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Research Article
Effects of Mirtazapine on Liver Ischemia-Reperfusion Injury in Rats

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Abstract

Background and Objective: Ischemia-reperfusion (I/R) injury begins with tissue oxygen deprivation and continues with oxidative stress and inflammatory response. Mirtazapine is an antidepressant drug with antioxidant and anti-inflammatory properties. The current study was to investigate the effect of mirtazapine against I/R induced liver injury in rats. **Materials and Methods:** Albino Wistar-type male rats were divided into sham operation (SHAM), I/R (IR) and I/R+mirtazapine administrated (IRM) groups. One hour before anaesthesia, 20 mg kg^{-1} mirtazapine was administered to the IRM group of the animals and distilled water was applied to the SHAM and IR groups as a solvent. I/R was achieved by clamping the hepatic artery (except for the SHAM group). Following I/R, all rat groups were killed with high-dose anaesthesia. Malondialdehyde (MDA), total glutathione (tGSH), nuclear factor kappa B (NF-κB), interleukin 1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α) were determined in liver tissues. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were measured in blood serum. In addition, histopathological examination was performed on liver tissue samples. **Results:** Mirtazapine prevented increased levels of MDA, NF-κB, IL-1β, TNF-α, ALT and AST in liver tissue with I/R and a decrease in tGSH. Furthermore, mirtazapine has alleviated I/R -associated severe hepatocyte degeneration, necrosis and other structural disorders in the liver. **Conclusion:** Biochemical and histopathological experimental results suggest that mirtazapine may be useful in the treatment of I/R-induced liver injury.

Key words: Ischemia reperfusion injury, liver, mirtazapine, rats

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ischemia is the reduction or complete cessation of blood flow and oxygen to the tissue. As such the first intervention to be made to ischemia tissue is providing reperfusion of the tissue[1]. However, providing reoxygenation during tissue reperfusion leads to the formation of excessive Reactive Oxygen Species (ROS)[2]. Hydrogen peroxide (H_2O_2), hydroxyl (OH) and the superoxide radical (O^{-2}) are reactive oxygen species that induce reperfusion injury after ischemia[3,4]. These ROSs lead to organ and tissue damage through the oxidation of cell membrane fatty acids (LPO)[5,6]. LPO reaction causes of formation of aldehydes such as MDA, which have toxic effects on cell membrane enzymes and proteins[7,8]. I/R damage is explained as a pathological process that starts with the lack of oxygen in the tissue, continues with the production of ROS and expands with the inflammatory response in literature[1].

The role of nuclear factor kappa B (NF-κB) in the initiation of inflammation is known. It is stated that NF-κB increases the severity of inflammation by increasing the expression of TNF-α, IL-1β and IL-6[9]. As it is known, I/R forms the basis of the pathophysiology of myocardial infarction, cerebral ischemia, stroke, hemorrhagic shock and organ transplantation[10]. In the treatment of benign and malignant tumours liver surgery is an inevitable treatment method. Especially, liver transplantation is one of the preferred treatment options in patients with end-stage liver disease[11]. Nevertheless, liver I/R injury leads to complications after liver transplantation which may cause tissue rejection[12]. This information received from the literature suggests the fact that antioxidant and anti-inflammatory therapy may be beneficial in liver I/R injury.

Mirtazapine, which was the plan to investigate the protective effect against thereof in liver I/R injury, is an antidepressant drug utilized in the treatment of depression. It has been reported that Mirtazapine can be utilized as a cell protective agent, particularly due to its suppressive effects on oxidant marker parameters[13]. It is also known that mirtazapine has anti-inflammatory activity[14]. Mirtazapine has been reported to protect the tissue from oxidative and inflammatory damage by preventing the overproduction of MDA and TNF-α as well as the consumption of endogenous glutathione[15]. There were no studies investigating mirtazapine's effect on liver I/R injury however, it has been revealed to protect kidney tissue from I/R damage by inhibiting enzymatic and nonenzymatic oxidant increase and antioxidant decrease[16]. Such findings suggest that mirtazapine may protect liver tissue from I/R injury. The objective of the study was to investigate if mirtazapine has a protective effect against I/R-induced liver injury in rats.

MATERIALS AND METHODS

Study area: The study was carried out at the Medical Experimental Application and Research Center of Ataturk University, Turkey from June-August, 2021.

Animals: A total of 18 albino male Wistar rats weighing between 218-230 g were used in the experiment. All animals were received from Atatürk University, Medical Experimental Application and Research Center. Animals were housed and fed in the laboratory at normal room temperature (22°C) for one week before experimentation, to allow them to adapt to the environment. Animal experiments were performed following the National Guidelines for the Use and Care of Laboratory Animals and were approved by the local animal ethics committee of Ataturk University, Erzurum, Turkey (Ethics Committee Number: 5-152 Dated: 25.06.2021).

Chemicals: Chemical Substances used for the experiments, ketamine was supplied by Pfizer Ltd. Sti (Turkey) and mirtazapine was obtained from Schering Plough A.Ş. (Turkey).

Experimental groups: The animals were divided into sham operation (SHAM), I/R (IR) and I/R+mirtazapine administrated (IRM) groups.

Experiment procedure: Anesthesia was provided through the administration of ketamine at a dose of 60 mg kg^{-1}. Surgical procedures were made under sterile conditions. The animals were kept for a while to obtain the appropriate period for the surgical intervention. The period when the animals are immobilized in the supine position is considered a suitable anaesthesia period for surgical intervention[17]. One hour before anaesthesia, 20 mg kg^{-1} mirtazapine was applied orally by gavage to the IRM group of animals. Distilled water as solvent was applied to the rat's SHAM and IR groups by the same method. Laparotomy was applied by opening the anterior abdominal part of the anaesthetized rats vertically with a length of 3.5-4 cm. A clamp was then placed on the hepatic artery (except the SHAM group) to induce total hepatic ischemia and the liver was left in ischemia for one hour. Reperfusion was provided after ischemia for six hours. At the end of this period, the rat groups were killed with high-dose anaesthesia. MDA, tGSH, NF-κB, IL-1β and TNF-α levels were measured in tissue samples taken. ALT and AST activities were measured in blood samples taken from the tail veins before the animals were killed. Furthermore, tissues were examined histopathologically. The results received from the SHAM and IRM groups were compared with the results received from the IR group.

Biochemical analyses

MDA and tGSH analysis in tissue: MDA measurements are based on the method utilized by Qiu *et al*., which includes the spectrophotometric measurement of the absorbance of the pink-coloured complex formed by thiobarbituric acid (TBA) and MDA[18]. The principle of tGSH measurement is based on measuring the colour intensity of dark yellow 5-thio 2-nitrobenzoic acid (TNB), which is released due to the reduction of Ellman's reagent [5,5-dithiobis (2-nitrobenzoic acid), DTNB] by free thiol groups, at a wavelength of 412 nm[19].

NF-κB, TNF-α and IL-1β analysis in tissue: Tissue-homogenate at NF-κB and TNF-α concentrations were measured using rat-specific sandwich enzyme-linked immunosorbent assay. Rat NF-κB ELISA immunoassay kits (Cat. No: 201-11-0288, SunRed). Rat TNF-α and Rat IL-1β ELISA kits (Catno: YHB1098Ra, Shanghai LZ). Analyses were performed according to the manufacturers' instructions.

ALT and AST analysis in serum: Venous samples were collected into tubes without an anticoagulant. After clotting, the serum was separated by centrifugation and stored at-80°C until assay. Using a Cobas 8000 (Roche Diagnostics GmBH, Mannheim, Germany) with commercially available kits (Roche Diagnostics), serum AST and ALT activities were measured spectrophotometrically for the liver function tests.

Histopathological examination: Necropsies of the rats were performed and liver tissues were fixed in 10% neutral formalin solution. Tissues were taken into paraffin blocks after routine alcohol-xylol follow-up procedures. Sections of 4 μm taken on slides were stained with hematoxylin-eosin and evaluated as absent (-), mild (+), moderate (++) and severe (+++) in terms of degenerative-necrotic hepatocytes, hydropic degeneration and fat degeneration.

Statistical analysis: For statistical analysis IBM SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used. The results were presented as a Mean±Standard error of the mean (SEM). The normality assumption was used with the Kolmogorov-Smirnov test. One way ANOVA test was applied to normally distributed data. In the follow-up, the Tukey HSD test was performed according to the results of the homogeneity of variance test as a post hoc test. While variables were not normally distributed, the Kruskal Wallis test was used with Dunn's test as a post-doc test. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Biochemical findings

Tissue MDA and tGSH analysis: As seen in Fig. 1a, MDA levels (μmol g^{-1} protein) in the IR group (3.5±0.08) were found to be significantly higher when compared to the IRM (1.65±0.07) and SHAM (1.42±0.11) groups ($p<0.001$). No statistically significant difference was found between the SHAM and IRM groups ($p = 0.191$). On the other hand, tGSH levels (±nmol g^{-1} protein) were lower in the IR group (1.15±0.03) than in the IRM (3.25±0.06) and SHAM (3.74±0.09) groups ($p<0,05$). There was no statistically significant difference between the IRM group and the SHAM group ($p = 0.198$) in Fig. 1b.

Tissue NF-κB, TNF-α and IL-1β analysis: There were significant differences in NF-kB (pg/mL protein) values when the IR group (4.79±0.14) was compared with the SHAM (2.53±0.06) and IRM (2.69±0.05) groups ($p<0.05$). There was no difference between the IRM and SHAM group ($p = 0.702$) in Fig. 2a. While there was a significant difference between the IR (4.05±0.17) group and the SHAM (1.70±0.60) and IRM (2.07±0.24) groups in terms of TNF-α (ng mL^{-1} protein) values ($p<0.05$), there was no statistically significant difference between the SHAM and IRM groups ($p = 1.000$) in Fig. 2b. IL-1β (ng mL^{-1} protein) values in the IR group (4.61±0.10) were higher than those in the SHAM (2.04±0.19) and IRM (2.43±0.15) groups ($p<0.001$). IL-1β values in the SHAM and IRM groups were close to each other ($p = 0.181$) in Fig. 2c.

Serum ALT and AST analysis: In terms of serum ALT levels (IU L^{-1}), a significant difference was observed when the IR group (93.00±2.10) was compared with the SHAM (42.50±1.26) and IRM (46.67±1.20) groups ($p<0.001$). The values in the SHAM and IRM groups were not different ($p = 0.181$) in Fig. 3a. Serum AST levels (IU L^{-1}) were also increased in the IR group (132.67±3.48) compared to the SHAM (32.17±1.00) and IRM (50.33±1.63) groups ($p<0.001$). A significant difference was also observed between the IRM group and the SHAM group ($p<0.001$) in Fig. 3b.

Histopathological findings: Statistically significant differences were found between the groups in histopathological examinations in Table 1. The control group who underwent sham operation had a normal histological appearance. Degenerative-necrotic hepatocytes and hydropic degeneration which were seen at a severe level in the IR group were observed to decrease to a moderate level in the group treated with mirtazapine. While necrotic and degenerative

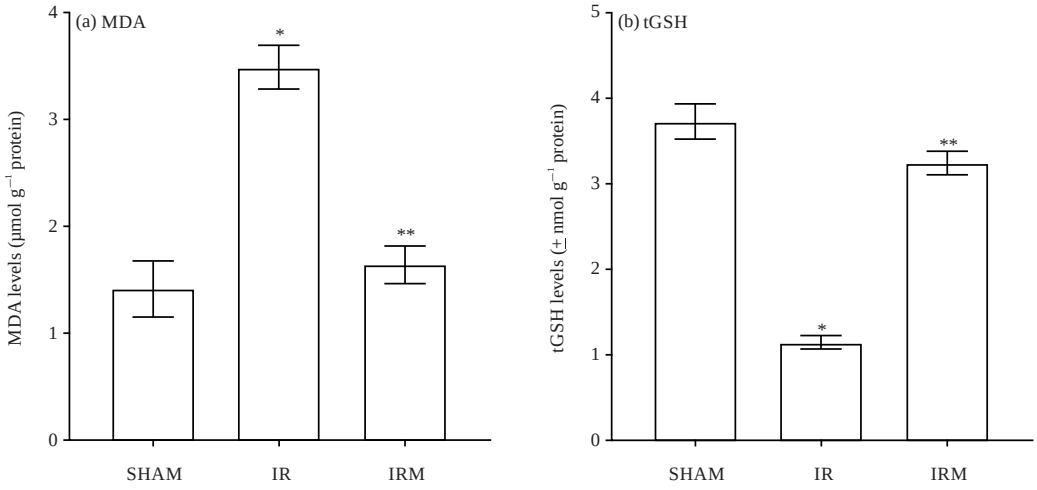

Fig. 1(a-b): MDA and tGSH analysis in study groups, (a) MDA analysis and (b) tGSH analysis

*p<0.05, according to SHAM and IRM groups, **p>0.05, according to SHAM group, SHAM: Sham operation, IR: Ischemia-reperfusion, IRM: Mirtazapine+ischemia-reperfusion, MDA: Malondialdehyde and tGSH: Total glutathione

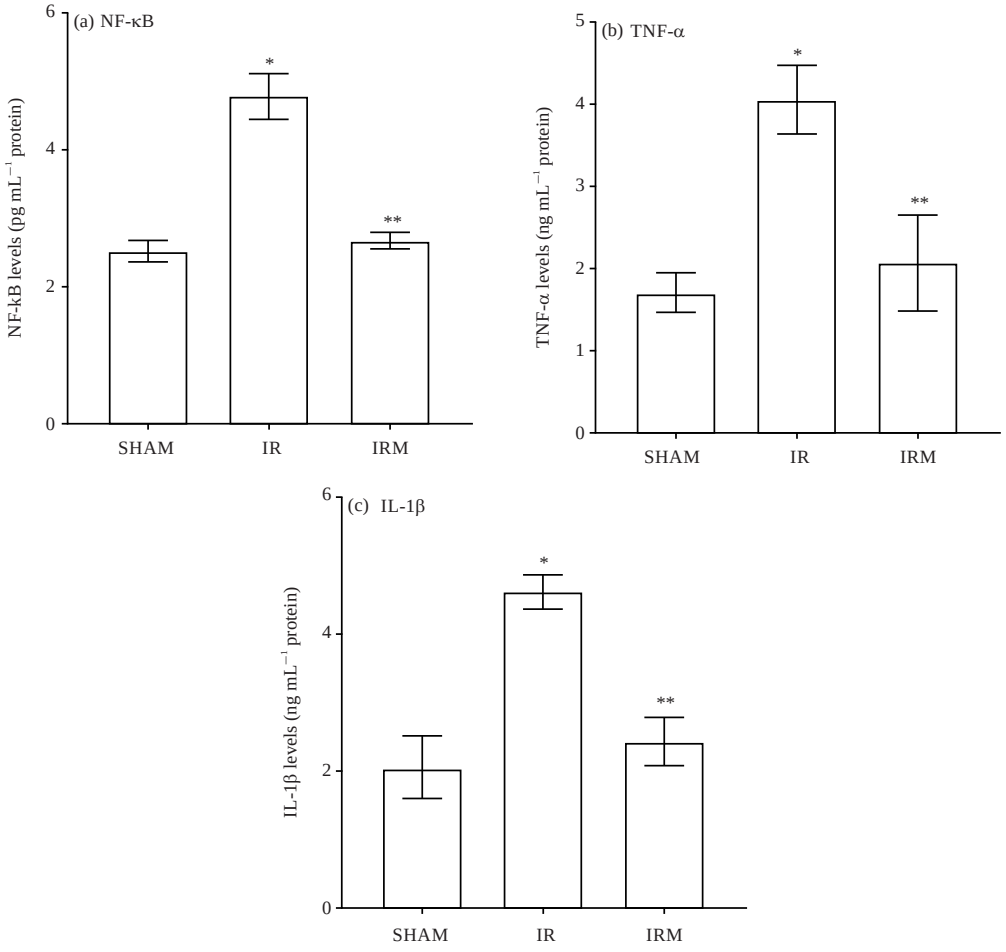

Fig. 2(a-c): NF-κB, TNF-α and IL-1β analysis in study groups, (a) NF-κB analysis, (b) TNF-α analysis and (c) IL-1β analysis

*p<0.05, according to SHAM and IRM group, **p>0.05, according to SHAM group, SHAM: Sham operation, IR: Ischemia-reperfusion, IRM: Mirtazapine+ischemia-reperfusion, NF-κB: Nuclear factor kappa B, TNF-α: Tumor necrosis factors-α and IL-1β: interleukin-1β

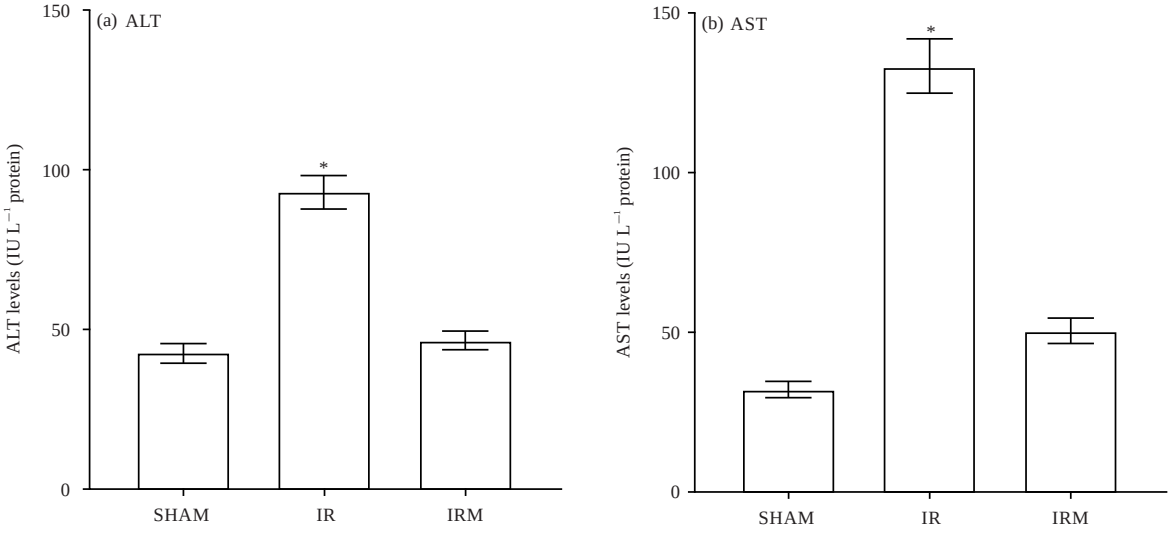

Fig. 3(a-b): ALT and AST analysis in study groups, (a) ALT analysis and (b) AST analysis

*p<0.001, according to SHAM and IRM groups, SHAM: Sham operation, IR: Ischemia-reperfusion, IRM: Mirtazapine+ischemia-reperfusion, ALT: Alanine aminotransferase and AST: Aspartate aminotransferase

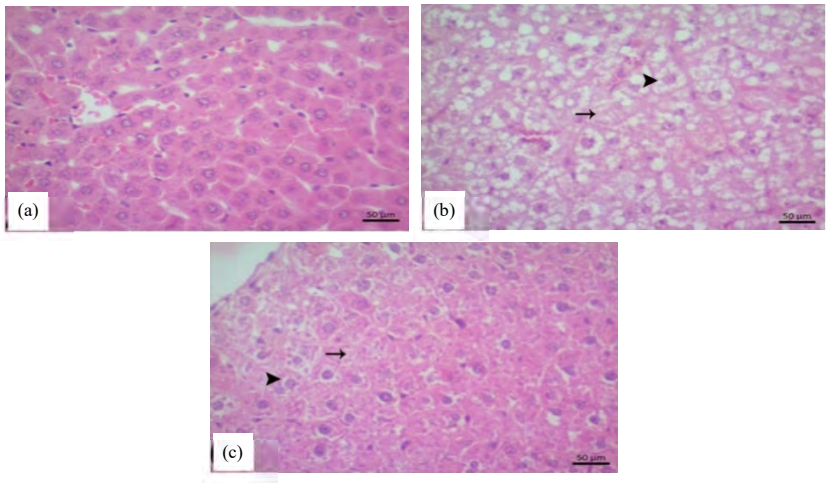

Fig. 4(a-c): Histopathological evaluation in terms of hydropic degeneration and degenerative-necrotic hepatocyte, (a) SHAM group, Normal histological appearance, (b) IR group, severe hydropic degeneration (arrowhead) and severe degenerative-necrotic hepatocytes (arrow) and (c) IRM group, Mild hydropic degeneration (arrowhead) and moderately degenerative-necrotic hepatocytes (arrow)

H-E, SHAM: Sham operation, IR: Ischemia-reperfusion and IRM: Mirtazapine+ischemia-reperfusion

changes were seen diffusely in the IR group, necrotic and degenerative changes were observed in the IRM group, but they were found in healthy hepatocytes from place to place ($p = 0.043$). In the necrotic changes detected in the IR group, it was determined that the cytoplasm of hepatocytes gained a granular appearance and the nuclei could not be seen, while the structure of the nuclei could be seen slightly in degenerative changes. However, it was determined that these changes, namely the number of necrotic and degenerative hepatocytes in the IRM group, were moderate. Similarly, it was determined that hydropic degeneration was intensely diffuse in the IR group and was located in the cytoplasm of all hepatocytes. In the IR group, hydropic degeneration was such that it covered the entire cytoplasm and caused the cytoplasm to grow. However, vacuoles formed due to hydropic degeneration were smaller and less numerous in the IRM group. In the IRM group, the hydropic degeneration was not in such a way as to cover the entire cytoplasm and enlarge the cytoplasm ($p = 0.037$) in Fig. 4a-c. Among the other histopathological findings, hydropic degeneration and fat

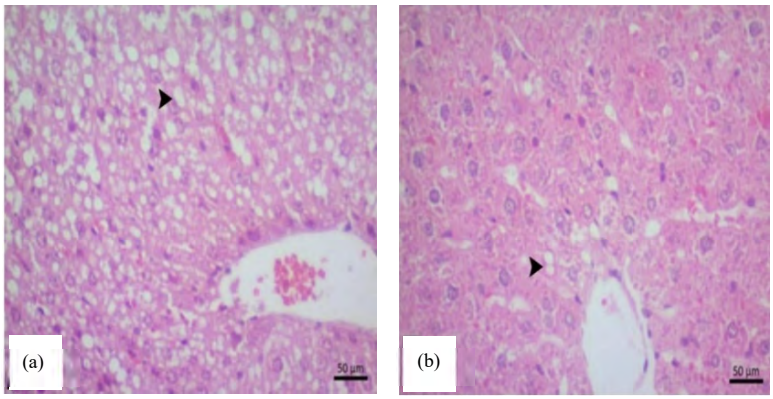

Fig. 5(a-b): Histopathological evaluation in terms of fat degeneration, (a) IR group, severe fat degeneration (arrowhead) and (b) IRM group, mild fat degeneration (arrowhead)
IR: Ischemia-reperfusion and IRM: Mirtazapine+ ischemia-reperfusion

Table 1: Histopathological evaluation of animal study groups

Groups	Degenerative-necrotic hepatocytes (X±SEM)	Hydropic degeneration (X±SEM)	Fat degeneration (X±SEM)
SHAM (n = 6)	0.33±0.51	0.33±0.51	0.16±0.40
IR (n = 6)	2.66±0.51	2.83±0.40	2.66±0.51
IRM (n = 6)	1.66±0.51	1.00±0.51	0.83±0.40
p value	0.043*	0.037*	0.026*

*p<0.05, comparing the IR group and the IRM group (Kruskal Wallis test, p<0.05), SHAM: Sham operation, IR: Ischemia-reperfusion, IRM: Mirtazapine+ischemia-reperfusion, (X±SEM) Mean±Standard error of the mean and n: number of animals

degeneration were observed to be severe in the IR group, but mild in the IRM group. Fat degeneration was in all of the hepatocytes around the vena centralis in the IR group and was large enough to fill the cytoplasm of these hepatocytes. In the IR group with severe fat degeneration, the nuclei were pushed to the periphery. On the other hand, it was determined that fat degeneration was found in some of the hepatocytes around the vena centralis in the IRM group and the vacuoles formed were smaller in microvesicular structure compared to the IR group. Although the nuclei were pushed to the periphery in the IRM group, similar to the IR group, the number of hepatocytes in this form was less than in the IR group ($p = 0.026$) in Fig. 5a and b.

DISCUSSION

The protective effect of mirtazapine against I/R-induced oxidative and inflammatory liver damage in rats was investigated biochemically and histopathologically in this study. Biochemical results showed that the levels of MDA, NF-κB, TNF-α and IL-1β in the liver tissue of the IR group increased compared to the IRM and SHAM groups, while tGSH decreased. These biochemical findings indicate that mirtazapine suppresses the I/R induction of oxidative stress and inflammation in liver tissue. As previously stated, no studies investigating the effect of mirtazapine on liver I/R injury were observed. However, it has been reported that mirtazapine protects the gastric tissue from the oxidative damage of indomethacin by preventing the increase of enzymatic and nonenzymatic oxidants such as MDA and myeloperoxidase[13]. It has also been reported that mirtazapine prevents the development of cisplatin-induced oxidative brain damage by inhibiting oxidant production and antioxidant consumption[20]. Furthermore, it has been stated that mirtazapine alleviates I/R-induced ovarian damage in diabetic rats with antioxidant activity[21]. MDA causes cross-linking and polymerization of cell membrane components as it is known. This event leads to serious injury to membrane receptors, enzymes and proteins[7]. Experimental results and this information obtained from the literature suggest the fact that oxidative stress develops in the liver tissue to which we apply I/R. In a current study investigating the effects of mirtazapine on liver I/R damage, DA and tGSH levels in the IRM group were observed close to the SHAM group. This result indicates that mirtazapine may have slowed down the LPO reaction. In the literature, there is information on the fact that the LPO reaction is either terminated by scavenging antioxidant reactions or continues with autocatalytic propagation reactions[22]. It is known that GSH detoxifies ROS and protects cells from oxidative stress with the help of

glutathioneperoxidase[23] which is compatible with the literature, MDA level was higher in the IR group than in the IRM group and tGSH was lower in this study. It is understood from our experimental results that the oxidant-antioxidant balance is maintained in the liver tissue of animals that underwent I/R treatment, with the predominance of oxidants and antioxidants in the IRM group. The state of maintaining the oxidant/antioxidant balance with the predominance of oxidants is defined as oxidative stress in the literature[24].

I/R injury is defined as a complex pathological process that begins with tissue oxygen deprivation, continues with ROS production and expands with an inflammatory response in the literature[1]. NF-κB, TNF-α and IL-1β levels were found to be higher in the liver tissue of the IR group, whose MDA level was measured to be high, compared to the healthy and IRM group in our study. As it is known, NF-κB induces the activation of various proinflammatory cytokine expression[25]. Oxidants, whose production is increased in an uncontrolled manner, are held responsible for this proinflammatory cytokine increase[26]. The fact that the oxidant, antioxidant and proinflammatory cytokine levels in the mirtazapine group were close to the healthy group reveals the fact that our experimental results are in agreement with the literature information. No studies investigating the effect of mirtazapine on the pro-inflammatory cytokine-induced in liver I/R injury were observed however, mirtazapine has been reported to reduce proinflammatory cytokine secretion from liver B cells[27]. In another study, it is defended that mirtazapine may reduce hepatic innate immune responses in the development of autoimmune liver damage[28]. Protective of mirtazapine against liver I/R damage was investigated and it was observed that the increase in blood serum ALT and AST levels was significantly inhibited compared to the IR group in our study. In a study, it was stated that serum ALT and AST activities increased significantly in liver I/R damage compared to healthy animals, furthermore, it was emphasized that increases in ALT and AST activity were associated with decreased tissue antioxidants and increased oxidants[29]. It has also been explained that the increase in ALT and AST is related to histopathological damage[3].

In this study, it was observed that biochemical test results overlapped with histopathological findings, it has been detected that mirtazapine alleviates I/R related degenerative-necrotic hepatocytes, hydropic degeneration and fat degeneration in liver tissue. Hepatocyte degeneration appears to be one of the histopathological signs of liver I/R injury[30]. It has been reported that the I/R event in the liver causes necrosis in hepatocytes[31]. It has been reported that excessive production of cytokines and ROS is a significant process in the pathogenesis of hepatocyte necrosis and other histopathological findings caused by liver I/R[32]. The fact that mirtazapine inhibits MDA and TNF-α overproduction and GSH consumption[15] shows the fact that it's a molecular mechanism underlying its antistress and anti-inflammatory effect.

CONCLUSION

Mirtazapine prevented the increase of oxidants and cytokines by I/R and the decrease of antioxidants in liver tissue. Mirtazapine attenuated I/R-related morphological injury in the liver. Our experimental results reveal the fact that mirtazapine protects liver tissue from I/R injury. Therefore, it is thought that mirtazapine may be useful in the treatment of. liver clinically in I/R injury. Histopathological examination of tissues at the molecular level may be required in the future to clarify the protective mechanism of action of mirtazapine against liver I/R injury.

SIGNIFICANCE STATEMENT

This study revealed that mirtazapine can be used in I/R injury. Mirtazapine prevented the increase of MDA, NF-kB, IL-1β, TNF-α, ALT and AST levels by I/R and decreased tGSH in liver tissue.

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