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Combined Effects of Acute Restraint Stress and Rapid Eye Movement (REM) Sleep Deprivation on Renal Inflammation in Female Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Psychological stress which is on the increase daily has emerged as a major contributor to the onset and progression of kidney disorders by promoting established risk factors such as hypertension and diabetes. Furthermore, stress is often associated with sleep loss and both factors are known to

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disrupt oxidative balance and pro and anti-inflammatory balance contributing to organ dysfunction. Despite extensive studies on their individual effects on the kidney, there are limited studies regarding the combined impact of acute stress and REM sleep deprivation in regards to renal inflammation. A total number of 24 female Wistar rats weighing 180-220 g were randomly categorized into 4 groups with 6 rats in each group: Control (CTL) were given feed and water ad libitum, Restraint stress (RSS) animals were restrained with wire mesh for 30 minutes each day for 28 days, Sleep deprivation (SSD) animals were subjected to 6 hours sleep deprivation every two days for 28 days using inverted flower pot, Restraint stress + Sleep deprivation (RSD) were exposure to both restraint stress and sleep deprivation. Twenty four hours after the last procedures, all rats were anesthetized and their kidneys were excised, weighed and homogenized for biochemical assays (Nitric oxide (NO), Myeloperoxidase (MPO) and Tumor necrosis factor-α (TNF-α). The results showed that body weight changes was significantly reduced ($p<0.05$) while NO, MPO and TNF-α levels were significantly higher ($p<0.05$) in the RSD group when compared with other groups. In conclusion, concomitant exposures to restraint stress and sleep deprivation triggered renal inflammation, indicating that interaction between psychological stress and sleep loss may accelerate kidney dysfunction.

Keywords: Psychological stress; REM sleep deprivation; Inflammation; kidney; inverted flower pot.

1. INTRODUCTION

Kidneys are identified as essential organs involved in the maintenance of homeostasis (Bernal et al., 2023). They achieve this by performing vital functions such as filtration and reabsorption of blood and essential solutes, balancing fluids and electrolytes, the removal of waste products, maintenance of acid-base balance, regulation of blood pressure and production of hormones like erythropoietin (Imenez-Silva and Mohebbi, 2022). The prevalence of kidney diseases is alarming, affecting millions of people worldwide and often progressing undetected until irreversible damage has occurred (Guerra et al., 2021). It has been estimated that by 2040, chronic kidney disease (CKD) will become the 5th leading cause of death worldwide (Francis et al., 2024).

The progression of this CKD is often influenced by modern lifestyle factors such as stress particularly psychological stress (Fuertes et al., 2025; Ebert et al., 2021). This form of stress has become a part of human daily routine, stemming from career hurdles, relationship and financial pressures, traumatic events, socioeconomic crisis and many more (Osborne et al., 2020; Ryu and Fan, 2023; Coelho et al., 2024). Sleep loss is another common factor that often accompanies psychological stress (Schwarz et al., 2018). Sleep, apart from replenishing energy expended during wakefulness and preparing the body for subsequent activity, plays a core role in daily stress resilience (Lo Martire et al., 2024). This outlines the essential contribution of sleep to survival, the maintenance of optimal health and the promotion of a high quality of life (Feingold & Smiley, 2022).

Rapid eye movement (REM) and non-rapid eye movement (NREM) sleep are the two stages that constitute a complete sleep cycle (Okechukwu, 2022). At night, about 4-5 sleep cycles are completed within 7-9 hours and a consistent restriction of total sleep time below this is referred to as sleep deprivation (Rezazadeh et al., 2025; Cao et al., 2025). Sleep deprivation can be considered a stressor because similar to psychological stress, it has been reported to activate the HPA axis (Messa et al., 2024). Numerous studies have established that alterations in duration and onset of sleep can cause a decline in renal function (McMullan et al., 2016). Furthermore, reduced duration and quality of sleep have also been identified has as risk factor for chronic kidney disease (Ricardo et al., 2017; Park et al., 2020).

Specifically, rapid eye movement sleep deprivation has been shown to activate the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis (Moraes et al., 2021). This activation promotes the production of pro-inflammatory cytokines and a drastic reduction in anti-inflammatory cytokines (Suresh et al., 2021). Although all types of stress have a psychological component, nevertheless, psychological stress is a specific type of stress that pertains to the cognitive and emotional processes occurring in response to a perceived threat or challenge (Manosso et al, 2022). It contributes significantly to the increasing burden of various diseases, including chronic kidney

disease due to the kidney's high susceptibility to metabolic and hemodynamic alterations (Kim et al., 2021; Scurt et al., 2024).

Furthermore, stress has been linked to obesity, diabetes and hypertension, which are risk factors for chronic kidney disease (Bruce et al., 2015; Osborne et al., 2020). Evidence from both animal and human studies indicate that psychological stress modulates the HPA axis and sympathetic-adreno-medullar (SAM), which may subsequently lead to impaired humoral, cell-mediated immunity and reduced blood flow (Heffner, 2011; Imig & Ryan, 2013; Srinivasan et al., 2016). A sustained state of activation can further induce renal ischemia and suppress immune function, thereby increasing the risk of chronic conditions such as chronic kidney disease (CKD) (Su et al., 2021).There is a research gap regarding the combined effects of stress and sleep deprivation on renal integrity, particularly when the sleep restriction involves the REM phase. Therefore, this study is designed to evaluate the effects of co-exposure to acute restraint stress (a model of psychological stress) and REM sleep deprivation on kidney inflammation in a female Wistar rat model.

2. MATERIALS AND METHODS

2.1 Experimental Procedures

In this study, twenty-four female Wistar rats (180 - 220g) were housed in standardized plastic cages on a 12h light-dark cycle in physiology animal house of Ladoke Akintola University of Technology, Ogbomoso, Oyo State. The animals were acclimatized for two weeks and allowed free access to standard rat chow and water *ad libitum*. All experimental procedures were performed in strict compliance with the laboratory animal care and handling protocol recommended by the Animal Ethical Committee of the Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Oyo State. After acclimatization the rats were divided into four groups with six rats in each group: a control (CTL) group, which were not subjected to restraint stress and sleep deprivation; a restraint stress (RSS) group subjected to restraint stress using wire mesh for 30 minutes daily for 28 days; a sleep deprivation (SSD) group subjected to intermittent REM sleep deprivation for 6 hours every 48-hours for 28 days and a restraint stress + sleep deprivation (RSD) group subjected to both restraint stress and sleep deprivation.

2.2 REM Sleep Deprivation

The study employed the inverted flower pot technique adapted for rats, which leverage on muscle atonia that occurs during REM sleep (jouvet et al., 1964). Each rat was placed on a small, flat platform surrounded by water in big container. Once the animals fall into REM sleep muscle atonia occurs and the animal falls into the water and wake up.

2.3 Restraint Stress Procedural

The animals were subjected to restraint stress according to the method of Owolabi et al. (2024). The rats were placed in restraint stress using wire mesh daily for 30 minutes for 28 days. The rats were restrained such that they had access to air. Pain, which will normally be indicated by the squeaking noise of the rats was prevented.

2.4 Collection and Preparation of Samples

Twenty- four hours after the last treatment regimen, rats were euthanized by placing them in desiccator with chloroform soaked cotton wool. The kidneys were excised, then rinsed in PBS and homogenized over ice in 0.1 M cold sodium phosphate buffer (pH 7.4). The homogenate was centrifuged at 4^{o}C for 3 minutes at 4,000 rpm. The supernatant obtained was aliquot for subsequent biochemical analysis.

2.5 Biochemical Tests

Renal Nitric oxide (NO), Myeloperoxidase (MPO) and Tumor necrosis factor-α (TNF-α) were measured colorimetrically according to the manufacturer's procedure using commercial kits purchased from MyBioSource (SanDiego,USA).

2.6 Statistical Analysis

SPSS (version 16.0) was used for all statistical analysis. All results obtained are expressed as Mean ± Standard Error of the Mean (SEM). Data were analyzed using one-way ANOVA and Duncan's *posthoc* test for multiple comparisons. P value < 0.05 was considered to be statistically significant.

3. RESULTS AND DISCUSSION

3.1 Results

Table 1 showed that restraint stress had no effect on body weight changes while sleep deprivation caused a significant decrease

(p<0.05) in body weight compared with control. The combination of restraint stress and sleep deprivation caused a significant decrease (p<0.05) in body weight changes compared with control and restraint stress with no significance when compared with sleep deprivation. The relative kidney weight showed no significant difference across all groups.

Table 1. Effect of restraint stress and REM sleep deprivation on body weight and relative kidney weight of female Wistar rats

GROUPS	CTL	RSS	SDD	RSD
Body weight changes (g)	51.50±3.36[a]	48.67±2.25[a]	33.83±2.01[b]	29.83±2.47[b]
Relative Kidney weight (%)	0.414±0.041[a]	0.453±0.016[a]	0.448±0.028[a]	0.421±0.026[a]

Values are expressed as mean ± SEM (n= 6). Mean values with superscript of different letters are significantly (p<0.05) different from each other. Mean values with superscript of same letters are not significantly different from each other

Table 2. Effect of restraint stress and REM sleep deprivation on renal nitric oxide (NO)of female Wistar rats

GROUPS	CTL	RSS	SDD	RSD
Renal NO (µmol/gtissue)	23.09±1.35[a]	26.36±1.30[a]	27.47±0.75[a]	33.41±1.15[b]

Values are expressed as mean ± SEM (n= 6). Mean values with superscript of different letters are significantly (p<0.05) different from each other. Mean values with superscript of same letters are not significantly different from each other

The renal nitric oxide (NO) level showed no statistical significance in the individual restraint stress and sleep deprivation groups compared with control. The combined restraint stress and sleep deprivation showed a significant increase (p<0.05) when compared with control, restraint stress-only and sleep deprivation-only groups.

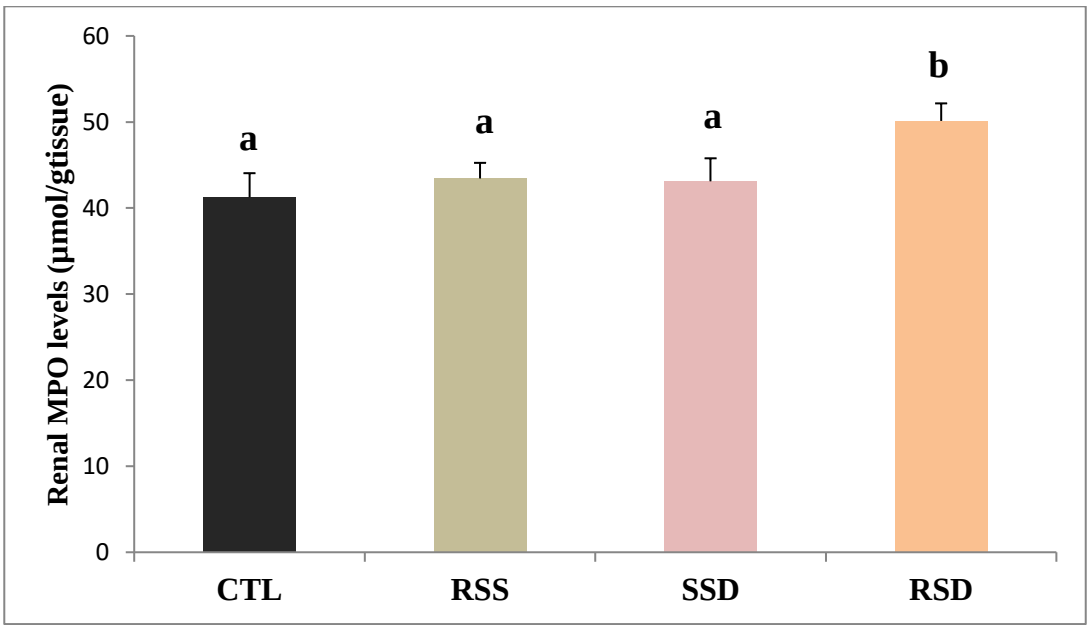

Fig. 1. Effect of restraint stress and REM sleep deprivation on renal myeloperoxidase (MPO) of female Wistar rats

Values are expressed as mean ± SEM (n= 6). Bars with superscript of different letters are significantly (p<0.05) different from each other. Bars with superscript of same letters are not significantly different from each other

The individual restraint stress and sleep deprivation groups showed no statistical difference in MPO levels when compared with control. Combined exposure to restraint stress and sleep deprivation led to a significant increase (p<0.05) when compared with control, restraint stress and sleep deprivation.

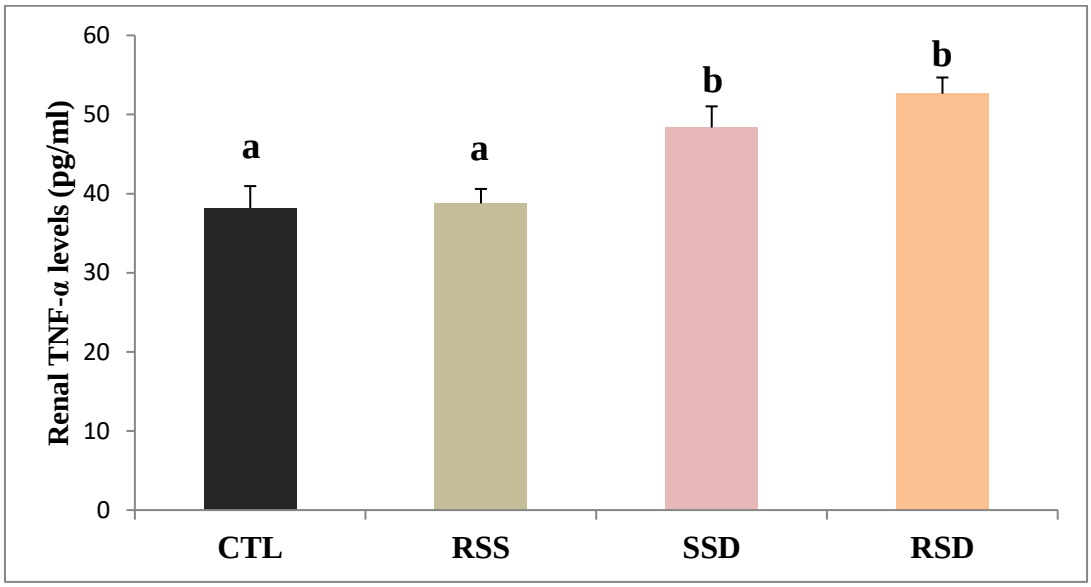

Fig. 2. Effect of restraint stress and REM sleep deprivation on renal tumor necrosis factor- α (TNF- α) of female Wistar rats

Values are expressed as mean ± SEM (n= 6). Bars with superscript of different letters are significantly (p<0.05) different from each other. Bars with superscript of same letters are not significantly different from each other The renal Tumor Necrosis Factor- α (TNF-α) level showed no statistical significance in the restraint stress compared with control while a significant increase (p<0.05) was observed in the TNF-α compared with control. However, the combined restraint stress and sleep deprivation showed a significant increase (p<0.05) when compared with control, restraint stress-only and sleep deprivation-only groups.

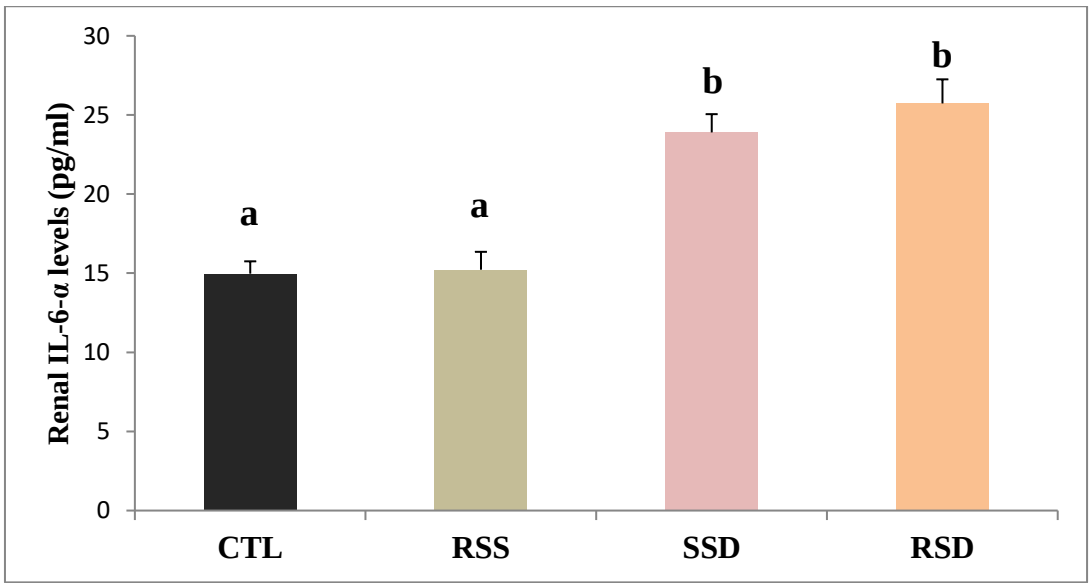

Fig. 3. Effect of restraint stress and REM sleep deprivation on renal interleukin-6 (IL-6) of female Wistar rats

Values are expressed as mean ± SEM (n= 6). Bars with superscript of different letters are significantly (p<0.05) different from each other. Bars with superscript of same letters are not significantly different from each other. Sleep deprivation caused an increase in renal interleukin-6 concentration while restraint stress had no effect on renal interleukin-6 when compared with control. However, the combined restraint stress and sleep deprivation showed a significant increase (p<0.05) when compared with control, restraint stress-only and sleep deprivation-only groups.

3.2 Discussion

Psychological stress has become a major public health concern as it contributes to the onset and progression of various diseases affecting multiple organs including the kidney which is highly susceptible to stress (Shchaslyvyi et al., 2024). Concurrently, the widespread decline in daily sleep quality and duration has emerged as another essential factor contributing to the rising incidence of kidney disorders (McMullan et al., 2016). Studies have shown that factors such as stress and sleep deprivation can independently alter kidney function via oxidative stress and inflammation. Hence, this study assessed the effect of restraint stress and REM sleep deprivation on renal inflammation in female Wistar rats.

REM sleep deprivation induced a loss in body weight which aligns with the findings of Moraes et al (2022) where paradoxical sleep deprivation for four (4) consecutive days resulted in a reduction in body weight. The reduction could occur despite an increase in appetite due to a rise in the orexigenic neuropeptide Y (NPY) and a reduction in the anorexigenic pro-opiomelanocortin (POMC), resulting in hyperphagia in rats (Martins et al., 2006). Rapid eye movement sleep loss has been shown to induce progressive hyperphagia alongside significant weight loss, indicating that the increased feeding rate could not compensate for the rise in energy expenditure (Everson & Szabo, 2011). Furthermore, sleep deprivation activates the HPA axis, resulting in the release of stress hormones, including corticosterone and norepinephrine (Nollet et al., 2022). This hormonal response increases the body's overall metabolic rate, characterized by increased catabolism and decreased anabolism leading to reduction in body fat stores (Bergmann et al., 1989; Hipolide et al., 2006). However, sleep restriction had no impact on the relative kidney weight of the sleep-deprived rats aligning with the report of Rezazadeh et al. (2025) that showed that sleep deprivation had no significant effect on the kidney index (kidney weight/body weight). Although sleep deprivation induces an increase in systemic catabolism, the results indicate that the kidney may be a secondary organ to be affected by the catabolic effect of sleep deprivation. The combined exposure to stress and sleep deprivation also had no impact on the relative kidney weight. Furthermore, the mechanism underlying the relationship between sleep deprivation and kidney remains unclear (Yu et al., 2025).

The normal body weight seen in stressed rats (Table 1) correlates with the findings of Kuti et al. (2022) where body weight remained constant following acute stress induction for one (1) hour per day for 3 days in male mice. Additionally, a constant relative kidney weight was observed in the stressed rats contradicting the previous study by Nwogueze et al. (2023) that revealed that restraint stress induction for 21 days over duration of three (3) hour per day caused a reduction in relative kidney weight in female Wistar rats. Therefore, the non-significance observed in this study could be attributed to the short duration of stress induction. Concurrent exposure to stress and sleep deprivation resulted in a notable decrease in body weight when compared to restraint stress alone, with no significant difference compared to sleep deprivation alone. This suggests that sleep deprivation alone might have caused a maximal effect on body weight that stress induction could not cause further decrease.

Oxidative stress and inflammation are recognized as primary mechanism that induce kidney damage in both acute stress and sleep deprivation (Yang et al., 2024). In Table 2, there was no significant difference in NO concentration level in the stressed rats compared to control, which is contradictory to the report of Tian et al. (2018) which states that immobilization stress using restraining chambers for two (2) hour over a duration of 14 days caused a surge in serum NO concentration. The result obtained in this study suggests that the stress duration and intensity might have not been prolonged enough to cause a significant alteration in NO production. Although, sleep loss has been reported to increase the production of pro-inflammatory cytokines, nevertheless, in this study there were no significant changes in the concentration of renal NO. This is in line with the study of Periasmy et al. (2015) who demonstrated that REM sleep deprivation for 24, 48 and 72 hours had no impact on renal nitric oxide of male C57BL/6J mice. Similarly, Mourad & Fahmy (2017) reported that 48 hours paradoxical sleep deprivation had no significant effect on renal NO. This suggests that the kidney may exhibit greater resistant to the direct impact of intermittent sleep deprivation on renal nitric oxide as observed in this study. Co-exposure to stress and sleep deprivation resulted in a significant increase in renal NO level when compared to the individual

stress and sleep deprivation groups. This suggests that the additive effect of stress and sleep deprivation led to the activation of stress and inflammatory pathways resulting in an increase in glucocorticoid and catecholamine secretion stimulating inducible nitric oxide synthase (iNOS), endothelial nitric oxide synthase (eNOS) ultimately increasing the production of nitric oxide.

Myeloperoxidase (MPO) is a peroxidase enzyme abundantly present in neutrophils and its concentration indicates neutrophil granulocytes, with elevation or reduction signifying activation or suppression of innate immunity respectively (Khan et al., 2018; Rizo-Téllez et al., 2022). The study observed that restraint stress had no effect on renal myeloperoxidase indicating that the intensity of stress was insufficient to induce neutrophil-mediated renal inflammation. Studies have shown that acute stress causes an increase in glucocorticoids which has anti-inflammatory properties that suppress the transcription of pro-inflammatory cytokines and chemokines as well as enzymatic markers including MPO (Xu et al., 2025). Therefore, the result attained in the stressed rats could be an indication of the immunosupressive effect of glucocorticoids on MPO concentration. Sleep deprivation has been reported to induce neutrophil migration into the interstitial spaces of organs including kidney, this is mediated by chemokines. In contrast to studies linking intermittent sleep deprivation to elevated MPO (Tang et al., 2009; Sang et al., 2023), the unchanged MPO concentration observed in this study suggests that the periods of unrestricted sleep during the intermittent deprivation procedure served as a recovery phase to mitigate any potential inflammation caused by neutrophils. Additionally, the selective model of REM sleep deprivation may have less impact on systemic inflammation than total or continuous sleep deprivation. Interestingly, simultaneous exposure to sleep restriction and restraint stress resulted in an elevation in MPO concentration. This suggests an interactive effect of chronic sleep loss and acute stress resulting in hyperactivation of the HPA axis influencing oxidative stress responses and stress-related immune activation. A previous study carried out on medical students undergoing psychological stress and sleep disturbance recorded an elevation in serum MPO outlining the additive effect of combined stressors (Singh et al., 2025).

In a study conducted by Wahed and Mehrez (2015), immobilization stress for two hour over five weeks resulted in a significant increase ($p<0.05$) in renal TNF-α compared to control which is contradictory to the unaltered concentration of renal TNF-α seen in this study indicating that 30 minutes restraint stress did not alter renal TNF-α levels. In parallel, the renal interleukin-6 concentration remained unchanged compared to the baseline. This finding may indicate habituation to the repeated stressor or that the upregulation of anti-inflammatory cytokine Interleukin-10 (IL-10) led to the suppression of TNF-α and IL-6 (Connor et al., 2005; Grissom & Bhatnagar, 2009). Serum IL-10 has been reported to increase in human studies following the Trier Social Stress Test (a procedure commonly used to induce psychological stress) suggesting that acute stress can induce IL-10 production (Altemus et al.,2001; Fredericks et al.,2010; Danielson et al., 2011; Kuebler et al., 2015). The sleep-deprived rats showed an increase in renal TNF-α level which aligns previous studies showing that sleep deprivation induces systemic inflammation and production of pro-inflammatory mediators (TNF-α and IL-6) via the activation of inflammatory signaling pathways such as NF-κB, JAKs/STATs and MAPKs. This results in an uncontrolled inflammatory response, increasing susceptibility to various systemic diseases (Irwin & Piber, 2018; Garbarino et al., 2021; Lin et al., 2024). Correspondingly, this could explain the spike in IL-6 concentration observed in the REM sleep deprived rats, as enhanced activation of NF-κB due to persistent stimulation of β-adrenergic receptor by adrenaline promotes the transcription of IL-6 (Kolmus et al., 2015; Irwin, 2019). Co-exposure to acute psychological stress and intermittent REM sleep deprivation initiated a surge in renal TNF-α and IL-6 levels with sleep deprivation being the major contributing factor and stress exerting minimal influence on the observed effects.

4. CONCLUSION

In conclusion, this study demonstrated that combined exposure to psychological stress and sleep deprivation induced renal inflammation, evident with alterations in the levels of inflammatory markers and may contribute to the acceleration of kidney dysfunction.

ETHICAL APPROVAL

This study was conducted according to the established guidelines of the Animal Ethical Committee of the Faculty of Basic Medical

Sciences, Ladoke Akintola University of Technology, Oyo State, Nigeria, and all regulations were adhered to throughout the research process.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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