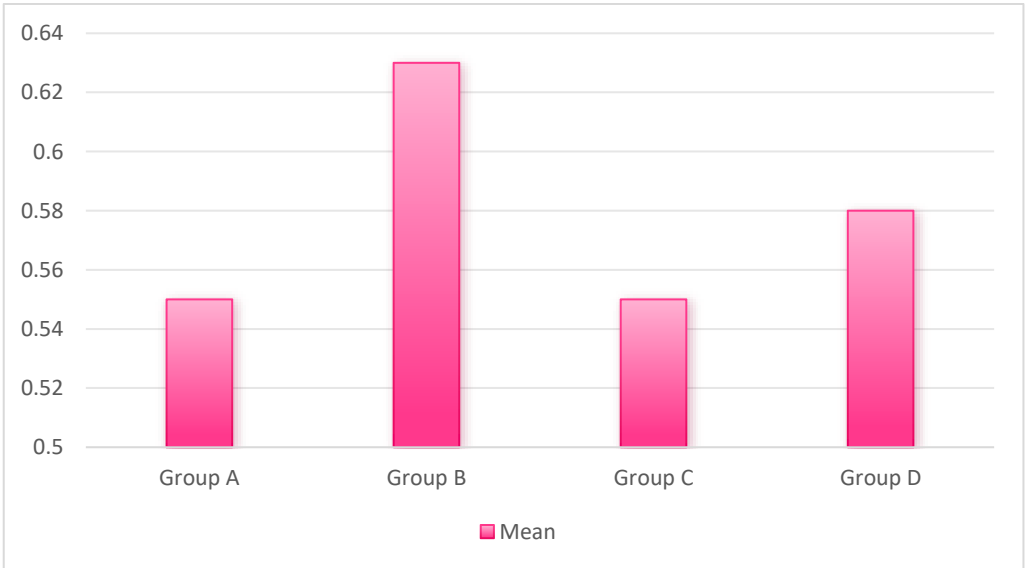

Figure 2. Bar chat showing Comparison of mean relative kidney weight for group A(control) and experimental groups (B, C, and D)

The bar chart illustrates the relative kidney weight across the experimental groups. The methamphetamine-treated group (Group B) recorded the highest relative kidney weight, indicating kidney enlargement following methamphetamine exposure. In contrast, the control group (Group A) and the low-dose vitamin A group (Group C) exhibited similar kidney weights, while the methamphetamine plus low-dose vitamin A group (Group D) showed a reduced kidney weight compared with the methamphetamine-only group. These findings suggest that low-dose vitamin A ameliorated methamphetamine-induced renal enlargement and preserved normal kidney morphology.

Table 2. Activities of serum urea creatinine levels of adult male Wistar rats

GROUP	UREA	CREATININE
A	23.40±3.14	1.30±0.00
B	27.05±0.00	1.65±0.00
C	23.56±0.04	1.33±0.45
D	24.20±0.26	1.35±0.10
F-RATIO	7.50	3.023
PROB. OF. SIG	<0.005	<0.005

The control group (Group A) recorded normal serum urea (23.40 ± 3.14 mg/dL) and creatinine (1.30 ± 0.00 mg/dL) levels. Rats treated with methamphetamine alone (Group B) showed the highest serum urea (27.05 ± 0.00 mg/dL) and creatinine (1.65 ± 0.00 mg/dL) levels, indicating impaired renal function following methamphetamine-induced nephrotoxicity. The low-dose vitamin A group (Group C) exhibited serum urea (23.56 ± 0.04 mg/dL) and creatinine (1.33 ± 0.45 mg/dL) values comparable to the control group, suggesting that vitamin A alone had no adverse effect on kidney function. The methamphetamine plus low-dose vitamin A group (Group D) demonstrated reduced serum urea (24.20 ± 0.26 mg/dL) and creatinine (1.35 ± 0.10 mg/dL) levels compared with the methamphetamine-only group, indicating that low-dose vitamin A ameliorated methamphetamine-induced renal dysfunction. These differences were statistically significant for both serum urea ($F = 7.50$, $p < 0.005$) and creatinine ($F = 3.023$, $p < 0.005$).

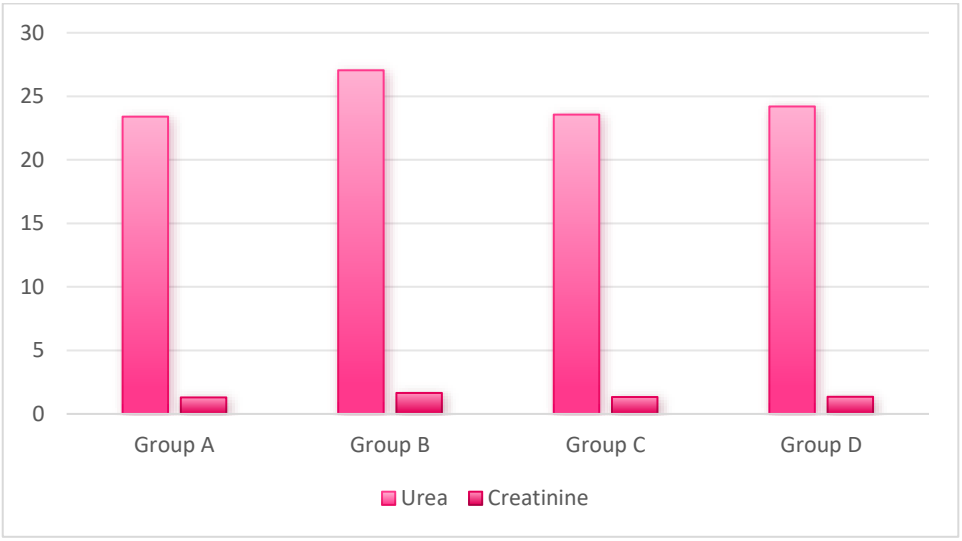

Figure 3. Bar chart showing Comparison of Activities of serum urea creatinine levels for group A(control) and experimental groups (B, C, and D)

The bar chart illustrates the serum urea and creatinine levels across the experimental groups. The methamphetamine-treated group (Group B) recorded the highest urea and creatinine levels, indicating renal impairment. In contrast, the control group (Group A), low-dose vitamin A group (Group C), and methamphetamine plus low-dose vitamin A group (Group D) exhibited comparable values, with Group D showing lower levels than the methamphetamine-only group. These findings suggest that low-dose vitamin A protected against methamphetamine-induced kidney dysfunction by restoring renal biochemical markers toward normal levels.

Histological Results

Photomicrograph of the kidney tissue from the control group (Group A) stained with H&E at ×400 magnification. The section demonstrates normal renal histological architecture, characterized by well-defined glomeruli (G), a distinct

Bowman's space (BS), intact renal tubules (RT), and healthy tubular cells (TC). No evidence of glomerular or tubular degeneration, inflammatory cell infiltration, or other pathological changes is observed, indicating normal kidney morphology.

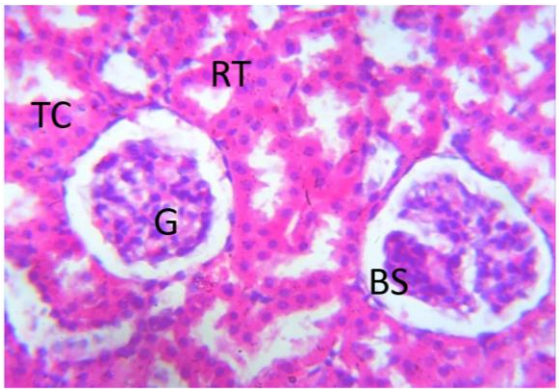

Figure 4. Photomicrograph of Group A (control) section of kidney (X400) (H/E) shows normal renal architecture with glomeruli (G), bowman space (BS), renal tubules (RT) and active tubular cell (TC)

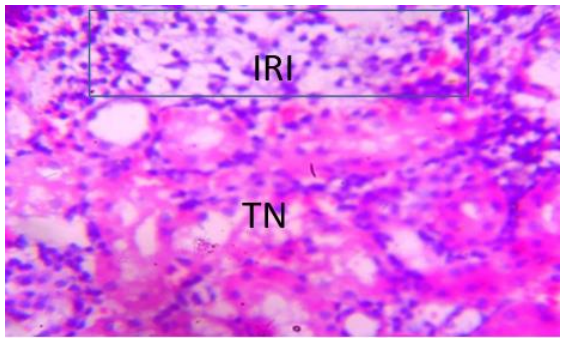

Figure 5. Photomicrograph of the kidney tissue from the methamphetamine-treated group (Group B) stained with H&E at ×400 magnification.

The section reveals severe renal degeneration characterized by acute tubular necrosis (ATN) and marked clusters of intrarenal inflammatory cell infiltration (IRI). These histopathological changes indicate significant methamphetamine-induced nephrotoxicity, resulting in extensive tubular injury and renal inflammation (Figure 5).

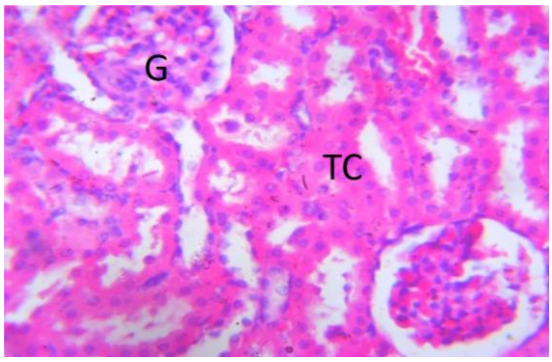

Figure 6. Photomicrograph of Group C section of kidney administered with vitamin A low dose (X400)(H/E) shows renal tissue with active glomeruli (G) and tubular cell (TC)

Photomicrograph of the kidney tissue from the low-dose vitamin A-treated group (Group C) stained with H&E at ×400 magnification. The section demonstrates well-preserved renal histological architecture, characterized by healthy, active glomeruli (G) and intact tubular cells (TC). No evidence of tubular degeneration, inflammatory cell infiltration, or other pathological alterations is observed, indicating that low-dose vitamin A maintained normal kidney morphology and did not produce adverse histological changes.

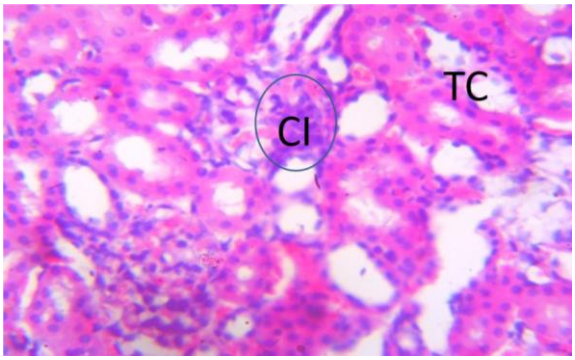

Figure 7. Photomicrograph of Group E section of kidney induced with meth and treated with vit A low dose (x400) (H/E) shows moderate regeneration with active tubular cells and mild cluster of inflammation (CI) around the glomeruli

Photomicrograph of the kidney tissue from the methamphetamine plus low-dose vitamin A-treated group (Group D) stained with H&E at ×400 magnification (Figure 7). The section demonstrates moderate renal regeneration characterized by active tubular cells and only mild clusters of inflammatory cells (CI) surrounding the glomeruli. These histopathological findings indicate that low-dose vitamin A ameliorated methamphetamine-induced renal damage, promoted tissue regeneration, and reduced renal inflammation, supporting its nephroprotective effect.

Discussion

The present study investigated the effect of low-dose vitamin A on the kidney of adult male Wistar rats exposed to a toxic dose of methamphetamine. The findings revealed that methamphetamine administration led to marked alterations in body weight, renal morphology, and biochemical parameters, whereas vitamin A supplementation mitigated most of these adverse effects. Methamphetamine (MA) is a potent central nervous system stimulant that is increasingly recognized for its systemic toxic effects, including significant damage to the renal system. The results from this study provide additional evidence that exposure to a toxic dose of methamphetamine can lead to acute kidney injury (AKI).Vitamin A, a fat-soluble micronutrient, is widely known for its role in vision, immune function, and cellular growth, but it also possesses antioxidant and anti-inflammatory properties that contribute to organ protection under toxic conditions. In the context of nephrotoxicity, Vitamin A is thought to protect renal tissue primarily by scavenging reactive oxygen species (ROS) and maintaining epithelial integrity. The significant reduction in body weight observed in the methamphetamine-only group reflects the catabolic and appetite-suppressing properties of the drug. Methamphetamine is known to increase metabolic rate and energy expenditure through excessive catecholamine release, leading to muscle and tissue protein breakdown (Krasnova and Cadet *et al.,*2009). This finding aligns with previous reports that chronic methamphetamine exposure causes systemic stress and weight loss in rodents (Volz, Fleckenstein and Hanson *et al.,* 2007). Conversely, co-administration with vitamin A resulted in significant weight gain comparable to the control group, suggesting that vitamin A ameliorated methamphetamine-induced metabolic disturbances. The vitamin A–only group also showed normal growth, confirming the safety of the administered dose. The significant reduction in body weight observed in the methamphetamine-only group (Group B) reflects the catabolic and appetite-suppressing properties of the drug. Methamphetamine is known to increase metabolic rate and energy expenditure through excessive catecholamine release, leading to muscle and tissue protein breakdown. This finding aligns with previous reports that chronic methamphetamine exposure causes weight loss and systemic stress in rodents. In contrast, co-administration with vitamin A (Group C) resulted in significant weight gain comparable to the control group, suggesting that vitamin A ameliorated methamphetamine-induced metabolic disturbances. The vitamin A–only group (Group D) also showed normal growth, confirming that the administered dose of vitamin A was non-toxic. Vitamin A co-treatment (Group C) significantly reduced both urea and creatinine levels toward normal values. This protective effect can be attributed to the antioxidant potential of vitamin A, which stabilizes cellular membranes, scavenges free radicals, and limits lipid peroxidation. Vitamin A has also been reported to support epithelial integrity and enhance enzymatic antioxidant defense, thereby preserving renal structure and function. The oxidative stress biomarker data further substantiate these findings. Methamphetamine exposure markedly increased malondialdehyde (MDA) levels while depleting glutathione (GSH) and superoxide dismutase (SOD) activities—an indication of lipid peroxidation and oxidative imbalance. These alterations confirm that methamphetamine induces oxidative stress in renal tissues. However, vitamin A co-administration effectively restored antioxidant enzyme levels and reduced MDA, demonstrating its ability to counteract reactive oxygen species and reinforce redox homeostasis.

Conclusion

This study investigated the effect of low-dose vitamin A administration on the kidney of adult male Wistar rats exposed to a toxic dose of methamphetamine. The findings revealed that methamphetamine exposure led to marked renal histopathological alterations, including glomerular distortion, tubular necrosis, interstitial congestion, and inflammatory infiltration. These changes indicate that methamphetamine induces oxidative stress and cellular damage within renal tissues, consistent with previous reports of its nephrotoxic potential. Conversely, administration of a low dose of vitamin A demonstrated partial restoration of normal renal histoarchitecture, evidenced by improved glomerular outline, reduced tubular damage, and minimal vascular congestion. This suggests that vitamin A possesses antioxidant and cytoprotective properties capable of mitigating free radical–mediated injury caused by methamphetamine. Vitamin A, being a fat-soluble micronutrient, plays a vital role in cell membrane stability, immune modulation, and oxidative defense. The interplay between methamphetamine and vitamin A underscores a delicate biochemical balance. While methamphetamine promotes oxidative stress and apoptosis, vitamin A enhances antioxidant enzyme activity and attenuates lipid peroxidation. Therefore, within controlled doses, vitamin A supplementation may offer renal protection against methamphetamine-induced toxicity. Overall, this study concludes that low-dose vitamin A administration can attenuate methamphetamine-induced renal injury in Wistar rats. However, caution must be exercised in extrapolating these findings to humans due to differences in metabolism, dosage sensitivity, and long-term effects.

Recommendation

1. **Dose Optimization and Safety Profiling**

Further studies should explore a range of vitamin A dosages to identify the optimal concentration that maximizes protective efficacy without inducing toxicity. Chronic administration studies are also recommended to assess long-term renal outcomes.

2. **Integration of Biochemical Markers**

Subsequent research should incorporate biochemical parameters such as serum creatinine, urea, uric acid, catalase, and malondialdehyde levels to correlate histological findings with renal function and oxidative stress indices.

3. Public Health Sensitization on Methamphetamine Abuse

Health authorities and educational institutions should intensify awareness campaigns on the detrimental effects of methamphetamine, particularly on vital organs like the kidney, liver, and brain. Preventive education remains the most effective strategy against drug-induced organ damage.

4**. Nutritional Intervention Strategies**

The inclusion of antioxidant-rich diets, such as those containing vitamin A, vitamin C, and vitamin E, should be encouraged among individuals prone to oxidative stress or substance abuse. This could serve as a preventive nutritional approach against renal and systemic toxicity.

Author contributions

Concept and study design: Ezejindu Damian Nnabuihe, Alozie Osinachi Prince.
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Final approval of the manuscript: All authors read and approved the final version of the manuscript.

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Conflict of interest

The author declared no conflict of interest.

Ethics approval

Approve by Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria. The number is NAU/CHS/NC/FBMS/1081 dated 06.01.2026

AI tool usage declaration

No AI tool was used in manuscript preparation.

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