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Antiulcerative effect of dexmedetomidine on indomethacin-induced gastric ulcer in rats

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Abstract:
A gastroprotective effect occurs when α_2 receptors are innervated. The dextro isomer of medetomidine, dexmedetomidine, is a highly selective α_2-adrenoreceptor agonist. The aim of this study was to investigate whether dexmedetomidine has an antiulcerative effect and to show whether the antiulcer mechanism of dexmedetomidine is linked with oxidant/antioxidant parameters. The antiulcerative effect of dexmedetomidine was studied in an indomethacin-induced ulcer model, and some oxidant/antioxidant parameters were measured in these gastric tissues. Whereas the average ulcerous areas for the groups that received 10, 25, 50, and 100 μg/kg dexmedetomidine doses were 29 ± 4.2, 8 ± 2.1, 0 ± 0 and 0 ± 0 mm^2, respectively, the ulcerous area was 52.1 ± 4.5 mm^2 in the indomethacin control group and 0.5 ± 0.2 mm^2 in the famotidine group. In conclusion, the α_2-adrenoreceptor agonist dexmedetomidine showed a significant antiulcerative effect in rat gastric tissue at all doses. This antiulcerative effect is stronger with increasing dosage; at the 50 and 100 μg/kg doses, no ulcerous areas were observed. In light of these results, we conclude that there is a correlation between antiulcer mechanisms and α_2-receptor activation. In rats given dexmedetomidine, all of the investigated antioxidant parameters increased, except for catalase (CAT). Conversely, aside from myeloperoxidase (MPO), all oxidant parameters decreased. Therefore, oxidant/antioxidant parameters play a role in the antiulcer mechanism of dexmedetomidine.

Key words:
dexmedetomidine, indomethacin, oxidant/antioxidant parameters, rat

Introduction

The dextro isomer of medetomidine, dexmedetomidine, is a highly selective α_2-adrenoreceptor agonist [35]. Other α_2-adrenoreceptor agonists include clonidine, brimonidine, guanfacine, guanabenz, methyldopa and tizanidine, all of which are known to have both central and peripheral effects [41]. Whereas presynaptic activation of α_2-adrenoreceptors in sympathetic nerve endings inhibits catecholamine release, the postsynaptic activation of α_2-adrenoreceptors in the central nervous system leads to inhibition of sympathetic activity and decreased blood pressure and heart rate [22, 29]. Suleyman et al. have shown that a gastroprotective effect occurs when α_2-receptors are innervated [38]. In other studies, it was shown that presynaptic α_2-adrenergic receptors play inhibitory roles in indomethacin-, aspirin-, stress-, and pyloric

ligation-induced ulcers [9, 12, 26]. α_2-Receptor subtypes such as α_{2A}-, α_{2B}-, and α_{2C}- have different functions: the α_{2A}-receptor is responsible for gastric emptying and increased motor activity, whereas the α_{2B}- and α_{2C}-receptors are responsible for gastroprotection [16, 19]. Reduced gastric secretions and motility also arise *via* the suppression of cholinergic activity [6]; cholinergic activity has been shown to be depressed by the activation of presynaptic α_2-adrenoreceptors in the vagus nerve as a result of the inhibition of acetylcholine release [16]. Gyires et al. have reported that the gastroprotective effect of α_2-adrenoreceptors develops *via* multiple mechanisms [19], and Kumtepe et al. have shown that one of these mechanisms is an increase in antioxidant parameters and decreases of oxidant parameters [25, 38].

A reduction in antioxidant levels and an increase in oxidant levels exhibit a correlation with the degree of damage to gastric tissue [7]. The inhibition of α_2-receptors with yohimbine shows an opposite effect in this regard [25]. A number of various diseases are associated with increased oxidative stress due to the formation of reactive oxygen [8, 17].

To our knowledge, there has been no prior study addressing the antiulcerative effect of dexmedetomidine. A thorough review of the literature, however, showed that dexmedetomidine inhibits gastrointestinal transit and gastric emptying [3].

The aim of this study was to investigate whether dexmedetomidine has an antiulcerative effect, and if so, to determine whether the antiulcer mechanism of dexmedetomidine is linked with oxidant/antioxidant parameters.

Materials and Methods

Animals

A total of 42 male albino Wistar rats obtained from the Medical Experimental Research Centre, Ataturk University, weighing between 200 and 220 g, were used in this study. The animals were fed under normal conditions (22°C) in 7 separate groups consisting of 6 rats. Animal experiments were performed in accordance with national guidelines for the use and care of laboratory animals and approved by the local animal care committee of Ataturk University.

Chemicals

For laboratory experimentation, indomethacin, famotidine, and sodium thiopental were obtained from Deva Holding A.S. (Istanbul), Fako (Istanbul) and IE-Ulagay (Istanbul), respectively, and dexmedetomidine was purchased from Abbott Co., UK.

Test for effects of dexmedetomidine on indomethacin-induced ulcers in rats

We investigated the antiulcerative effect of dexmedetomidine using an indomethacin-induced ulcer model in rats [18]. Dexmedetomidine was administered intraperitoneally at 10, 25, 50 and 100 μg/kg dosages in distilled water to groups of rats fasted for 24 h. At the same time, 20 mg/kg famotidine in distilled water was given to a fifth group of rats fasted for 24 h. After 5 min, 25 mg/kg indomethacin was given to each rat in all groups (10, 25, 50 and 100 μg/kg dexmedetomidine groups, 20 mg/kg famotidine group and indomethacin control group) by oral gavage in distilled water. An identical volume of distilled water was given to the healthy group. Six hours after the indomethacin administration, all groups (including the healthy group) were sacrificed by administering a high dose (50 mg/kg) of thiopental anesthesia. The stomachs of the rats were removed, and ulcerous regions were examined macroscopically. Ulcerous areas were measured on millimeter paper. The antiulcerative activity of dexmedetomidine was evaluated by comparison with the results obtained from the control and the famotidine (20 mg/kg) groups.

Biochemical analyses

After the macroscopic analyses, we determined glutathione peroxidase, catalase, superoxide dismutase and myeloperoxidase enzyme activities and the amounts of malondialdehyde and glutathione in stomach tissues. To prepare the tissue homogenates, stomach tissue was ground with liquid nitrogen in a mortar. Approximately 0.5 g tissue for each rat was treated with 4.5 ml of an appropriate buffer. This mixture was homogenized on ice using an Ultra-Turrax homogenizer for 15 min. Homogenates were filtered and centrifuged at 4°C. The supernatants were used for the determination of enzymatic activities. All assays were carried out at room temperature.

Glutathione peroxidase (GPO) activity

GPO activity was determined according to the method of Lawrence and Burk [27]. The absorbance at 340 nm was recorded for 5 min, and the activity was defined as the rate of NADPH oxidation (mmol/min/mg tissue).

Catalase (CAT) activity

Decomposition of H_2O_2 in the presence of CAT was measured at 240 nm [1]. CAT activity was defined as the amount of enzyme required to process 1 nanomole of H_2O_2 per min at 26°C and pH 7.8. Results are expressed as mmol/min/mg tissue.

Superoxide dismutase (SOD) activity

SOD activity was measured according to Sun et al. [39]. Estimates were based on the generation of superoxide radicals produced by xanthine and xanthine oxidase, which react with nitroblue tetrazolium (NBT) to form formazan dye. SOD activity was then measured at 560 nm by relation to the degree of inhibition of this reaction; SOD activity is expressed as mmol/min/mg tissue.

Myeloperoxidase (MPO) activity

MPO activity was measured according to the method of Bradley et al. [5]. The homogenized samples were frozen and thawed three times and then centrifuged at 1,500 rpm for 10 min at 4°C. MPO activity in the supernatant was determined by adding 100 ml of the supernatant to 1.9 ml of 10 mmol/L phosphate buffers (pH 6.0) and 1 ml of 1.5 mol/L o-dianisidine hydrochloride containing 0.0005% w/v hydrogen peroxide. The changes in absorbance at 450 nm of each sample were recorded using a UV-visible spectrophotometer. MPO activity in tissues is expressed as μmol/min/mg tissue.

Determination of lipid peroxidation (malondialdehyde (MDA) measurement)

The level of gastric mucosal lipid peroxidation was determined by estimating MDA concentrations using the thiobarbituric acid test [34]. Rat stomachs were immediately excised and rinsed with cold saline. To minimize the possibility of interaction of hemoglobin with free radicals, any blood adhering to the mucosa was carefully removed. The corpus mucosa was scraped, weighed and homogenized in 10 ml of 100 g/l KCl. The homogenate (0.5 ml) was added to a solution containing 0.2 ml of 80 g/l sodium lauryl sulfate, 1.5 ml of 200 g/l acetic acid, 1.5 ml of 8 g/l 2-thiobarbiturate and 0.3 ml distilled water. The mixture was incubated at 98°C for 1 h. Upon cooling, 5 ml of n-butanol:pyridine (15:1, v/v) was added. The mixture was vortexed for 1 min and centrifuged for 30 min at 4000 rpm. The supernatant was measured at 532 nm. The standard curve was obtained by using 1,1,3,3-tetramethoxypropane. Recovery was over 90%. All samples were measured in duplicate. The results are expressed as nanomoles of MDA per gram wet tissue (nmol/g tissue).

Total glutathione (GSH) determination

The amount of GSH in the gastric mucosa was measured according to the method described by Sedlak and Lindsay [36]. The mucosal surface of the stomach was collected by scraping, weighed, and homogenized in 2 ml of 50 mM Tris–HCl buffer containing 20 mM EDTA and 0.2 M sucrose, pH 7.5. The homogenate was centrifuged. After centrifugation at 4,200 rpm for 40 min at 4°C, the levels of GSH were determined in the supernatant using DTNB [5,5'-dithiobis(2-nitrobenzoic acid)]. Absorbance was measured at 412 nm using a spectrophotometer. The results of the GSH level in the gastric mucosa are expressed as nmol/mg tissue.

Statistical analyses

All data were analyzed by one-way ANOVA using SPSS 13.0 software. Differences among groups were obtained using the LSD option and Duncan test, and significance was declared at $p < 0.05$.

Results

Effects of dexmedetomidine on indomethacin-induced ulcers

Macroscopic examination showed ulcerous areas in the stomachs of all rats in the dexmedetomidine 10 and 25 μg/kg groups and in the control group (25 mg/kg indomethacin group). The number and size of the ulcerous areas were determined. In all rats, the

ulcer focus was composed of mucosal defects that were circular and/or oval shaped and dispersed to all stomach surfaces. Ulcer edges were clear, and a blister was observed on the edge. Hyperemia in the stomachs of the control group was clearer than in all the chronic indomethacin groups. As seen in Table 1, the average ulcerous area decreased with increasing dexmedetomidine dose. Ulcers were absent at dexmedetomidine doses of 50 and 100 μg/kg. At these doses, the antiulcer effects of dexmedetomidine are similar to those of famotidine.

Biochemical analyses

GPO, CAT, and SOD analyses

As seen in Table 2, GPO and SOD activities were significantly increased by famotidine and by all doses of dexmedetomidine when compared to activity levels in the indomethacin control group. At 100 μg/kg dexmedetomidine, while the antioxidant activities of both GPO and SOD were higher than at 20 mg/kg famotidine; GPO, but not SOD, activity was significantly higher than in controls. The CAT activity was significantly decreased by famotidine and all doses of dexmedetomidine when compared to activity levels in the indomethacin control group. Among all dexmedetomidine doses and in the famotidine treatment, 100 μg/kg dexmedetomidine decreased CAT activity the most. At this dose, CAT activity was significantly lower than in the healthy rat group.

MPO, MDA, and GSH analyses

As shown in Figure 1, the MPO activity was significantly increased by treatment with 25, 50 and 100 μg/kg dexmedetomidine when compared to activity in the indomethacin control group. MPO activity was the highest in the 100 μg/kg dexmedetomidine group. MPO activity was similar in the famotidine and

Tab. 1. Effects of different doses of dexmedetomidine administration on indomethacin-induced ulcers in rat stomach

Drugs	Dose	N	Ulcer area mm^2	Anti-ulcer effect %	p
Dexmedetomidine	10 μg/kg	6	29 ± 4.2	44.3	< 0.0001
Dexmedetomidine	25 μg/kg	6	8 ± 2.1	84.6	< 0.0001
Dexmedetomidine	50 μg/kg	6	0 ± 0	100	< 0.0001
Dexmedetomidine	100 μg/kg	6	0 ± 0	100	< 0.0001
Famotidine	25 mg/kg	6	0.5 ± 0.2	99.0	< 0.0001
Control (indomethacin)	25 mg/kg	6	52.1 ± 4.5	–	–

Tab. 2. Effects of dexmedetomidine and famotidine on the activities of glutathione peroxidase (GPO), catalase (CAT) and superoxide dismutase (SOD) in rat gastric tissue. Means in the same column by the same letter are not significantly different by the Duncan test ($\alpha = 0.05$)

Drugs	N	GPO activity (mmol/min/mg tissue)	CAT activity (mmol/min/mg tissue)	SOD activity (mmol/min/mg tissue)
Dexmedetomidine (10 μg/kg)	6	4.5 ± 0.2b	96.6 ± 0.5e	107.7 ± 0.8b
Dexmedetomidine (25 μg/kg)	6	5.6 ± 0.2c	85.5 ± 0.5d	121.3 ± 2.7c
Dexmedetomidine (50 μg/kg)	6	6.9 ± 0.1d	73.0 ± 0.4b	133.0 ± 0.1d
Dexmedetomidine (100 μg/kg)	6	9.8 ± 0.2e	62.6 ± 0.7a	143.1 ± 0.1e
Famotidine (25 mg/kg)	6	4.7 ± 0.1b	79.8 ± 0.5c	136.8 ± 0.1d
Control (indomethacin 25 mg/kg)	6	2.9 ± 0.1a	107.6 ± 0.6f	98.0 ± 1.07a
Healthy	6	7.1 ± 0.1d	79.4 ± 0.6c	143.1 ± 1.5e

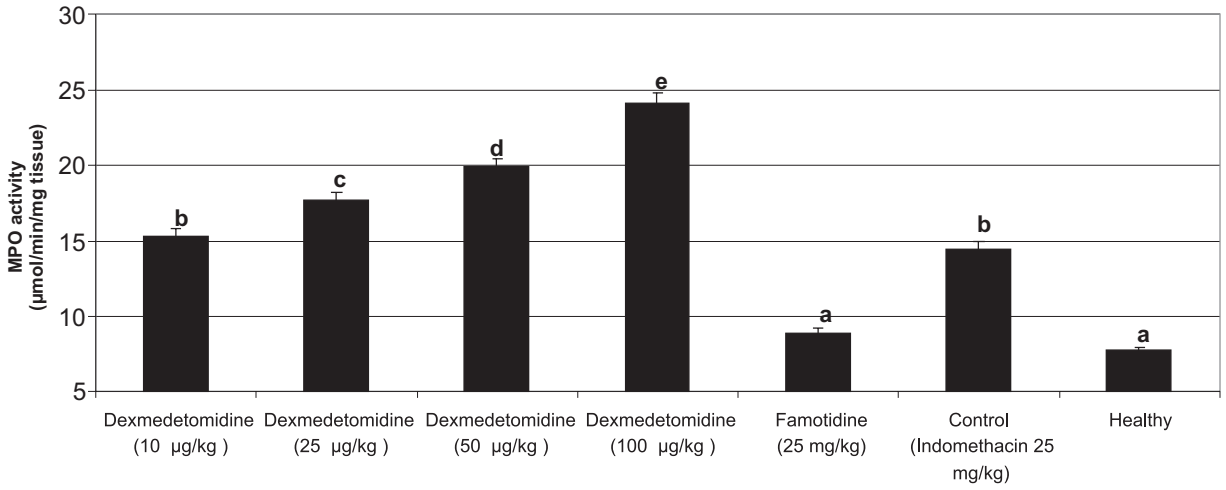

Fig. 1. Effects of dexmedetomidine and famotidine treatments on the activity of myeloperoxidase (MPO) in indomethacin-induced ulcer model in rat gastric tissue. Means in the same column by the same letter are not significantly different by the Duncan test (α = 0.05). Results are the means ± SE of three measurements. (N = 6)

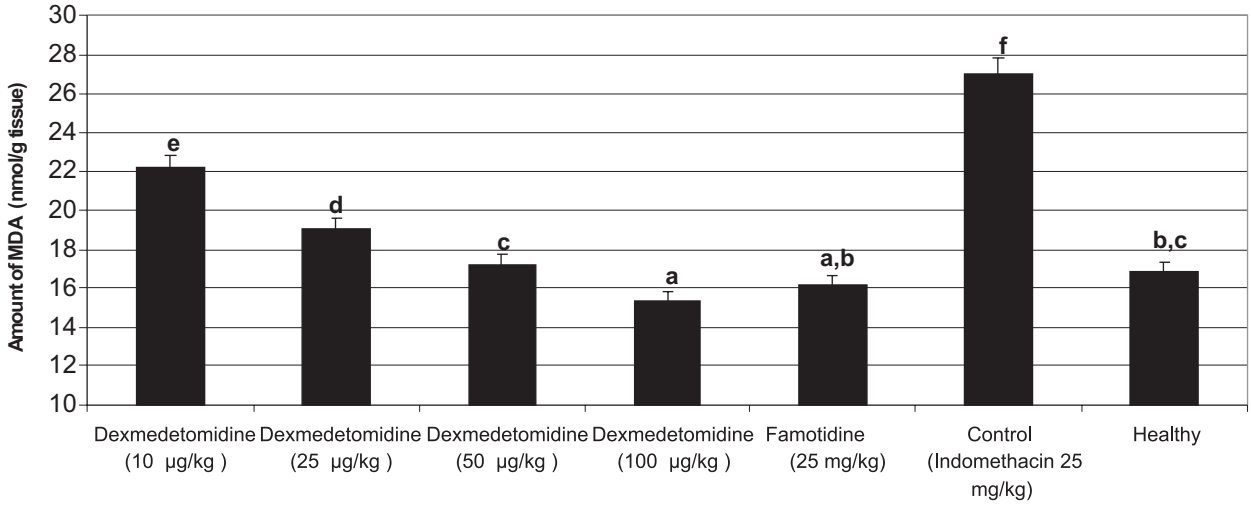

Fig. 2. Effects of dexmedetomidine and famotidine treatments on the level of lipid peroxidation (malondialdehyde (MDA) level) in indomethacin-induced ulcers in rat gastric tissue. Means in the same column by the same letter are not significantly different by the Duncan test (α = 0.05). Results are the means ± SE of three measurements. (N = 6)

healthy rat groups and was significantly lower than indomethacin controls in both of these groups.

The level of MDA was significantly decreased by all doses of dexmedetomidine when compared to the indomethacin control group (Fig. 2). Among all dexmedetomidine treatment groups, rats treated with 100 µg/kg dexmedetomidine showed the lowest MDA levels. The MDA level of the famotidine, dexmedetomidine 100 µg/kg and healthy rat groups were similar and significantly lower than those recorded in the indomethacin control group.

GSH levels were significantly increased by all doses of dexmedetomidine when compared to results from the indomethacin control group (Fig. 3). The level of GSH was the highest in the 100 µg/kg dexmedetomidine group. GSH levels in the famotidine and healthy rat groups were significantly higher than in the indomethacin control group.

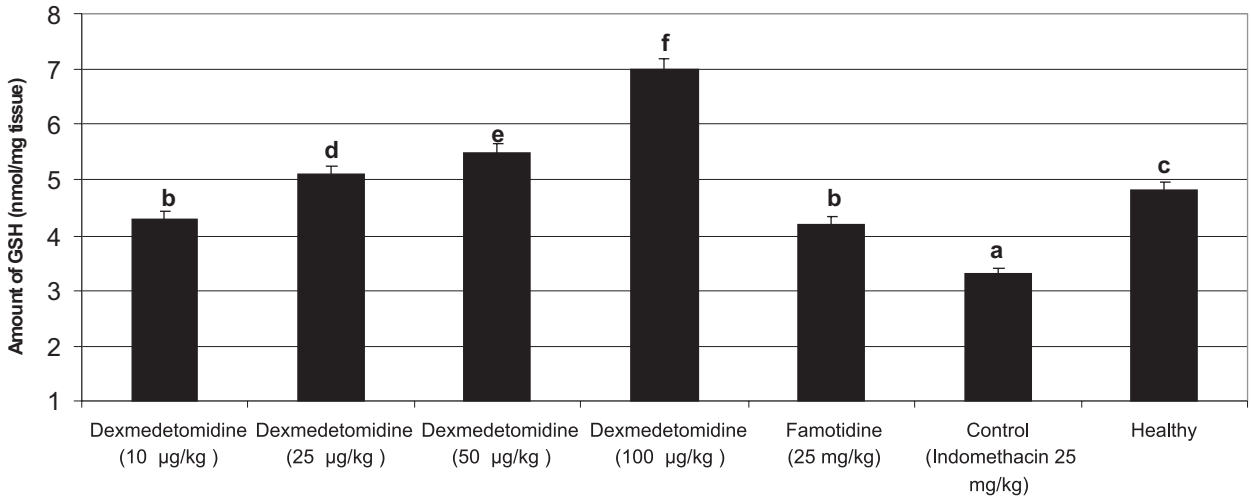

Fig. 3. Effects of dexmedetomidine and famotidine treatments on level of total glutathione (GSH) in indomethacin-induced ulcers in rat gastric tissue. Means in the same column by the same letter are not significantly different by the Duncan test ($\alpha = 0.05$). Results are the means ± SE of three measurements. (N = 6)

Discussion

This study investigated whether four different doses (10, 25, 50, and 100 µg/kg) of dexmedetomidine, a selective α_2-adrenoreceptor agonist, have antiulcerative effects in an indomethacin-induced ulcer model in rats. The antiulcerative effects of dexmedetomidine were compared to those of 25 mg/kg famotidine, an H_2-receptor blocker. In addition, the roles of oxidant and antioxidant parameters were evaluated in existing antiulcer mechanisms. We found no ulcerous areas in rat gastric tissue after the administration of 50 or 100 µg/kg dexmedetomidine. Additionally, at lower doses (10 and 25 µg/kg), dexmedetomidine significantly inhibited indomethacin-induced ulcers. Thus, except for the dose of 10 µg/kg, all doses of dexmedetomidine were almost as effective as famotidine in preventing ulcers.

The sympathetic nervous system is important in ulcer etiology, and numerous studies have addressed its function in this regard [38]. In the sympathetic (adrenergic) nervous system, three subtypes of α_2-adrenergic receptors are responsible for gastric emptying and increased motor activity (α_{2A}) and gastroprotection (α_{2B} and α_{2C}) [16, 19]. Central, not peripheral, α_{2B}-adrenoreceptors are involved in gastric mucosal protection [20]. In other studies, it was shown that yohimbine, an α_2-adrenoreceptor blocker, contributed to ulcer formation [38], whereas clonidine, an α_2-adrenoreceptor agonist, prevented ulcers [24]. Thus, α_2-receptor activation is correlated with gastroprotection. Here, we showed that another α_2-receptor agonist, dexmedetomidine, significantly prevented ulcer formation in rat gastric tissue. In addition, we observed that the antiulcerative effect of dexmedetomidine was dose-dependent. Our review of the literature found no prior data regarding the antiulcerative effect of dexmedetomidine.

Experimental studies have shown that reactive oxygen species (ROS) play roles in indomethacin- or other agent-induced gastric mucosal damage [7, 37]. Agents such as indomethacin initiate lipid peroxidation by functioning as oxidants and cause damage by producing ROS [33, 42]. A number of enzymatic and non-enzymatic defense mechanisms reduce or prevent ROS-mediated damage: SOD, CAT, GPO, and GSH [5].

It has been reported that SOD activity in rat gastric tissue is reduced by NSAIDs [37], and our results agree with this finding. SOD plays an important role in the prevention of gastric damage by turning superoxide, a highly reactive radical, into the less reactive hydrogen peroxide, which can be broken down by CAT. In our study, we also observed that indomethacin reduced SOD activity, suggesting that the superoxide radical cannot be converted to hydrogen peroxide by SOD. However, indomethacin increased CAT

activity, while decreasing SOD activity. As mentioned above, because indomethacin can act as an oxidant [31], the activity of SOD is decreased by indomethacin. On the other hand, the indomethacin-induced decrease in SOD activity causes an increase in CAT activity. The increase in CAT activity points to an increase in hydrogen peroxide levels. It has also been reported that superoxide radicals are converted into hydrogen peroxide and peroxyl radicals spontaneously at acidic pH levels; this spontaneous dismutation is very rapid at pH 4.8 [28]. In addition, superoxide and perhydroxyl radicals can react with each other. At the end of this dismutation, hydrogen peroxide and superoxide may form. CAT is a highly reactive enzyme that reacts with hydrogen peroxide to produce water and molecular oxygen [5, 14, 15, 36]. In our study, famotidine and all doses (10, 25, 50, and 100 μg/kg) of dexmedetomidine significantly reduced CAT activity. As the dose of dexmedetomidine increased, CAT activity was reduced. In contrast, CAT activity increased significantly in the control group administered indomethacin.

In this study, we also showed that SOD activity is significantly reduced by indomethacin. We observed that all doses of dexmedetomidine and famotidine increased this activity. Higher SOD activity levels were correlated with increasing dexmedetomidine dose. This result suggests that the observed reduction in hydrogen peroxide levels was a result of SOD activity increased by dexmedetomidine. As a consequence of reduced hydrogen peroxide, we observed a reduction in CAT activity. Our results were in accordance with those of Dengiz et al. [11].

GSH and GSH-bound enzymes in tissues, especially GPO, have been proposed as potential chemopreventive agents due to their antioxidant and detoxification properties [30]. It has been suggested that these antioxidants play protective roles in the control of indomethacin-induced damage; furthermore, it has been reported that the levels of these antioxidant parameters are reduced in gastric tissues administered indomethacin [13]. Our results are in accordance with those of earlier studies on GSH levels in damaged and healthy tissues [11]. GSH and other antioxidant substances (melatonin, vitamins) inhibit tissue damage by maintaining lower levels of ROS at determined concentrations [2]. In this study, we observed that 25 mg/kg of indomethacin significantly reduced GPO activity and GSH levels compared with the healthy rat group. When 10, 25, 50, or 100 μg/kg dexmedetomidine was given with indomethacin, these antioxidants increased significantly compared with the group given indomethacin alone. This effect was positively correlated with dexmedetomidine dosage. In the group administered famotidine, the levels of these parameters were high compared with the indomethacin group. These data indicate that dexmedetomidine prevents gastric tissue damage by activation of antioxidative defense mechanisms and increasing the activity of antioxidant enzymes, and not by acting directly as an antioxidant.

Neutrophil infiltration of gastric mucosal tissues is controlled by the enzyme MPO; for this reason, MPO is accepted as an indicator of neutrophil infiltration in experimental gastric damage [4, 21]. A significant increase in the MPO activity was observed in the gastric tissues of indomethacin-treated rats compared to healthy rats. This increase in MPO level corresponded to an increase in neutrophil infiltration of indomethacin-damaged gastric tissue. The secretion of MPO by gastric cells is used as an indicator of ulcer degree, and antiulcer drugs generally show their effects by inhibiting the MPO pathway [31]. However, here, the antiulcerative effect of dexmedetomidine is produced *via* another mechanism. It has been shown that acidic environments increase MPO enzyme activity [23, 32]. Thus, dexmedetomidine also increased MPO activity as a result of the hydrochloric acid in its structure. For this reason, all doses of dexmedetomidine, except 10 μg/kg, significantly increased MPO activity compared with the indomethacin group. In the famotidine group, MPO activity decreased significantly compared with the indomethacin group.

Lipid peroxidation in the gastric tissue of the indomethacin group also increased significantly compared with the healthy rat group. All doses of dexmedetomidine significantly decreased the MDA levels in gastric tissue when compared to controls. In the gastric tissue of the famotidine group, MDA levels showed a significant decrease compared with the indomethacin group. It is known that toxic oxygen radicals stimulate lipid peroxidation in tissues exposed to oxidative stress [40]. Moreover, high levels of MDA in damaged gastric tissue have been observed in previous studies [10].

In conclusion, the α_2-receptor agonist dexmedetomidine showed a significant antiulcerative effect in rat gastric tissue at all doses. The antiulcerative effect showed a positive correlation with dosage, and no ulcerous areas were observed in rat gastric tissue at the dose levels of 50 and 100 μg/kg. Consequently, we

can say there is a correlation between the antiulcer mechanism and α_2-receptor activation. In rats administered dexmedetomidine, all antioxidant parameters, except CAT, increased. In contrast, aside from MPO, all oxidant parameters decreased. Therefore, oxidant/antioxidant parameters likely are involved in the antiulcer mechanism of dexmedetomidine.

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