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The effects of sugammadex on gastric ischemia-reperfusion injury in rats: Biochemical and histopathological evaluation

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Abstract. The primary sources of reactive oxygen species (ROS) that cause ischemia-reperfusion (I/R) injuries are enzymes xanthine oxidase (XO) and nicotinamide adenine dinucleotide phosphate oxidases (NOXs) in the literature, whereby one of the main ROS producing cells *via* NOX activity are polymophonuclear leukocytes (PNL). Sugammadex, the effect of which we plan to research against gastric I/R damage, is a modified gamma-cyclodextrin that antagonizes the action of steroidal neuromuscular blocking drugs. Previous studies have reported that sugammadex inhibits PNL infiltration. However, it is unknown whether an inhibitory effect on XO is present. We aimed to biochemically and histopathologically investigate the effects of sugammadex on I/R-induced stomach damage in rats. The animals were divided into groups that underwent gastric ischemia-reperfusion (GIR), 4 mg/kg sugammadex + gastric ischemia-reperfusion (SGIR), and a sham operation group (SG). The effect of sugammadex was evaluated by measuring oxidant-antioxidant and PNL parameters. There was no significant difference in XO levels between the SGIR and GIR groups. In the SGIR group, sugammadex inhibited the increase in myeloperoxidase (MPO) and malondialdehyde (MDA) levels ($p < 0.001$). The amount of MDA and MPO in the SGIR group was similar as in the SG group. Sugammadex significantly suppressed the decrease in tGSH levels in the SGIR group ($p < 0.001$). The difference between tGSH levels in the SG and SGIR groups was slight. In the SGIR group, sugammadex significantly suppressed the increase in tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL1-β) levels compared to the GIR group ($p < 0.001$). Additionally, sugammadex corrected histopathological modifications as much as sham group. In conclusion, sugammadex may be beneficial in preventing oxidative stress.

Key words: Sugammadex — Gastric ischemia-reperfusion damage — Xanthine oxidase — MDA — TNF-α

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Introduction

Ischemia is defined as a condition of decreased or complete interruption of blood supply to tissues. Hypoxia occurs in tissues as a result of ischemia (Yapca et al. 2013). Reperfusion is the state of rebbleeding of ischemic tissue. Reperfusion also provides abundant reoxygenation to ischemic tissue with rebbleeding (Suleyman and Ozcicek 2020). Therefore, ischemia/reperfusion (I/R) is characterized by interruption of blood flow to organs followed by restoration of blood flow and reoxygenation (Lv et al. 2021). Some mediators and cytokines that occur during the I/R process can cause a physiopathological process defined as secondary tissue injury. Oxygen delivered to tissues by abundant blood during reperfusion induces the metabolism of hypoxanthine accumulated in tissues by xanthine oxidase (XO) during the ischemia period and causes the production of reactive oxygen species (ROS) (Suleyman and Ozcicek 2020). ROS, known as reperfusion mediators, oxidize lipids from the cell membrane (LPO), producing toxic products such as malondialdehyde (MDA) from lipids (Halladin 2015). The literature has found that the primary enzymes of ROS causing I/R damage are XO and the nicotinamide adenine dinucleotide phosphate oxidase complex (NOX) (Francis and Baynosa 2017). Polymorphonuclear leukocytes (PNL) are the main source of ROS produced by the activity of NOX (Schofield et al. 2013). Activated PNL secretes myeloperoxidase (MPO); MPO oxidizes chloride ions with hydrogen peroxide, resulting in the formation of hypochlorous acid (HOCl), a toxic oxidant (Suleyman et al. 2010). Activated PNLs also secrete proinflammatory cytokines (Choi et al. 2019). Information from the literature suggests that drugs that inhibit XO or PNL activity may be helpful in the treatment of I/R injury.

In the clinic, gastric I/R injury occurs because of a series of events, such as peptic ulcer, vascular rupture, surgical intervention, and hemorrhagic shock (Wu et al. 2015). In our study, sugammadex, whose effect we will test against gastric I/R damage, is a modified gamma-cyclodextrin used to reverse the effect of steroidal neuromuscular blockers (ET 2015). Sugammadex is a drug potentially used to antagonize the effects of nondepolarizing muscle relaxants, particularly rocuronium, and to facilitate emergency neurologic examinations by allowing the return of spontaneous breathing when used shortly after rocuronium administration (Lentz et al. 2021). Sugammadex has been shown to reduce rocuronium-induced allergic inflammation by inhibiting lymphocytic infiltration and alveolar thickening in the lungs (Yesiltas et al. 2021). In the study of Alagöz et al. (2020) sugammadex was reported to significantly inhibit degeneration, vascular congestion, edema, and infiltration of inflammatory cells in lower extremity muscles after an I/R process. Ozbilgin et al. (2016) reported that sugammadex protects brain tissue from I/R damage.

However, no studies have linked the protective effect of sugammadex against I/R-induced tissue damage with its antioxidant activity. Our study aimed to biochemical and histopathological investigation of the effect of sugammadex on I/R-induced gastric injury in rats. In addition, we aimed to determine whether the protective effect of sugammadex against I/R injury was related to the inhibition of XO and PNL activities.

Materials and Methods

Animals

A total of 18 male albino Wistar rats weighing between 280 and 295 g were used for the experiment. The rats were obtained from Binali Yildirim University Medical Experimental Application and Research Center. Before the experiment, the rats were housed and fed in groups at average room temperature (22°C) with 12 h of light and 12 h of darkness under appropriate conditions.

Animal experiments were performed following the National Guidelines for the Use and Care of Laboratory Animals. They were approved by the Local Animal Ethics Committee of Erzincan Binali Yildirim University, Erzincan, Turkey (Ethics Committee Number: 2022/03 Date:31.03.2022).

All surgical procedures were performed under sterile conditions. Anesthesia was provided by intraperitoneal (i.p.) administration of 60 mg/kg ketamine. For uninterrupted continuation of surgical procedures, animals sniffed xylazine at appropriate intervals. Surgical procedures were performed within the appropriate anesthesia period. The period during which the animals are immobilized in the supine position is considered an appropriate anesthetic period for surgical procedures (Demiryilmaz et al. 2014).

Chemicals

The ketamine used for the experiment was obtained from Pfizer Ltd. (Turkey). Sugammadex (200 mg/2 ml injectable solution) was purchased from Sanofi Pharmaceutical Industry (Turkey). Xylazine (10 ml, 100 mg/ml) was purchased from Bioveta PLC (Czech Republic).

Experimental groups

Animals were divided into groups subjected to gastric I/R (GIR), 4 mg/kg sugammadex + gastric I/R (SGIR), and a sham-operated group (SG).

Sugammadex was i.p. injected at a 4 mg/kg dose into the SGIR group's experimental animals. The same method administered distilled water as a solvent to the GIR and SG groups. One hour after administration of sugammadex and distilled water, all animal groups were anesthetized as described above. A laparotomy was performed under anesthesia with a 2.5 cm midline incision, and the stomach was reached. Then, ischemia

was performed for one hour, and reperfusion was performed for three hours by attaching a clip to the celiac artery of the SGIR and GIR animal groups. The abdominal region of the SG group, which was opened without clipping the celiac artery, was closed by suturing (Wada et al. 1996). Immediately after three hours of reperfusion, all animals were killed under high-dose (120 mg/kg) ketamine anesthesia. The biochemical and histopathological examinations were then performed on gastric tissues collected from the euthanized animals. The biochemical and histopathological results of the experiment were compared between the groups and evaluated.

Biochemical analyses

Determination of XO activity

Following the method of Prajda and Weber, the activity of xanthine oxidase (XO, EC 1.1.3.2) was determined according to the principle of spectrophotometric measurement of the increase in absorbance at 293 nm during the formation of xanthine uric acid (Prajda and Weber 1975).

Determination of MDA, MPO, and total glutathione (tGSH) levels

The MDA measurements were based on the method used by Ohkawa et al. (1979) involving spectrophotometric measurement of the absorbance of the pink complex formed by thiobarbituric acid (TBA) and MDA. Serum was mixed with a solution of sodium dodecyl sulfate, acetic acid, 2-thiobarbiturate, and distilled water. The combination was incubated. After cooling the mixture, n-butanol:pyridine was added. The mixture was shaken for 1 min and centrifuged. The absorbance of the supernatant was measured at 532 nm. 1,1,3,3-tetramethoxypropane was used to prepare the standard curve.

The MPO activity was measured according to the modified method of Bradley et al. (1982). H_2O_2 from the phosphate buffer served as the substrate. The test buffer was prepared. Serum/tissue homogenate was added to the assay buffer. MPO activity was measured kinetically at 460 nm for 5 minutes.

The tGSH measurement was performed according to the method described by Sedlak and Lindsay (Sedlak and Lindsay 1968). DTNB (5,5'-dithiobis-[2-nitrobenzoic acid]) disulfide is chromogenic in the medium and is rapidly reduced by DTNB sulfhydryl groups. The yellow color formed upon reduction is measured spectrophotometrically at 412 nm.

Quantification of tissue tumor necrosis factor-alpha (TNF-α) and interleukin 1-beta (IL-1β)

Analysis of TNF-α and IL-1β levels in homogenates obtained from gastric tissue was performed using ELISA immunoassay kits (Cat. No.: YHB1098Ra, Shanghai LZ) according to the manufacturer's instructions.

Histopathological analyses

Subject tissues were fixed in 10% formaldehyde solution for 72 h. After fixation, the tissues were placed in a cassette and washed with running water for 24 h. They were then dehydrated by an increasing series of alcohols (70, 80, 90 and 100%). Gastric tissues purified in xylene were embedded in kerosene blocks, and sections with a thickness of 4–5 microns were taken. The removed sections were stained with hematoxylin-eosin double stain and evaluated and photographed using the Olympus DP2 firmware program SAL (Olympus® Inc. Tokyo, Japan). In serial sections taken, deviations from the typical histological tissue structure were selected for each experimental group by selecting six areas, one central and five marginal, at 100× magnification in six sections; the criteria of mucosal degeneration, vascular dilation/occlusion (occlusion), polymorphonuclear cells, and mucosal edema were scored. Criteria were scored from 0 to 3, where 0 = none, 1 = minor, 2 = moderate, and 3 = severe. Histopathologic evaluation was performed by a double-blind histologic method for the study groups.

Statistical analysis

The biochemical results of the experiments were expressed as the mean ± standard error of the mean (SEM). The Shapiro-Wilk test confirmed the normality of the distribution for continuous variables. The significance of differences between groups was determined using one-way ANOVA. Then, a Tukey HSD (honest significant difference) *post hoc* test was performed. All statistical operations were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, 22.0, and $p < 0.05$ was considered significant. In addition, the histopathological data obtained were analyzed using the program SPSS for Windows 22.0. The difference between the groups was determined by the Kruskal-Wallis test, one of the nonparametric tests, and the group that caused the difference was determined by the Mann-Whitney U test.

Results

Results of the analysis of the amount of XO and MDA in gastric tissue

As shown in Figure 1, the XO level in the gastric tissue of the GIR group that underwent I/R was significantly higher than that of the SG group in the sham operated group ($p < 0.001$). In the SGIR group, in which both I/R and sugammadex were applied, sugammadex failed to suppress the increase in XO

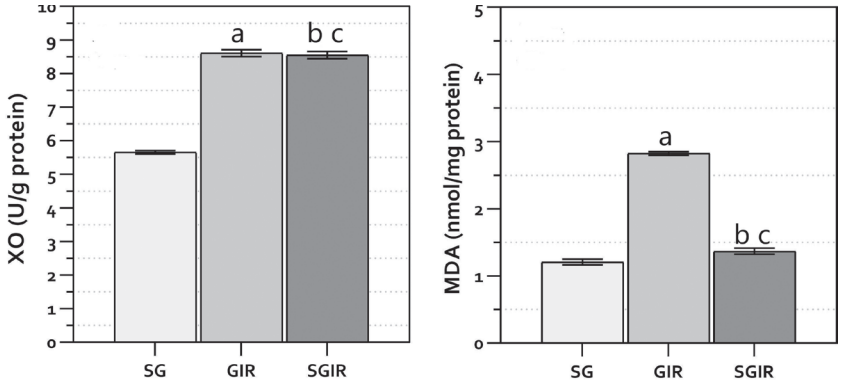

Figure 1. The amounts of XO and MDA in the gastric tissue in the experimental groups. Data are mean ± SEM ($n = 6$). [a] $p < 0.001$ *vs.* SG group, [b] $p < 0.05$ *vs.* SG group, [c] $p < 0.001$ *vs.* GIR group. XO, xanthine oxidase; MDA, malondialdehyde; SG, sham-operated control group; GIR, gastric ischemia-reperfusion group; SGIR, received sugammadex+gastric ischemia-reperfusion group.

levels in the GIR group. There was a statistically significant difference in XO levels between the SGIR and SG groups ($p < 0.001$) and no statistically significant difference in XO levels between the SGIR and GIR groups.

The MDA level in gastric tissue of the GIR group that underwent I/R was statistically significantly higher than that of the SG group ($p < 0.001$). In the SGIR group in which both I/R and sugammadex were administered, sugammadex inhibited the increase in I/R-induced MDA with statistical significance ($p < 0.001$). The amount of MDA in the SGIR group was similar to that in the SG group.

Results of the analysis of the amount of MPO and tGSH in gastric tissue

The MPO levels in the gastric tissue of the GIR group exposed to I/R were significantly higher than those in the SG group ($p < 0.001$) (Fig. 2). Sugammadex significantly suppressed this increase in MPO production in the SGIR group coadministered with I/R and sugammadex ($p < 0.001$). There were no statistically significant differences in MPO levels between the SGIR and SG groups.

The gastric tissue tGSH levels were significantly lower in the GIR group subjected to I/R than in the SG group ($p < 0.001$). In the SGIR group treated with I/R and sugammadex, sugammadex significantly suppressed the decrease in tGSH levels ($p < 0.001$). The difference between tGSH antioxidant levels in the SG and SGIR groups was slight.

Quantification results of TNF-α and IL-1β in gastric tissue

TNF-α and IL1-β levels increased significantly in gastric tissues of the GIR group that underwent I/Rcompared to the SG group ($p < 0.001$) (Fig. 3). In the SGIR group, in which I/R and sugammadex were administered together, sugammadex suppressed this increase in TNF-α and IL1-β levels with statistical significance compared to the GIR group, in which only I/R was applied ($p < 0.001$). In the SGIR group, in which I/R and sugammadex were applied together, TNF-α levels were similar to those of the SG group, which was the sham-operated group, and there was no significant difference between these two groups in terms of IL-1β levels.

Histopathological findings

As shown in Figure 4A and Table 1, histopathological examination of the gastric tissue sections of the SG sham-operated control group revealed the surface epithelium of the *tunica mucosa* and glands and typical gastric stratification and

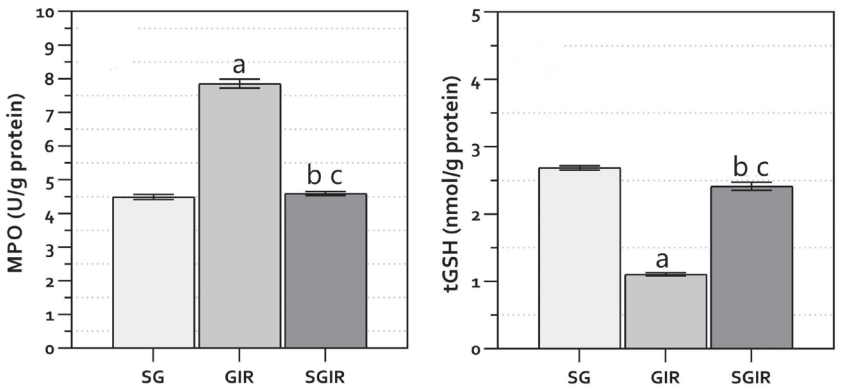

Figure 2. The levels of MPO and tGSH in the gastric tissue in the experimental groups. Data are mean ± SEM ($n = 6$). [a] $p < 0.001$ *vs.* SG group, [b] $p < 0.05$ *vs.* SG group, [c] $p < 0.001$ *vs.* GIR group. MPO, myeloperoxidase; tGSH, total glutathione. For more abbreviations, see Figure 1.

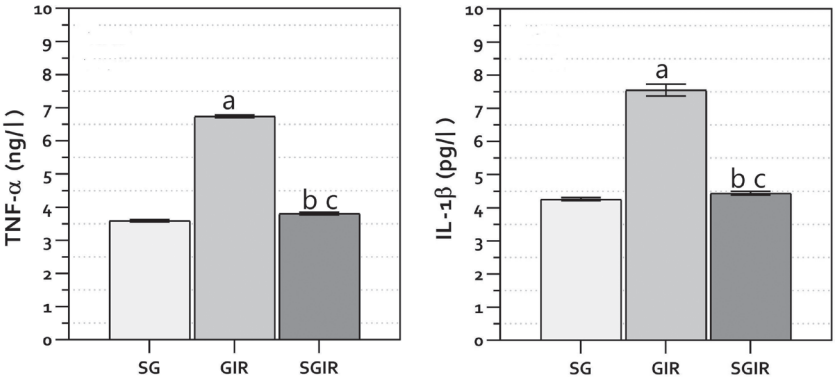

Figure 3. The amounts of TNF-α and IL-1β in the gastric tissue in the experimental groups. Data are mean ± SEM ($n = 6$). [a] $p < 0.001$ *vs.* SG group, [b] $p < 0.05$ *vs.* SG group, [c] $p < 0.001$ *vs.* GIR group. TNF-α, tumor necrosis factor alpha; IL1-β, interleukin one beta. For more abbreviations, see Figure 1.

wall structure typical histological architecture. However, in sections of the GIR group, it was observed that the surface epithelium broke off in places and formed rashes in the lumen, glandular recesses were reduced, the neck regions of the glands were opened, the base regions were moderately edematous, and the blood capillaries showed moderate dilatation and congestion. The specimens from this group also showed heavy infiltration with polymorphonuclear cells in the connective tissue area around the vessels and near the gland bases (Fig. 4B). The evaluation of the samples from the SGIR group treated with sugammadex revealed that the surface epithelium was as expected, the mucosa and gland bases were slightly edematous, the blood vessels were moderately dilated and congested, and the areas around the blood vessels were slightly infiltrated with polymorphonuclear cells (Fig. 4C).

Discussion

Although previous studies have evaluated numerous experimental agents for their protective effects in global I/R models, many are inaccessible, difficult to use, or not approved for regular clinical practice. Several studies have

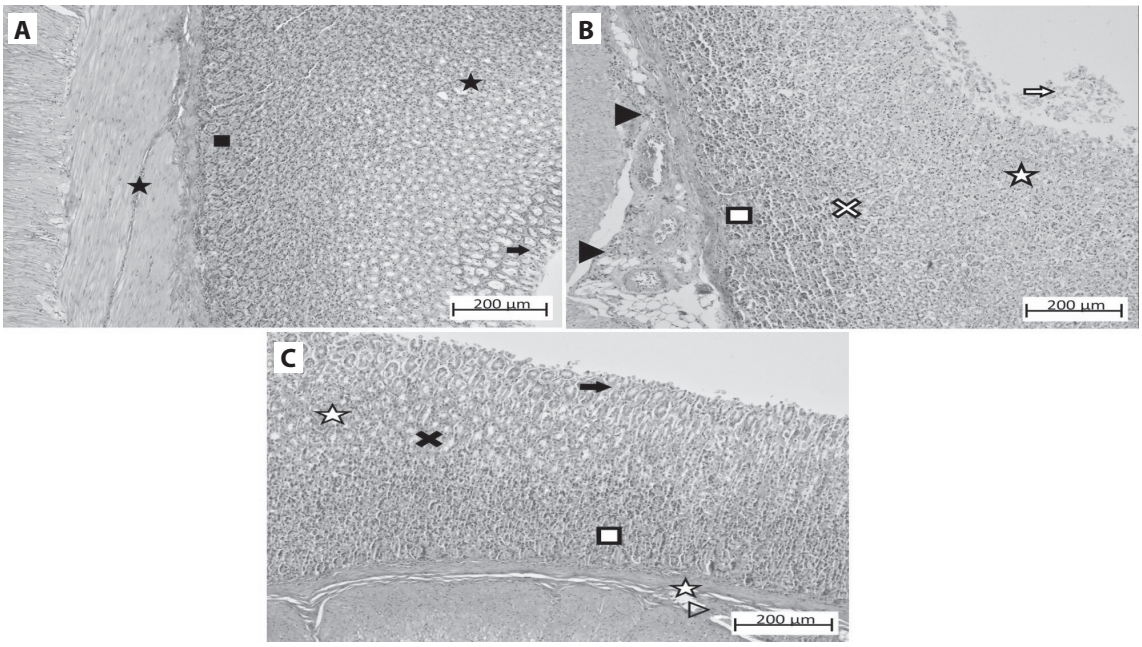

Figure 4. Hematoxylin-eosin staining in the gastric tissue of the SG control group (**A**), the GIR group (**B**) and the SGIR group (**C**). (HE ×100). ➡ normal surface epithelium, ■ gastric glands; ★ blood vessel, ⇨ locally exfoliated and degenerated surface epithelium, ◘ edematous gastric glands, ✖ mild edema of the mucosa, ▶ severe polymorphonuclear cell infiltration, ☆ moderately dilated and congested blood vessel, ◘ slightly edematous gastric glands, ▷ weak polymorphonuclear cell infiltration. For more abbreviations, see Figure 1.

Table 1. Effect of sugammadex on gastric ischemia-reperfusion injury-induced histopathological damage

		Group		
		SG	GIR	SGIR
Mucosal degeneration	median (Min–Max)	0.00 (0–0)[a]	2.25 (1.33–2.83)[b]	0.67 (0–1.17)[a,b]
	mean ± SEM	0.00 ± 0.00	2.11 ± 0.25	0.64 ± 0.16
Dilation/Congestion	median (Min–Max)	0.00 (0–0)[a]	2.50 (2.5–3.00)[b]	2.00 (1.33–2.00)[a,b]
	mean ± SEM	0.00 ± 0.00	2.64 ± 0.09	1.83 ± 0.11
PNL cell infiltration	median (Min–Max)	0.00 (0–0)[a]	2.67 (2.33–3.00)[b]	0.83 (0.00–1.50)[a,b]
	mean ± SEM	0.00 ± 0.00	2.69 ± 0.12	0.81 ± 0.27
Mucosal edema	median (Min–Max)	0.00 (0–0)[a]	1.83 (1.00–2.83)[b]	0.75 (0.00–1.17)[a,b]
	mean ± SEM	0.00 ± 0.00	1.89 ± 0.32	0.64 ± 0.19

[a,b] groups marked with the same letter are statistically similar, but there is a statistically significant difference at the level of $p < 0.05$ among groups with different letters. Min–Max, minimum and maximum; PNL, polymorphonuclear leukocyte; SG, sham-operated control group; GIR, gastric ischemia-reperfusion group; SGIR, received sugammadex+gastric ischemia-reperfusion group.

been conducted to determine the extent of neuroprotective effects and the impact of volatile inhalants on brain metabolism and neurological outcomes. These results suggest that the neuroprotective effects of volatile agents may be related to factors such as activation of ATP-dependent potassium channels, upregulation of nitric oxide synthase, reduction of excitotoxic stressors, cerebral metabolic rate, improvement of periischemic cerebral blood flow, upregulation of antiapoptotic factors and mitogen-activated protein kinases (Matchett et al. 2009). The neuroprotective effect of dauricin after cerebral I/R injury was demonstrated by researchers. They proposed that the mechanism of the neuroprotective effect of dauricine after cerebral I/R injury is related to the suppression of neuronal cell death in the penumbra (Yang et al. 2009). Reactive oxygen species play an essential role in neuronal cell death after cerebral ischemia. Punicalagin is an antioxidant with neuroprotective properties against ROS (Yaidikar et al. 2014).

Anesthetics such as ketamine and propofol have been reported to have antioxidant and protective effects in various organs, especially the kidney and brain (Xing et al. 2022; Zhu and Zhang 2022). As mentioned earlier, many studies in the literature examine the harmful or protective effects of many anesthetics on other organs. While organs such as the kidneys and brain are often considered in the literature, the effect of drugs used in anesthetic practice on I/R injury, particularly in the stomach, is of great interest.

In recent years, the frequency of use of sugammadex, a life-saving drug, has flourished in difficult airways. Clinics that routinely use neuromuscular blockers as antagonists are also not uncommon. In our study, we investigated the effect of sugammadex on gastric-induced I/R injury. Although evidence-based information on the organ-protective effects of anesthetics used in the past and today exists, scientific data on next-generation drugs are sparse. Sugammadex, a modified g-cyclodextrin molecule, has been used in clinical neuromuscular pharmacology (Ozbilgin et al. 2016). The distinct molecular structure of sugammadex encapsulates the neuromuscular blocker rocuronium and removes it from the muscle-nerve junction, selectively and rapidly reversing neuromuscular blockade (Ozbilgin et al. 2013).

There are studies on the effects of sugammadex on organs. In particular, the effect on the central nervous system has been studied frequently. Many cyclodextrin groups protect cortical neurons grown in the absence of normal calcium signaling from glutamate excitotoxicity, N-methyl-d-aspartate (NMDA), and oxygen-glucose deprivation and exhibit neuroprotective properties (Rivers et al. 2012; Yao et al. 2012). Sugammadex increases the production of monoclonal cytochrome *c* protein, apoptosis-inducing factor (AIF), and caspase 3 (CASP-3) proteins in cell cultures. Palanca et al. hypothesized that the effect of sugammadex might be related to oxidative stress, which alters cholesterol homeostasis and triggers apoptotic activation (Palanca et al. 2013). Another study showed that 100 mg/kg sugammadex administered at the beginning of reperfusion after one hour of ischemia in rats had a histopathologically detectable nephroprotective effect, suggesting that sugammadex may protect against renal injury (Tercan et al. 2021).

Sugammadex exerts its protective effects on the brain and kidney by preventing oxidative stress and apoptosis. In our study, sugammadex was found to have both anti-inflammatory and antioxidant effects on MPO. Many chemical agents have been studied for their effects on I/R injury in the stomach. Melatonin, zinc, estrogen, and progesterone complexes can prevent gastric damage through their antioxidant properties (Keshavarzi et al. 2018; Mubarak et al. 2018; Akbari 2020).

In these studies, the I/R model used in the stomach shows differences. Keshavarzi et al. (2018) provided the I/R model in their study by clamping the celiac artery for 30 minutes and then allowing perfusion for 24 hours. In contrast,

Mubarak et al. (2018) provided an I/R model that allowed perfusion of the celiac artery for 1 hour after clamping for 30 minutes. Our study investigating the effect of sugammadex on gastric I/R injury found that TNF-α and IL-1β levels decreased statistically significantly in our study group. We showed the anti-inflammatory effect of sugammadex. However, we found that the increase in XO levels was not suppressed by sugammadex. While we found a decrease in another oxidative parameter, it also caused an increase in the levels of antioxidant parameters, such as tGSH. In the study by Kuyrukluyildiz et al. (2021), investigating the protective effect of dexmedetomidine on the stomach, levels of oxidants such as MDA and MPO decreased in the dexmedetomidine-treated group; they found that tGSH and SOD decreased. Therefore, biochemically and histopathologically demonstrated that the I/R process causes oxidative damage in gastric tissues, and dexmedetomidine was found to prevent oxidative damage in the stomach by increasing antioxidant activity.

Kip et al. (2015) found significantly more inflammation, degeneration/necrosis, tubular dilation, tubular cell degeneration, Bowman space dilation, tubular hyaline eruptions, and lymphocyte infiltration in the 96 mg/kg sugammadex group. Sugammadex 96 mg/kg had higher tissue MDA levels and lower NO activity. In the study by Ozbilgin et al. (2016), sugammadex 16 mg and 100 mg were administered in the cerebral I/R model, and compared to the I/R group, the observed increases in the values of TAS, GPx, SOD and MDA were not statistically significant. They also found no statistically significant difference between the values of these parameters and the sham group. In our study, sugammadex did not cause changes in NO activity. While MPO and MDA levels decreased, tGSH levels were high.

In a study using sugammadex to treat verapamil intoxication, sugammadex was administered at a 16 mg/kg dose and demonstrated antioxidant activity (Tulgar et al. 2016). In the studies of Tomak et al. (2012), the effects on mast cell degranulation were investigated by using sugammadex at doses of 16 mg/kg and 100 mg/kg. In our study, sugammadex was administered at 4 mg/kg, similar to the usual application dose in clinical practice. Its anti-inflammatory and antioxidant effects were demonstrated in gastric tissue.

Histopathological examination of gastric tissue has also been studied. Kalkan et al. (2012a) reported that the rocuronium-sugammadex compound caused edema and degeneration in the diaphragm and myocardial cells. Rocuronium and sugammadex are long-term drugs that can cause skeletal muscle myopathy, vacuolization, pyknotic nuclear aggregates, hypertrophy, and fiber weakness. Alagöz et al. (2020) did not observe significant histopathological changes in the group in which they administered sugammadex at a dose of 4 mg/kg, but in the group in which it was administered at a dose of 16 mg/kg, they found widespread disorganization of muscle fibers, degeneration, and openings between muscle fibers. Vascular congestion and widespread infiltration of inflammatory cells occurred between the muscle fibers. Boston et al. (2011) reported that rats given rocuronium and high doses of sugammadex (96 mg/kg) exhibited enhanced glomerular vacuolation compared with control group tubular dilation, vascular vacuolation, hypertrophy, lymphocyte infiltration, and tubular cell sloughing. Another study showed that high-level sugammadex-rocuronium complexes accumulate little histopathologically in testicular tissue. Long-term circulation of rocuronium-sugammadex complexes reduced interstitial space, testis size, germ cell, and Leydig cell populations (Kalkan et al. 2012b). In our study, we found that the surface epithelium was as expected, with mild edema in the mucosa and glandular bases, moderate dilation of the blood vessels, congestion, and mild infiltration of polymorphonuclear cells in the areas around the blood vessels in the SGIR group that received sugammadex after I/R injury.

In conclusion, we believe that sugammadex, which is increasingly used in clinical practice, may be beneficial due to its anti-inflammatory and antioxidant effects in preventing oxidative stress-induced damage resulting from ischemia and reperfusion but not over the XO pathway. However, this mechanism should also be substantiated by clinical trials.

Conflicts of interest. We have no conflicts of interest to declare.

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