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Effect of Exposure to Noise Stress on Liver Tissue Histopathology in Rats

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ABSTRACT

Background: The adverse effects of stress on liver function and tissue pathology have been demonstrated by many studies. However, the full mechanism is still not fully understood. This study aimed to investigate the effects of noise stress on the histopathological structure of the liver and contribute to the literature in elucidating the relevant mechanism.

Methods: In the study, 20 rats (10 control and 10 study group rats) weighing 250-300 g were used. The animals and ethics approval were provided by A.Ü. Medical Faculty, Experimental Animal Unit, and the studies were carried out in the same unit. Rats were exposed to 70 decibels (dB) of white noise, provided by a digital noise generator placed next to the cages for one hour per day for one month. They were euthanized with halothane. Liver tissue was removed and fixed in 10% formalin solution for 24-48 hours. Routine histological procedures were performed. H and E-stained preparations were examined under a light microscope.

Result: In histopathological examination, moderate steatosis in the liver tissue, dissociation in recurrent cords, moderate enlargement of sinusoids and mild hyperplasia in the bile ducts were observed in the group exposed to stress. Statistically, $p<0.05$ was defined as significant.

Key words: Histopathology, HXE staining, Noise stress, Rat.

INTRODUCTION

Stress is the body's response to various internal and external stimuli. Mild and moderate stress is important for alertness and adaptation to the environment and even necessary for survival. In addition, chronic and excessive stress negatively affects the immune mechanism, disrupting the body's functioning, tissue and organ structure and functions. It causes both physiological and psychological problems (Demirel *et al.,* 2009). At an advanced level, it makes the body susceptible to cancer (Eckerling *et al.,* 2021).

There are two types of stress: acute and chronic. Acute stress is a short-term stress that decreases and disappears after the event is over. An example of this is a gazelle being chased by a lion and when the stress factor is removed, the event ends and life continues. However, chronic stress is a type of stress that lasts for a long time, can last for weeks or months and does not have a specific endpoint. and this type of stress is harmful. It weakens the immune system. It can create a predisposition to many histopathological, hormonal, neurological and behavioral changes in the body, autoimmune diseases and ultimately cancer development (Demirel *et al.,* 2009).

In the literature review, it was seen that although there are many studies on various stress factors such as radiation, smoking and heat-cold stress, there are a limited number of studies on noise stress (Dou *et al.,* 2020; El Marzouki *et al.,* 2021, Kirimlioğlu *et al.,* 2024, Tran *et al.,* 2021). Moreover, in today's conditions, we are constantly exposed to noises above 65-70 decibels and we have very little information about their effects. Brain histopathology was evaluated in Wistar rats subjected to cold water swimming stress for 14 days and congestion of blood vessels in the hippocampus and mononuclear cell inflammation in the hypothalamus were observed (Kranthi *et al.,* 2022). It was determined that the body weight and feed utilization capacity of chicks exposed to heat stress decreased (Reddy *et al.,* 2018).

Digested foods, damaged cells and microorganisms, as well as various foreign substances and antigens, are delivered to the liver *via* the portal vein, which activates the immune system. An immune tolerance is formed in the liver (Racanelli and Rehermann, 2006; Tiegs and Lohse, 2010). However, this process can be interrupted by many negative stimuli, especially stress. In this case, immunity decreases and it becomes difficult for the liver to eliminate these antigens. This leads to changes in tissue pathology and blood parameters. Inflammation occurs in the liver (Kunkel *et al.,* 2000; Srivastava and Boyer, 2010). Liver enzymes increase, tissue histology changes and hepatocytes are severely damaged depending on the severity and duration of stress (Campbell *et al.,* 2003, D'Mello and Swain, 2011). Manat *et al.* (2017) conducted a

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study to investigate postpartum oxidative stress in Surti goats and concluded that the period between day 0 and day 14 is the most stressful, requiring intensive care during this period.

Indirectly, all body functions are damaged and result in metabolic disorders (Luo *et al.,* 2024; Zhou *et al.,* 2001). There is evidence of a connection between the brain and liver (Campbell *et al.,* 2003; D'Mello and Swain, 2011).

Under stress conditions, hepatic blood flow decreases, which can cause cell necrosis. The production of inflammatory cells, neutrophils, lymphocytes and monocytes increases due to oxidative stress. This activity causes an increase in inflammation and hepatic necrosis. This causes leakage of intracellular substances (Mittal *et al.,* 2014).

This study aims to investigate the effect of exposure to noise stress on liver tissue anatomy and histopathology in rats.

MATERIALS AND METHODS

Animal materials

In this study, 250-300 g a total of 20 Wistar albino rats (10 control (5 males and 5 females) and 10 study (exposed to noise stress) (5 males and 5 females) were used. The animals were provided by A.Ü. Medical Faculty, Experimental Animals Unit and the studies were carried out in the A.Ü. Medical Faculty in April 2025. Ethical approval was obtained from the Ankara University Animal Experiments Local Ethics Committee. The animals were housed in wire cages of 38*30*25 cm in groups of 3 and 3 in groups, with a 12-hour light/dark cycle, a temperature of 22±1°C and a humidity of 50±0%, with free access to drinking water and food.

Experimental procedure

The experimental group rats were taken to a separate room. They were exposed to 70 dB SPL broadband white noise for one hour for a month according to the protocols in the literature (Rajan *et al.,* 2005). A setup consisting of a white noise generator and a loudspeaker was placed next to their cages. The noise level was set to 70 dB and measured with a digital sound level meter. Afterwards, they were euthanized by international standards. For this purpose, 4% halothane was used. Euthanasia was achieved by cardiac suppression with halothane for 90 seconds (Reilly, 2001).

Histopathological examination

Liver tissue was removed and fixed in 10% formalin solution for 24-48 hours. After one day, it was kept under running water for 12 h to be freed from the fixation solution. Then, it was passed through 70%, 80%, 90%, 96%, absolute alcohol solutions. After the alcohol series, it was rinsed in three separate containers of xylene solution. Then, the tissue was put through the paraffin embedding process to obtain paraffin blocks. Then, 4-micron-thick sections were taken in a microtome (Shandon, Finesse, Made in UK) and kept in a 37°C oven for 40 min. Then, the HXE staining process was applied (Luna, 1968) and examination was performed with a light microscope (Leica DM 2500 LED, Leica 170 HD, manufactured in Singapore). 4-micron-thick sections taken from paraffin blocks were stained with Hematoxylin-Eosin and examined under light microscopy (Akcakavak *et al.,* 2023, 2024; Kılınç and Oruç, 2024). The effect of chronic continuous stress on liver macroscopy and histopathology was investigated. Microscopic evaluations were performed by modifying the scoring model developed by Meyerholz *et al*. (2009). Liver tissues were examined in 10 different microscope fields. The presence of a lesion in 0-1 image field was evaluated as (-), the presence of a lesion in 2-3 image fields (+, mild lesion), the presence of a lesion in 4-6 image fields (++, moderate lesion) and the presence of a lesion in 7-10 fields (+++, very severe).

Statistical analysis

Graphpad Prism software (GraphPad Software, version 9) was used for all statistical analyses. Histopathological scores were analyzed using the Kruskal-Wallis test and the Mann-Whitney U test. All values are presented as mean ± standard deviation. $P<0.05$ was defined as statistically significant.

RESULTS AND DISCUSSION

In this study, histopathological changes related to stress in liver tissue were examined in rats exposed to 70 dB white noise for one hour per day for one month. Preparations prepared from liver tissue were examined considering hemorrhage, edema, steatosis, dissociation, bile duct hyperplasia, expansion of sinusoids and degeneration of hepatocyte nuclei lesions and the results were evaluated statistically. Statistical results of histopathological findings are given in Table 1. In the study group, histopathological examination revealed moderate steatosis (Fig 1A), dissociation in the remark cords, moderate expansion in the sinusoids (Fig 1B) and mild hyperplasia in the bile ducts (Fig 1C), as shown below.

Stan (2018) showed that rat liver had four lobes (Left lateral, median, right and caudate lobe). Lobes were different sizes and dark red in color.

Hemorrhage in liver sinusoids increased in male and female experimental groups compared to the male control group ($P<0.05$). Increased edema was observed in the female experimental group compared to the female control group ($P<0.05$). No statistically significant difference was found between the male control group and the experimental group ($P>0.05$). Fatty and dissociation in hepatocytes in the liver were observed to be statistically more severe in the male experimental group compared to the female and male control groups ($P<0.01$). Hyperplasia in the bile ducts was statistically more severe in the male experimental group ($P<0.05$). Degeneration of hepatocyte nuclei and dilatation of sinusoids were statistically more severe in the female and male experimental groups compared to the control groups ($P<0.01$). This finding is consistent with the study conducted on rats by Helal *et al.* (2011).

In a noise stress study conducted on rats by Helal *et al.* (2011), the findings of steatosis in hepatocytes, expansion of enlarged sinusoidal spaces, destruction in hepatocytes and presence of hemorrhagic areas were observed to be parallel to our study.

Ahmad Shawer *et al.* (2016) reported that noise and crowd stress had almost similar effects. Changes in liver tissue histopathology caused by stress were reported as irregular and dilated and obstructed veins, an increase in the number of lymphocytes and Kupffer cells and hepatocyte degeneration. Luo *et al.* (2024) found that stress causes an increase in plasma ACTH levels and lipid storage. Un and Myung, (2014) found that chronic stress causes hyperlipidemia. And stated that this may be due to decreased insulin secretion. In our study, moderate fatty liver tissue was detected in parallel with the literature.

Researchers suggest that the increase in serum glucose levels during stress may be due to stress-related excessive food consumption and a dysfunction triggered by fear. Weight gain due to food consumption creates a predisposition to diabetes (Çakır, 2014; Yavuz *et al.,* 2022). This explains the cause of the fatty liver in our findings. Eosinophilic cytoplasm was detected in the liver tissue of rabbits exposed to white noise at an intensity of 85 dB (Mehrizi *et al.,* 2021). In our study, no findings of eosinophilic cytoplasm were found. It was also found that acute psychological stress causes deeper oxidative damage than acute physical stress by increasing lipid peroxidation and corticosterone levels (Jafari *et al.,* 2014). In this way, lesions such as steatosis, degeneration and dissociation in hepatocyte nuclei and expansion in sinusoids occur as a result of oxidative stress in the liver tissue.

It was determined that serum malondialdehyde (MDA), nitric oxide (NO) level and glutathione peroxidase activity increased in rats exposed to 100 dB noise (Demirel *et al.,* 2009). The current study determined that noise stress caused disorders such as hyperplasia and steatosis. As evidence of this, no lesions reflecting a negative situation were observed in the liver tissue of rats not exposed to stress. Xu *et al.* (2014) observed dilatation in the hepatic sinus, central and interlobular veins of the liver in rats exposed to 95 dB noise for 2 weeks. They detected cell infiltration and lymph node formation in the hepatic lobe. In the current study, the dilatation detected in the hepatic sinusoids was found to be consistent with Xu *et al.* (2014).

Oliveira *et al.* (2012) found that noise exposure resulted in a significant increase in the area of collagen-rich connective tissue in the centrilobular area of rat liver. Since staining showing the presence of collagen in liver tissue was not performed in this study, we do not have any reports on this.

Ahmad Shawer *et al.* (2016) found that exposure to crowd and noise stress caused many pathologies in the liver tissue of rats. These changes were determined asincreased numbers of von Kupffer cells, an altered walled dilated congested central vein, destructive nucleated vacuole hepatocytes and lymphocytic infiltration. It was observed that similar results were obtained in this study. In particular, the findings of steatosis vacuole formation in hepatocytes and destruction of hepatocyte nuclei completely overlap.

Table 1: Statistical analysis of liver histopathological data of female and male rats exposed to noise stress.

	Female control	Male control	Female experiment	Male experiment	*P value*
Hemorrhagia	0.60±0.55	0.20±0.45	2.20±45*	2.20±0.44*	0.001
Odema	0.40±0.55	0.80±0.45	1.80±0.45$^{\#}$	1.80±0.84	0.009
Steatosis	0.20±0.45	0.20±0.45	1.60±0.55	2.00±0.00*$^{\#}$	0.001
Dissociation	0.40±0.55	0.60±0.55	1.80±0.45	2.20±0.45*$^{\#\#}$	0..002
Bile duct hyperplasia	0.40±0.55	0.20±0.45	1.40±0.55	1.80±0.45*$^{\#}$	0.004
Expansion of sinusoids	0.40±0.55	0.60±0.55	2.00±0.00*$^{\#}$	1.80±0.45$^{\#}$	0.002
Degeneration of hepatocyte nuclei	0.60±0.55	0.00±0.00	2.00±0.00**	2.00±0.00**	<0.001

*****: Compared to male control group, $^{\#}$: Compared with the female control group.

*: P<0.05; *: P<0.01; $^{\#}$: P<0.05; $^{\#\#}$: P<0.01.

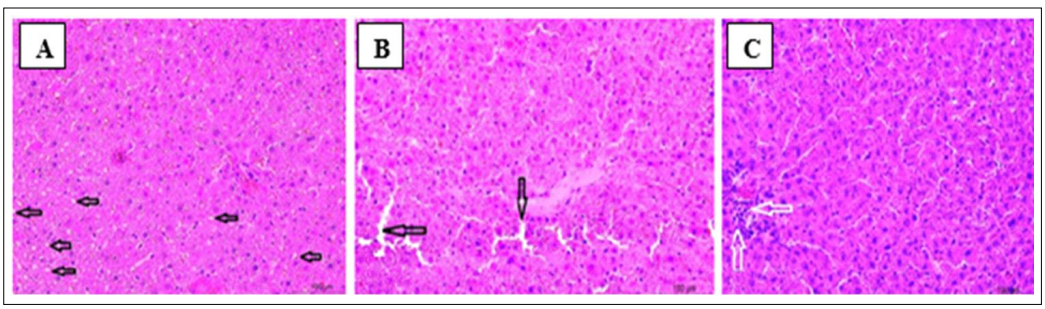


Fig 1: A. Rat moderate steatosis in liver tissue, black arrows, hematoxylin and eosin staining, 20× magnification. B. Moderate enlargement of sinusoids in rat liver tissue in experimental group, black arrows, hematoxylin and eosin staining, 20× magnification C. Mild hyperplasia in bile ducts in rat liver tissue in control group, white arrows, hematoxylin and eosin staining, 20× magnification.

CONCLUSION

Noise stress was found to be one of the stress factors affecting metabolism. It was understood that the liver tissue, which plays a key role in the healthy continuity of the body's metabolism, could not continue its normal function under stress. It was statistically demonstrated that pathological findings caused moderate lesions in the rats in the experimental group when compared to the control group. Noise stress is thought to have an effect on living beings at a level that can cause chronic diseases. We believe that it is necessary to take the highest possible precautions against noise stress for living beings to live at a minimum level of health and well-being. Being sensitive to noise in experimental animal production and experiment rooms, paying utmost attention to minimum noise levels is important in terms of protecting the welfare of experimental animals and ensuring that the experiments performed yield accurate results. The results of this study are important for humans and animals.

It is thought that the relevant study can inspire many studies to be conducted in the human field on this subject.

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Authors' contributions

The Esin ÜNSALDI participated in the conceptualization, the interpretation of data, methodology, validation, investigation, original draft, writing, manuscript review, acquisition of data and analysis. Aslan KALINBACAK participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethical statement

24/07/2024 dated and 2024-10-81 numbered was given by Ankara University Animal Experiments Local Ethics Committee.

Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal Care and Handling Techniques were approved by the University of Animal Care Committee.

Consent for publication

Not applicable.

Conflict of interest

Authors declare that there is no conflict of interest.

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