Indian Journal of Experimental Biology
Vol. 64, January 2026, pp. 43-50
DOI: 10.56042/ijeb.v64i01.14584

Melatonin agonist tasimelteon ameliorates traumatic brain injury induced liver damage in a dose-dependent manner by enhancing IL-10 expressions

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Received 07 November 2024; revised 21 November 2025

Traumatic brain injury (TBI) is a prevalent neurological disorder with significant morbidity and mortality rates, often leading to systemic inflammatory responses and secondary organ damage. Among the organs affected, the liver is particularly vulnerable, with the inflammatory process following TBI impairing liver function and worsening disease progression. Despite existing treatments, there remains a need for effective therapies to mitigate organ damage in the aftermath of TBI. Melatonin, a neurohormone known for its anti-inflammatory and antioxidant properties, has shown potential as a therapeutic agent for reducing such damage. Tasimelteon (TASI), a melatonin agonist, binds to melatonin receptors and exhibits similar biological effects. However, limited research exists on the protective effects of TASI against TBI-induced liver damage, and its potential dose-dependency remains unclear.This study aimed to investigate the impact of TASI on the inflammatory response in traumatic secondary liver injury (TSLI) induced by TBI, specifically evaluating the role of anti-inflammatory cytokine interleukin (IL)-10 levels. Forty Wistar Albino male rats were divided into four groups: sham, TSLI (trauma induced by dropping a 50 g weight from a height of 80 cm to create 0.2 N severity according to Newton's law), TASI-1 (TSLI+TASI 1 mg/kg, ip) and TASI-10 (TSLI+TASI 10 mg/kg, IP). After 48 hours, rats were sacrificed under anesthesia and the liver tissues were collected for histopathological and immunohistochemical examination. The TSLI group exhibited moderate hyperemia, mild hemorrhages, inflammatory cell infiltrations, and necrosis, along with increased IL-1β, TNF-α, and decreased IL-10 expression levels compared to the sham group. Treatment with TASI significantly reversed these findings in both TASI-treated groups. Our results suggest that TASI, a melatonin agonist, effectively attenuates inflammatory liver damage induced by TBI in a dose-dependent manner by increasing IL-10 levels. However, these positive effects should be further explored in future studies.

Keywords: Head trauma, Liver, Tasimelteon, Pathology, Inflammation

Mortality and morbidity rates from head trauma due to traffic accidents, falls, sports impacts, or assaults are alarmingly high[1]. Most studies focus on neuroprotective therapies to improve motor and cognitive functions in traumatic brain injury (TBI) but prognosis is influenced by various pathological conditions[2]. These include neurological deficits due to brain tissue damage and distant organ damage resulting from the cytokine storm[3,4].

Brain injury not only affects the brain but also causes significant changes in peripheral organs and circulation, with recent research highlighting the complex relationship between brain inflammation and peripheral organ damage, particularly the liver's susceptibility to inflammation[5]. Because of brain-periphery connection, the liver and other organs' systemic synthesis of cytokines and chemokines in reaction to brain injury is a crucial part of the brain's secondary inflammatory response[6].

The inflammatory secondary reaction in the brain, driven by brain-periphery communication, relies on the systemic synthesis of cytokines and chemokines by the liver and other organs in response to brain damage, where the cytokine storm triggered by brain trauma increases inflammatory cytokines like tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) in brain tissue, causing progressive damage, enhancing blood-brain barrier permeability and leading to damage in peripheral organs[7,8]. It is well known that circulating cytokines cause secondary disorders in the liver the body's detoxification center as well as in many other organs following head trauma (TSLI)[9,10].

Studies have shown that brain injury triggers a rapid hepatic response where, chemokines produced by the liver amplify the focal injury response and

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establish a communication route between CNS and liver[5,6]. The reversal of inflammatory damage in the liver involves the endogenous antioxidant system and anti-inflammatory cytokines such as IL-4 and IL-10[11]. These molecular communication signals initiated by the injured brain are transmitted to the periphery, playing a crucial role in regulating CNS inflammatory responses. However, the contribution of these inflammatory mediators to the harmful sequelae of TBI and the pathogenesis of this reaction remains unclear.

Melatonin, a well-known antioxidant and anti-inflammatory agent, protects tissues through various cellular mechanisms[12,13]. Tasimelteon (TASI), a melatonin agonist, mimics melatonin′s structure and regulates the sleep-wake cycle by binding to melatonin receptors[14-18]. However, research on TASI′s effects on damage mechanisms is limited.

In conclusion, while the brain and peripheral system interaction is crucial in CNS injuries like TSLI, liver alterations at cellular level remain underexplored. This study aims to evaluate the effects of TASI on inflammation, liver histology, and the immunohistochemical expressions of IL-10, TNF-α, and IL-1β following head trauma; the proposed mechanistic pathways are summarized in Fig. 1.

Materials and methods

Animals and experimental design

All experimental processes applied in the study were performed following the guidelines for animal research outlined by the Animal Research: Reporting *in vivo* Experiments (ARRIVE) 2.0 and were approved by the Committee on Animal Research at Suleyman Demirel University. (Approval no: 11.07.2024/08-314). Furthermore, support for the study was provided by the Suleyman Demirel University Scientific Research Project Unit (SDU-BAP) under the project number TSG-2023-9092. The rats obtained from Suleyman Demirel University Animal Experiments Laboratory were housed at 21-22 °C and 60% ± 5% humidity with a 12-hour light and 12-hour dark cycle and fed with standard commercial feed *ad-libitum* and water during the experiments.

Weighing 250-300 grams forty Wistar Albino male rats were divided into four groups. Groups were. Sham group: Anesthetized rats were kept without trauma and immediately afterward 0.5-1 mL of saline (SF) was administered by oral gavage. After 48 hours, rats were sacrificed under anesthesia, and liver tissues were removed; TSLI group: Trauma was induced in anesthetized rats and 0.5-1 mL saline (SF) was administered by oral gavage immediately afterwards. After 48 hours, rats were sacrificed under anesthesia, and liver tissues were removed; TASI-1: Trauma was induced in anesthetized rats and immediately afterward 0.5-1 mL of 1 mg/kg TASI was administered by oral gavage. After 48 hours, rats were sacrificed under anesthesia, and liver tissues were removed[19];TASI-10: Trauma was induced in anesthetized rats and immediately afterward, 0.5-1 mL of 10 mg/kg TASI was administered by oral gavage. After 48 hours, rats were sacrificed under anesthesia, and liver tissues were removed.

For all experimental procedures, 90 mg/kg ketamine (Ketalar, Pfizer, Türkiye) and 8-10 mg/kg xylazine (Xylazinbio %2, Bioveta, Czech Republic) were used for anesthesia.

To create a head trauma model, the impact acceleration model made by Marmarou *et al.* by dropping a 50 g ball from a height of 80 cm was used. Thus, it was aimed to create a trauma of 0.2 N severity according to Newton's law[20].

Histopathological analysis

Liver samples were collected during the necropsy and fixed in a 10% neutral formalin solution. Subsequently, the tissues were routinely processed by a tissue processor following standard procedure. Using a rotary microtome, the paraffin blocks were sectioned to a thickness of 5 µm. These sections were

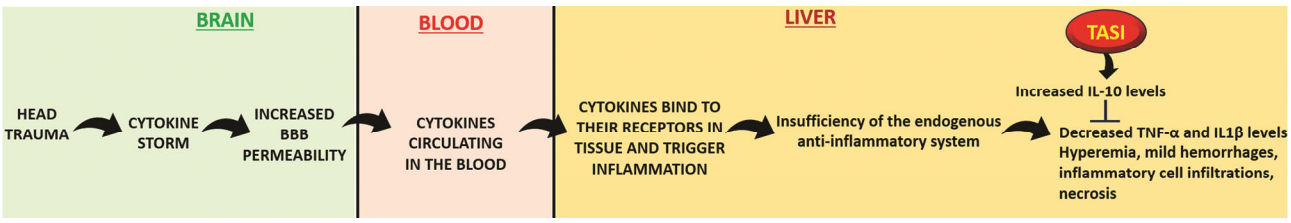


Fig. 1 — Pathophysiologic mechanism of head trauma-induced liver injury and potential action of tasimelteon. [TASI: Tasimelteon, IL-10: Interleukin-10, IL-1β: Interleukin 1 beta, TNF-α: Tumor necrosis factor alpha]

then examined under a light microscope. Rat liver tissues were stained with hematoxylin and eosin (H&E) to identify and assess histopathological findings such as hyperemia, hemorrhage, inflammation, and necrosis. The criteria outlined in Table 1 were adapted to evaluate the lesions in line with Veteläinen *et al.*[21].

Immunohistochemical examination

Three sets of sections were cut from the paraffin blocks and placed on poly-L-lysine-coated slides for immunohistochemistry analysis. The expression of IL-10 (Anti-IL-10 antibody (ab217941)), IL-1β (Recombinant Anti-IL-1 beta antibody [RM1009] (ab283818)), and TNF-α (Recombinant Anti-TNF alpha antibody [RM1005] (ab307164)) was measured using the streptavidin-biotin peroxidase method as per the manufacturer's instructions. Primary antibodies obtained from Abcam (Cambridge, UK) were diluted to a ratio of 1/100. Subsequently, the sections were subjected to immunohistochemistry using a biotinylated secondary antibody and a streptavidin-biotin peroxidase after incubation with the primary antibodies for 60 minutes at room temperature (20-25°C).

In this study, Mouse and Rabbit Specific HRP/DAB IHC Detection Kit - Micro-polymer (ab236466) from Abcam (Cambridge, UK) and chromogen 3,3′-Diaminobenzidine (DAB) were utilised as secondary kit. Negative controls were conducted by substituting primary antibodies with antigen dilution solution. Blinded samples were utilised, and each investigation was conducted by a certified pathologist from a different university.

The percentage of cells that stained positively for each marker in ten distinct locations on each slide, across all groups, was calculated at an objective magnification of 40×. The output of the image analyzer was compiled using the ImageJ software (National Institutes of Health, Bethesda, MD, version 1.48). Microphotographs were captured using the Database Manual Cell Sens Life Science Imaging Software System (Olympus Co., Tokyo, Japan).

Table 1 — Histopathological scoring and description of hepatic lesions

Histological criteria	Severity	Description	Score
Hemorrhage	Absent		0
	Mild	< 3 foci	1
	Marked	4-6 foci	2
	Severe	> 7 foci	3
Inflammation	None		0
	Moderate	Scattered	1
	Marked	Foci	2
	Severe	Diffuse	3
Necrosis	Absent	0%	0
	Mild	<10%	1
	Marked	10–50%	2
	Severe	>50%	3

Statistical analysis

The GraphPad prism v10.1.0 program was used for statistical analysis. Initially, the Shapiro-Wilk method was employed to assess the normality of the data distribution. One-way ANOVA test was employed as a means of comparing the groups since the data showed a normal distribution *(P*>0.05). The pairwise differences between the groups were obtained using the post hoc Tukey test. The significance threshold was set at $P<0.05$ and the findings are shown as means ± standard deviation.

Results

Histopathological examination

Liver sections from the control group exhibited normal tissue histology during microscopical examination. However, noticeable changes were observed in the TSLI group, including moderate hyperemia, mild hemorrhages, inflammatory cell infiltrations, and necrosis. The inflammatory infiltrate primarily consisted of neutrophils, with fewer lymphocytes and mononuclear cells also present. These lesions were typically more prominent near the cenral veins. The histological results for the TASI-1 and TASI-10 therapy groups demonstrated significant improvement. Moreover, TASI- 10 treatment proved to be more effective than TASI-1 treatment (Fig. 2).

Immunohistochemical examination

According to immunohistochemistry analysis, the control group exhibited marked IL-10 expressions, while IL-1β and TNF-α expressions were either nonexistent or very low. In contrast, liver cells in the TSLI group displayed decreased IL-10 expression and notable increases in IL-1β and TNF-α expressions. Treatment with TASI resulted in increased IL-10 expression and decreased IL-1β and TNF-α expressions (Fig. 3). Hepatocytes were the primary source of these expressions, although bile duct epithelial cells and inflammatory cells also exhibited expressions. It was observed that the majority of the expressions were located in the cytoplasm. TASI-10 treatment was found to be more effective than TASI-1 treatment.

The results of the investigation demonstrate that TASI protects against liver damage induced by TRAV. Moreover, the TASI-10 treatment was found to be more effective than the TASI-1 treatment.

Discussion

Traumatic brain injury (TBI) is recognised for its complex pathology and the systemic repercussions it elicits extend beyond the primary injury site. The liver, as a central organ in regulating systemic inflammation, emerges as a critical target for secondary damage after TBI. This study highlights the liver's susceptibility to injury following brain trauma showing pronounced inflammatory responses marked by increased pro-inflammatory cytokines and a reduction in anti-inflammatory cytokine expression, particularly in the TSLI group. These findings underscore the potential for TBI to disrupt hepatic function, exacerbating overall disease severity and leading to a worsened prognosis.

Given the unique protection provided to brain tissue by the skull and blood-brain barrier, the brain is often shielded from blunt trauma[22,23]. However, the permeability of the blood-brain barrier can be increased under inflammatory conditions, particularly those induced by trauma. Numerous molecular studies have demonstrated that cytokines circulating in the bloodstream, especially following traumatic events, can bind to their receptors in distant organs, including the liver, thus instigating inflammatory and pathological damage[24,25]. These mechanisms can lead to cascading detrimental effects on distant tissues. In this study, liver tissue samples from rats with experimentally induced TBI were collected 48 hours post injury and examined histopathologically. The observed findings, including hyperemia, hemorrhage, infiltrations, and tissue necrosis in the TSLI group were absent in the sham group, underscoring that liver injury is secondary to brain trauma[6].

Our results suggest that the liver, as an organ with a substantial blood supply, is highly vulnerable to inflammatory damage in the context of TBI[26]. The presence of neutrophilic infiltration in the liver tissue during the acute phase of injury supports the notion that the inflammatory response triggered by brain trauma can propagate to distant organs. Specifically, the predominance of neutrophils among the inflammatory cells in the liver indicates that liver damage occurs in the immediate aftermath of brain injury, consistent with findings of acute inflammatory processes in distant organs post-TBI. When the histopathological results of this study are examined, the presence of inflammatory cell infiltration in the TSLI group and the accompanying hyperemia, hemorrhagic foci, and necrosis support the pathological process mentioned above. The predominance of neutrophils among the inflammatory cells indicates that liver damage occurs shortly after brain injury.

Moreover, the regression of histopathological damage in the low-dose (TASI-1) and high-dose (TASI-10)

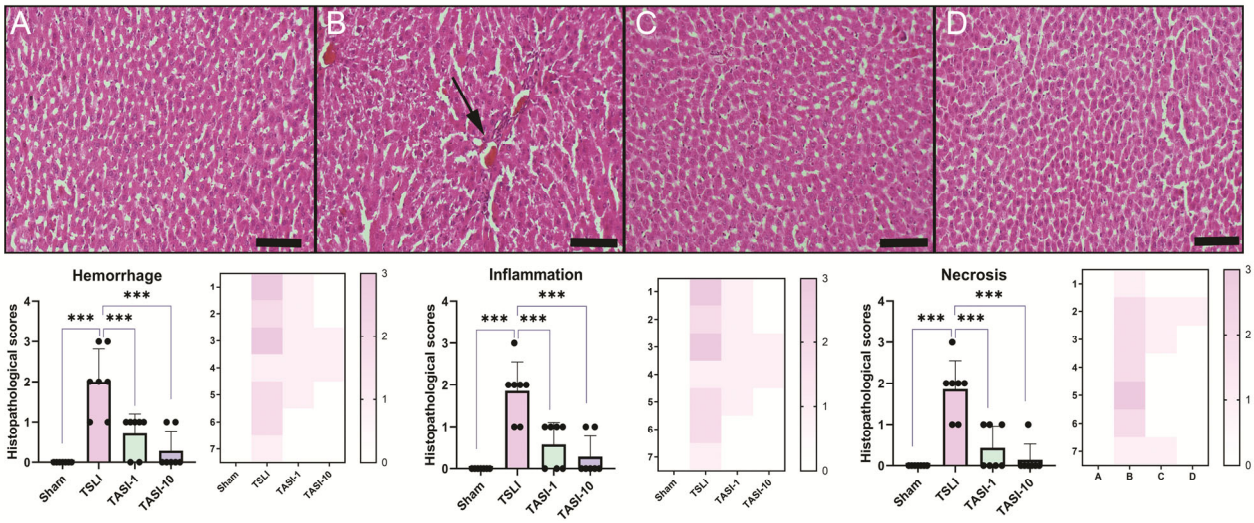
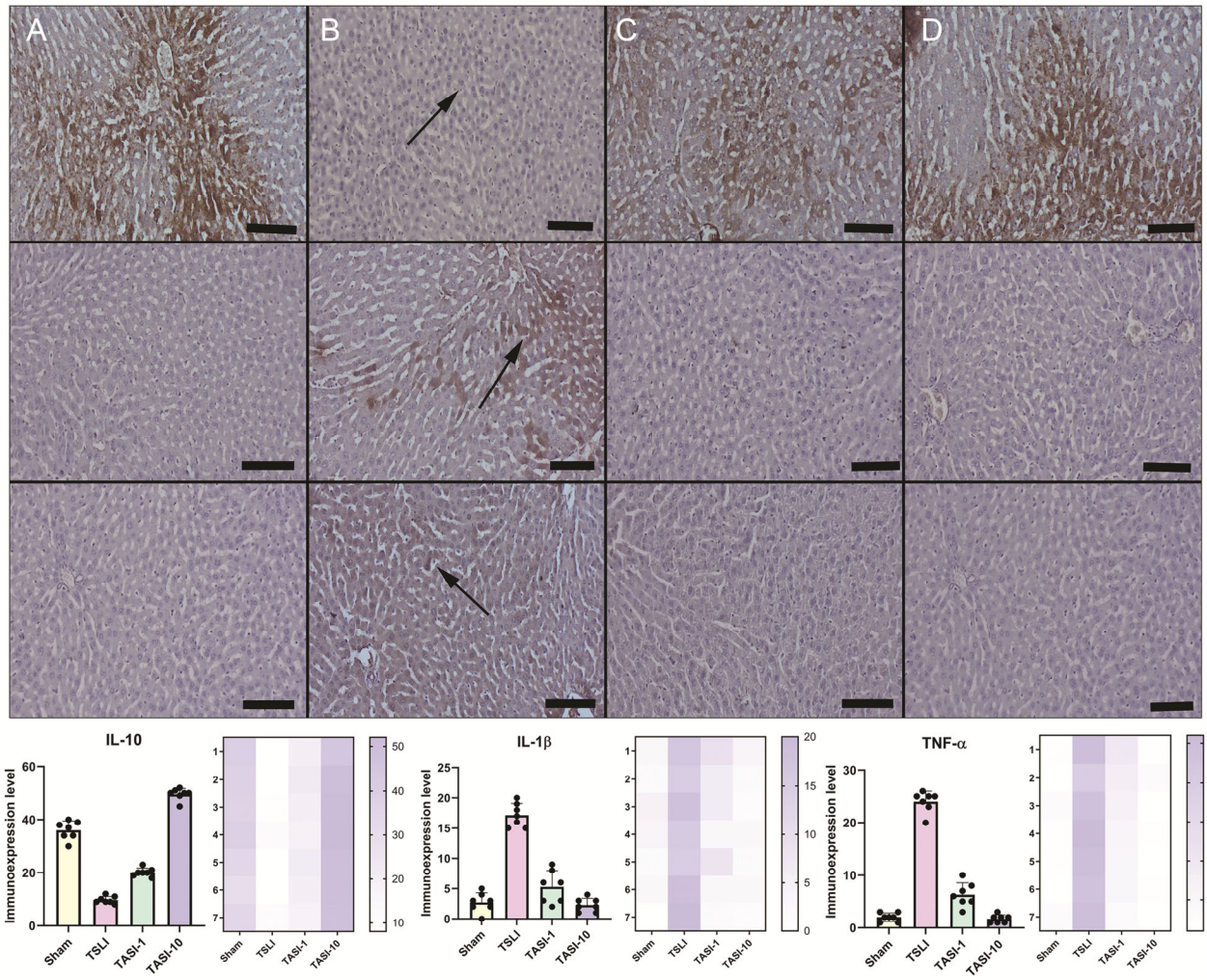


Fig. 2 — Representative histopathological images and statistical analysis of livers across the groups. (A) Normal tissue architecture in the control group. (B) Marked hyperemia (thick arrow), inflammatory cell infiltrations (thin arrow), micro hemorrhage (thin arrowhead) and hepatocyte degeneration (thick arrowhead) in the TSLI group. (C) Reduced pathological findings in the TASI-1 group. (D) Normal liver histology in the TASI-10 group. [H&E staining; scale bars = 50 µm. TSLI: Head trauma-induced liver injury, TASI: Tasimelteon, Values are represented as means ± SD. *NS: not significant, ***$P \leq 0.001$]



	IL-10		IL-1β		TNF-α	
	Summary	P Value	Summary	P Value	Summary	P Value
Control vs. TSLI	***	<,001	***	<,001	***	<,001
Control vs. TASI-1	***	<,001	ns	,086	***	<,001
Control vs. TASI-10	***	<,001	ns	,975	ns	,987
TSLI vs. TASI-1	***	<,001	***	<,001	***	<,001
TSLI vs. TASI-10	***	<,001	***	<,001	***	<,001
TASI-1 vs. TASI-10	***	<,001	*	,036	***	<,001

Fig. 3 — Immunohistochemical expressions and statistical analysis of IL-10 (upper row), IL-1β (middle row), and TNF-α (bottom row) in the liver among the groups.(A) Marked IL-10 and negative IL-1β and TNF-α expressions in the Control group. (B) Decreased IL-10 and increased IL-1β and TNF-α expressions in hepatocytes (arrows) in the TSLI group. (C) Increased IL-10 and decreased IL-1β and TNF-α expression (arrows) in the TASI-1 group. (D) Increased IL-10 and negative IL-1β and TNF-α expression in the TASI-10 group. [Streptavidin-biotin peroxidase method; scale bars = 50 µm. TSLI: Head trauma induced liver injury, TASI: Tasimelteon, IL-10: Interleukin-10, IL-1β: Interleukin 1 beta, TNF-α: Tumor necrosis factor alpha, Values are represented as means ± SD. NS: not significant, **P*≤0.05, ****P*≤0.001]

groups suggests that TASI may exert a protective effect, akin to melatonin, by attenuating inflammation. Notably, the TASI-10 group demonstrated a higher protective effect compared to the TASI-1 group implying a dose-dependent response to the treatment. However, the statistical analysis did not reveal significant differences in histopathological scores between the two treatment groups indicating that the

drug's therapeutic impact may plateau at a certain dosage threshold.

By increasing the expression of intercellular adhesion molecule 1, IL-1β operates on liver sinusoidal endothelial cells to enhance liver inflammation, which in turn encourages the liver to attract neutrophils[27]. By encouraging the development of lipid droplets and the buildup of triglycerides and cholesterol in primary liver hepatocytes, this leads to hepatic steatosis[28,29]. Chronic inflammation is also caused by the liver's synthesis of IL-1β, pro-inflammatory IL-6, and TNF-α, which stimulate the body's immune cells and attract more leucocytes to the wounded liver.[30]

The inflammatory cytokines IL-1β and TNF-α are key players in the development of hepatic inflammation and tissue injury. IL-1β enhances liver inflammation by upregulating intercellular adhesion molecule 1, thereby attracting neutrophils to the liver and promoting further damage. Additionally, the chronic synthesis of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α by the liver exacerbates systemic inflammation and perpetuates the inflammatory cycle. In this study, immunohisto-chemical analyses revealed IL-1β and TNF-α expressions in the TSLI group, corroborating the histopathological findings and supporting the model of acute liver damage secondary to TBI. These cytokines were markedly reduced in the TASI-treated groups, further demonstrating the anti-inflammatory potential of TASI in mitigating liver damage. These findings suggest that TASI could have broader applications in treating acute inflammatory conditions, particularly those triggered by traumatic events. Although our findings are based on data collected 48 hours post-injury, they also support the ideas that this damage have the potential to lead to cirrhotic changes in the liver in the long term[31].The decreased expressions in the TASI groups demonstrated that the active substance can reverse the damage with a single dose by showing acute effects. This characteristic indicates that TASI could be tested in other acute experimental models as well[31]. Some endogenous defense mechanisms can be activated in the fight against such damages that occur in the body for various reasons. Just like antioxidant enzymes whose synthesis increases in the body in case of oxidative stress, the levels of anti-inflammatory cytokines may increase for defense purposes in case of inflammation[32-35].

IL-10, an anti-inflammatory cytokine, plays a pivotal role in counterbalancing inflammatory processes and promoting tissue repair[36-38]. IL-10 is reported to be a valuable diagnostic and prognostic tool for brain damage[39-42]. In this study, the reduced levels of IL-10 observed in the TSLI group suggest an inadequate defense response to the liver injury, which allowed the observed histopathological damage to manifest. Conversely, the administration of TASI led to a dose-dependent increase in IL-10 expression, indicating that TASI not only reduces inflammation but also enhances the liver′s capacity to combat inflammation and facilitate recovery. The fact that IL-10 levels in the TASI-10 group exceeded those in the sham group further supports the therapeutic potential of TASI as a modulator of the immune response. While the study's findings strongly suggest that TASI, a melatonin agonist, can ameliorate liver damage following TBI by enhancing IL-10 expression and mitigating inflammatory processes, the results should be interpreted cautiously. The absence of a group receiving the drug alone, without trauma, and the need for more detailed molecular analyses (e.g., PCR and Western Blot) to confirm the mechanistic pathways at play highlight the need for future research to validate and further elucidate these observations. Future studies should also explore the long-term effects of TASI on liver function and investigate whether repeated or prolonged administration could provide more sustained protection against trauma-induced hepatic injury. These positive effects need to be supported by more detailed studies in the future.

Conclusion

In conclusion, this study demonstrates that blunt trauma to the brain can lead to secondary liver injury, characterised by inflammation, cell death, and impaired function. The administration of TASI, a melatonin agonist, effectively mitigated these effects by enhancing IL-10 levels and reducing pro-inflammatory cytokine expression in a dose-dependent manner. These findings suggest that TASI could be a promising therapeutic agent for managing secondary organ damage following brain injury, although further studies are necessary to fully understand its therapeutic potential and long-term efficacy.

Ethical statement

This study was approved by the Committee on Animal Research at Suleyman Demirel University. (Approval no: 11.07.2024/08-314).

Acknowledgement

This study was supported by the Suleyman Demirel University Scientific Research Project Unit (SDU-BAP) under the project number TSG-2023-9092.

Conflict of interest

The authors declare no competing interests.

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