MELATONIN PROTECTS AGAINST HYDROGEN PEROXIDE-INDUCED GASTRIC INJURY IN RATS

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SUMMARY

1. Melatonin (MT) is a pineal hormone that is also abundant in the gut and has a well known role in scavenging oxygen free radicals. The aim of the present study was to evaluate the potential protective effects of MT against H2O2-induced gastric lesions in rats.

2. An experimental model of gastric ulceration was established in rats using 15% H2O2. Melatonin (12.5, 25 or 50 mg/kg, intagastrically) was administered to rats 30 min before H2O2 challenge.

3. Intragastric administration of H2O2 resulted in haemorrhagic lesions in the fundic area of the stomach. Furthermore, H2O2 induced gastric oxidative stress, as indicated by depletion of reduced glutathione (GSH), inhibition of glutathione peroxidase (GPx) activity and elevation of malondialdehyde (MDA) levels. These effects were accompanied by decreased gastric tissue levels of prostaglandin (PG) E2 and nitric oxide (NO), as well as increased levels of tumour necrosis factor (TNF)-α. Administration of MT (12.5, 25 or 50 mg/kg) 30 min before H2O2 significantly attenuated the development of gastric lesions in a dose-dependent manner. The protective effects of MT were accompanied by significant inhibition of the H2O2-induced reduction in gastric content of GSH and GPx activity and elevation in MDA levels. Furthermore, MT antagonized H2O2-induced reduction of gastric PGE2 and NO levels and elevation of TNF-α.

4. In conclusion, MT protects rat gastric mucosa against H2O2-induced damage. The observed protective effects of MT can be attributed, at least in part, to its anti-oxidant properties, preservation of PGE2 and NO levels, as well as inhibition of TNF-α induction in gastric tissues.

Key words: hydrogen peroxide, melatonin, rat stomach.

INTRODUCTION

Oxidative stress contributes to ulcerative and inflammatory diseases of the gastric mucosa, including those induced by ethanol, non-steroidal anti-inflammatory drugs (NSAIDs), cold stress, burns stress and ischaemia–reperfusion. In addition, involvement of reactive oxygen species (ROS) in gastric lesions has been demonstrated in different experiment models.1

In vivo, hydrogen peroxide (H2O2) is metabolised to several ROS, including the hydroxyl radicals, which represent the most potentially damaging free radicals.2 Accidental ingestion of H2O2 (3%) in children has been reported to be associated with severe gastric injury.3 Acute administration of H2O2 to rats produces gastric mucosal lesions and erosions.4 These deleterious effects of H2O2 have been shown to be attributed to generation of ROS and imbalanced oxidant/anti-oxidant cellular status.5

Melatonin (MT, N-acetyl-5-methoxytryptamine) is an indole amine secreted from the pineal gland in the brain.6 It has been estimated that there is 400-fold more MT in the gut than in the pineal gland. Furthermore, MT concentrations in the gastrointestinal tract (GIT) surpass levels in the blood by 10–100-fold.7 This raised the suggestion that MT serves as local anti-oxidant and protective factor.8 The physiological role of MT generated in the digestive system has been studied extensively. Melatonin has been implicated in the regulation of interdigestive motility patterns and is able to accelerate intestinal transit after the feeding.9 Further, Sjoblom and Flemstrom have shown that luminal MT is a potent stimulant of duodenal bicarbonate secretion in response to gastric acid entering the duodenum.10 Receptors for MT have been identified and characterized in the GIT of several species.11 The biological anti-oxidant activity of MT is well known and stands out as a powerful scavenger of ROS.12 Melatonin has been suggested as a free radical scavenger, particularly of hydroxyl radicals.13-16 In addition to its direct free radical-scavenging activity, MT is also an indirect anti-oxidant via its stimulatory actions on anti-oxidant17,18 and pro-oxidant enzymes.19 Melatonin has been studied in animal models of peptic ulcer induced by ischaemia reperfusion,20 stress,21 indomethacin,22 piroxicam,23 aspirin24 and ethanol.25 These beneficial effects of MT in the GIT against several insults have been attributed to the ability of MT to neutralize the toxic effects of free oxygen- and nitrogen-based radicals and have been reviewed by Reiter et al.26

Nevertheless, the effect of MT on H2O2-induced gastric ulceration in the rat model has not been thoroughly investigated. Therefore, the present study was designed to evaluate the potential protective effects of MT against H2O2-induced gastric lesion in rats.

METHODS

Chemicals

Hydrogen peroxide, MT, glutathione, 5,5′-dithio-bis-(2-nitrobenzoic acid), t-cysteine, thiobarbituric acid (TBA), 1,1,3,3-tetraethoxypropane,
of N-1-naphthylethylene diamine dihydrochloride (Griess reagent I), sodium nitrite and sulphanilamide (Griess reagent I) were purchased from Sigma-Aldrich Chemical (St Louis, MO, USA). Prostaglandin (PG) E₂ and tumour necrosis factor (TNF-α) kits were purchased from Assay Designs (Ann Arbor, MI, USA). All other chemicals were of the highest grade available commercially.

Animals and animal treatment

Thirty male Sprague-Dawley rats, weighing 190–210 g, were obtained from the animal facility of King Fahd Medical Research Center, King Abdulaziz University (Jeddah, Saudi Arabia). Guides for the care and use of laboratory animals were approved by the local ethics committee at the King Abdulaziz University. Rats were housed in wire-floored cages under a 12 h light–dark cycle for at least 5 days prior to treatment and were fed standard laboratory chow and tap water *ad libitum*. All experiments were performed during the same time of the day (0800–1000 hours).

Gastric haemorrhagic damage was induced by intragastric administration of 15% H₂O₂ in a volume of 1 mL/100 g bodyweight. Melatonin was dissolved in ethanol before being diluted with saline for i.p. injection. The final concentration of ethanol in the MT solution was 1%. Melatonin was administered 30 min before H₂O₂. The dosing volume was kept at 1 mL/100 g bodyweight. Rats were randomly divided into five groups, with six rats in each group: Group 1 was treated with MT vehicle; Group 2 was given H₂O₂; Group 3 was given H₂O₂ and 12.5 mg/kg MT; Group 4 was given H₂O₂ and 25 mg/kg MT; and Group 5 was given H₂O₂ and 50 mg/kg MT. Doses were selected based on pilot experiments and previous studies.

Determination of gastric erosions

Animals were killed 3 h after vehicle or H₂O₂ administration. Abdomens were opened and stomachs were rapidly dissected out, everted and washed with ice-cold saline. The cumulative area of gastric glandular mucosal injury was determined under a dissecting microscope with an ocular micrometer by an observer blinded to the treatment group. Gastric mucosal lesions are expressed as the total area of erosions (mm²).

Tissue preparation

The pylorus was ligated under light ether anaesthesia. The anterior abdominal wall was incised and the pyloric portion of the stomach was gently mobilized and ligated with a silk ligature around the pyloric sphincter, taking great care not to interfere with the blood supply of the stomach, and the abdominal wall incision was closed. Rats were allowed to recover from anaesthesia for approximately 5 min. Animals were given the assigned treatment. Three hours after administration of vehicle or H₂O₂, rats were killed by an overdose of ether. Their stomachs were rapidly dissected out and opened along the greater curvature and the gastric contents of each stomach were collected for determination of pH, volume and total acidity. The stomachs were washed with ice-cold saline, followed by indomethacin (10 µg/mL) to stop cyclooxygenase (COX) enzymes from producing prostaglandins. Mucosal lesions were scored and the total area of erosions was calculated by the method of Yoshikawa et al. Stomachs were scrapped gently to separate the gastric mucosa, which was then weighed, suspended in phosphate buffer (0.1 mol/L, pH 7.4) and homogenized using a motor-driven homogenizer in an ice jacket. The homogenate was centrifuged for 10 min at 3000 g and the precipitate discarded. The supernatant was stored at −70°C until used for assessment of gastric mucosal content of reduced glutathione (GSH), glutathione peroxidase (Gpx) activity, total nitrates, NO, lipid peroxides, PGE₂, TNF-α and total protein.

Gastric juice

Collected gastric juice was centrifuged for 15 min at 3000 g to remove any solid debris and the volume of the supernatant was determined. Then, the supernatant was analysed for pH and total acidity. The pH of the gastric juice was determined using a pH meter. Total acidity was determined by titration of a given volume of gastric juice against 0.01 mol/L sodium hydroxide up to pH 7, as guided by a pH meter. The total acidity was calculated and expressed as mEq/L, which equals the number of mL of 0.01 mol/L sodium hydroxide required to neutralize 100 mL gastric juice. Total acid output is the total amount of acids (mineral + organic) produced in the gastric juice collected over the 3 h period. Total acid output was determined by multiplying the volume of gastric juice by the total acid concentration (amount of total acids/mL gastric juice).

Gastric mucosal parameters

Assay for lipid peroxidation

Lipid peroxidation (LPO) was determined by measuring malondialdehyde (MDA) content in tissue homogenates according to the method of Mihara and Uchiyama, with some modifications. Briefly, 0.01 g gastric tissue was homogenized with 0.9 mL of 1.15% KCl solution and the MDA content was measured spectrophotometrically at 532 nm. The MDA content was calculated based on a standard curve using 1,1,3,3-tetraethoxypropane as a standard.

Assay of GSH levels and GPx activity

Reduced glutathione was determined according to the method of Adams et al. and expressed as nmol/mg protein. Glutathione peroxidase activity was measured spectrophotometrically according to the method of Paglia and Valentine and expressed as U/mg protein.

Assay for PGE₂

Prostaglandin E₂ was quantified in the collected homogenate using a quantitative binding PGE₂ enzyme immunoassay kit (Assay Designs). The kit uses a monoclonal antibody to bind, in a competitive manner, the PGE₂ in the sample as well as alkaline phosphatase-labelled PGE₂ provided in the kit. The enzyme bound through the PGE₂ molecule to the monoclonal antibodies processes the specific substrate to produce a colour that is measured spectrophotometrically.

Assay for NO

Nitric oxide was assayed by measuring nitrite accumulation using the Griess reaction. Briefly 100 µL gastric homogenate was combined with 100 µL of a 1 : 1 mixture of Griess reagent I (1% sulphanilamide in 5% phosphoric acid) and Griess reagent II (0.1% N-1-naphthylethylene diamine dihydrochloride in water) in a flat-bottomed microtitre plate. The reaction mixture was incubated for 40 min at 37°C in a shaking water bath. In the presence of nitrite, the azo-dye reaction proceeds in an acid medium, producing scarlet colour that can be measured spectrophotometrically at 540 nm in an ELISA reader. The concentrations of nitrite samples were calculated from a standard curve run in the same plate. Gastric mucosal nitrate/nitrite concentrations were expressed in µmol/g protein.

Assay for TNF-α

Tumour necrosis factor-α was assayed using a rat TNF-α enzyme immunoassay kit (Assay Designs). Rat TNF-α was immobilized on a polyclonal antibody bound to a microtitre plate. Excess sample was washed. A monoclonal antibody specific to rat TNF-α, coupled to horseradish peroxidase, was added. The monoclonal antibody binds specifically to the immobilized rat TNF-α. Excess monoclonal antibody was washed and the substrate, tetramethyl benzidine, was added. After an incubation period of 30 min, the colour developed was measured spectrophotometrically at 450 nm.
acid output compared with control values (data not shown). Data in 36.0 ± 1.12, respectively. None of the doses of MT tested could alter any of the parameters of gastric juice evaluated (volume, pH and total acidity) compared with corresponding control values. This indicates that the ischaemia–reperfusion.39,40 These gastroprotective effects of MT are supported by several studies showing the ability of MT to protect against acute gastric lesions induced by ethanol, stress, aspirin and ischaemia–reperfusion.39,40 These gastroprotective effects of MT are mainly attributed to its known radical-scavenging activity.41,42 This is strengthened by our observations that indicated that MT is able to reduce any of the parameters of gastric juice evaluated (volume, pH and total acidity) compared with control values.

Pretreatment with MT ameliorated the formation of acute haemorrhagic red bands of different sizes along the longitudinal axis of the glandular stomach. It was observed that administration of H2O2 can be attributed to oxidative stress induced in gastric tissues following generation of ROS. In addition to oxidative stress, mucosal damage is known to be due to other aggressive factors, including hypersecretion of HCl and inhibition of prostaglandin synthesis.38 This is in agreement with the results of the present study, which showed that H2O2 caused a substantial reduction in gastric tissue GSH content associated with reduction in GPx activity and elevation of LPO. However, the damaging effects of H2O2 on gastric mucosa were not accompanied by significant changes in gastric juice volume, pH or total acidity. This indicates that the pathogenesis of the gastric erosions induced by H2O2 does not embrace shifting of gastric juice parameters to the aggressive side. Therefore, other pathways were examined in the present study.

Pretreatment with MT ameliorated the formation of acute haemorrhagic gastric mucosal lesions induced by H2O2. These findings are supported by several studies showing the ability of MT to protect against acute gastric lesions induced by ethanol, stress, aspirin and ischaemia–reperfusion.39,40 These gastroprotective effects of MT are mainly attributed to its known radical-scavenging activity.41,42 This is strengthened by our observations that indicated that MT is able to prevent any of the parameters of gastric juice evaluated (volume, pH and total acidity) compared with control values.

**RESULTS**

Intragastric administration of 15% H2O2 induced haemorrhagic lesions in the fundic area of the stomach. Gross examination revealed that these lesions were characterized by multiple haemorrhagic red bands of different sizes along the longitudinal axis of the glandular stomach. It was observed that administration of H2O2 resulted in a total area of erosions of 84.3 ± 4.8 mm². Administration of MT (12.5, 25 or 50 mg/kg) 30 min before H2O2 significantly prevented the development of gastric lesions in a dose-related manner compared with H2O2 alone (Fig. 1). The total area of erosions after pretreatment with melatonin was 62.9 ± 3.37, 50.0 ± 3.07 and 36.0 ± 1.12, respectively. None of the doses of MT tested could reduce the ulcer index to control values.

Preclinical results indicated that MT alone, at the three doses tested, had no observable effect on gastric juice volume, pH or total acid output compared with control values (data not shown). Data in Table 1 indicate that administration of H2O2 did not significantly alter any of the parameters of gastric juice evaluated (volume, pH and total acidity) compared with control values. However, 25 and 50 mg/kg MT significantly raised the pH of the gastric juice compared with control and H2O2-treated rats.

Oxidative status-related parameters listed in Table 2 indicate that intragastric H2O2 significantly reduced GSH levels and GPx activity (58% and 39% of corresponding control values, respectively). Pretreatment of rats with MT inhibited the reductions in GSH content and GPx activity in a dose-related manner compared with H2O2 alone. Further, H2O2 induced an approximate threefold increase in lipid peroxidation in gastric tissues, as indicated by MDA levels, compared with control value. Melatonin (12.5, 25 or 50 mg/kg) given 30 min prior to H2O2 significantly and dose-dependently antagonized the H2O2-induced increases in MDA. Maximum protection against lipid peroxidation was observed in rats receiving the highest dose of melatonin (50 mg/kg), because MDA levels were restored to almost control values.

The protective effects of MT were substantiated by assessing levels of PGE2, NO and TNF-α in gastric tissues. Data are presented in Table 3.

Intragastric H2O2 significantly reduced PGE2 levels by 64% compared with control rats. Melatonin pretreatment had an obvious preventive role, as indicated by the dose-related elevation in PGE2 levels compared with H2O2 alone.

The NO content of gastric tissues was significantly reduced by administration of H2O2. Pretreatment with MT (12.5 mg/kg) was able to restore the NO content of gastric tissues to normal. It is of note that 25 and 50 mg/kg MT significantly elevated NO to levels higher than those observed in the H2O2-treated and control groups. Administration of H2O2 resulted in a greater than twofold increase in gastric mucosal TNF-α content. Melatonin (12.5, 25 and 50 mg/kg) significantly and dose-dependently reduced elevated level of the cytokine by 22, 35 and 52%, respectively, compared with H2O2 alone. Restoration of TNF-α to control values was observed only in rats given the highest dose of MT (50 mg/kg).

**DISCUSSION**

Melatonin has been implicated in the mechanisms of gastric mucosal integrity, as well as gastroprotection against various irritants.37 The present study was designed to evaluate the potential protective effects of MT against H2O2-induced gastric lesions in rats. The results indicate that administration of H2O2 to rats induced gastric mucosal haemorrhagic lesions. This finding is supported by several studies reporting the deleterious effects of H2O2 on rat gastric mucosa.43 H2O2 can be metabolised to any of ROS including hydroxyl radicals. Therefore, the observed damaging effects of H2O2 can be attributed to oxidative stress induced in gastric tissues following generation of ROS. In addition to oxidative stress, mucosal damage is known to be due to other aggressive factors, including hypersecretion of HCl and inhibition of prostaglandin synthesis.38 This is in agreement with the results of the present study, which showed that H2O2 caused a substantial reduction in gastric tissue GSH content associated with reduction in GPx activity and elevation of LPO. However, the damaging effects of H2O2 on gastric mucosa were not accompanied by significant changes in gastric juice volume, pH or total acidity. This indicates that the pathogenesis of the gastric erosions induced by H2O2 does not embrace shifting of gastric juice parameters to the aggressive side. Therefore, other pathways were examined in the present study.

Pretreatment with MT ameliorated the formation of acute haemorrhagic gastric mucosal lesions induced by H2O2. These findings are supported by several studies showing the ability of MT to protect against acute gastric lesions induced by ethanol, stress, aspirin and ischaemia–reperfusion.39,40 These gastroprotective effects of MT are mainly attributed to its known radical-scavenging activity.41,42 This is strengthened by our observations that indicated that MT is able to prevent any of the parameters of gastric juice evaluated (volume, pH and total acidity) compared with control values.

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The observed gastroprotection afforded by MT was further confirmed by evaluating volume, pH and total acidity of gastric secretion. Otherwise, none of the parameters assessed was significantly altered by MT. This indicates that the protective effects of MT are not related directly to volume, pH or the acidity of the gastric juice. Therefore, subsequent studies were aimed at investigating other potential underlying mechanisms of gastroprotection.

The impact of MT pre-administration on H$_2$O$_2$-induced oxidative stress in gastric tissues was evaluated. Melatonin significantly inhibited the reduction in gastric GSH content and GPx activity induced by H$_2$O$_2$. It is of note that the protection by MT against a reduction in GPx activity was dose related. There is increasing evidence indicating that endogenous sulphydryls (SH), mostly reduced glutathione, play an important role in the maintenance of gastric integrity and in the protection against chemically induced lesions. In addition, gastric tissues are highly dependent on GSH, which is required for their normal function, and inhibition of the synthesis of GSH leads to marked cellular degradation. Lipid peroxides and peroxiradicals in the gastric mucosa can be detoxified by GPx and GSH. Glutathione peroxidase, a scavenging enzyme of H$_2$O$_2$, plays a critical role in the protection against oxidants and products of oxidative stress. Thus, the observed reduction in LPO levels can be explained on the basis of the preservation of GPx activity and GSH levels in gastric tissues.

The mechanisms of MT gastroprotection were further investigated by assessing changes in the levels of gastric prostaglandins, NO, and TNF-α. Prostaglandins are the major factors involved in gastric mucosal protection. However, prostaglandin E$_2$ stimulates mucus and bicarbonate secretion, maintains mucosal blood flow, inhibits acid secretion, enhances the resistance of epithelial cells to injury induced by chemicals and inhibits leucocyte recruitment. Data of the present study indicate that intragastric H$_2$O$_2$ substantially reduces PGE$_2$ levels and that MT pretreatment exerted an obvious preventive role, as indicated by the dose-related elevation of PGE$_2$ levels compared with H$_2$O$_2$ alone. This observation is supported by the finding that 16,16-dimethyl PGE$_2$ was able to protect the gastric mucosa against H$_2$O$_2$-induced injury. Further, the protective effects of MT have been attributed to activation by MT of mucosal COX–PG and NO synthase (NOS)–NO systems. This could be linked to the

### Table 1: Effect of melatonin on H$_2$O$_2$-induced changes in gastric juice volume, pH and total acid output

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume (mL)</th>
<th>pH</th>
<th>Total acid output (µEq/3 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.10 ± 0.32</td>
<td>2.32 ± 0.16</td>
<td>127 ± 13</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>4.80 ± 0.21</td>
<td>2.21 ± 0.12</td>
<td>126 ± 11</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (12.5 mg/kg)</td>
<td>4.95 ± 0.32</td>
<td>2.45 ± 0.12</td>
<td>126 ± 10</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (25 mg/kg)</td>
<td>5.20 ± 0.35</td>
<td>2.96 ± 0.31</td>
<td>127 ± 11</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (50 mg/kg)</td>
<td>5.30 ± 0.26</td>
<td>3.81 ± 0.23</td>
<td>127 ± 12</td>
</tr>
</tbody>
</table>

Data are the mean±SEM of six rats. *P < 0.05 compared with control; †P < 0.05 compared with H$_2$O$_2$; ‡P < 0.05 compared with 12.5 mg/kg melatonin (MT); §P < 0.05 compared with 25 mg/kg MT.

### Table 2: Effect of melatonin on H$_2$O$_2$-induced changes in gastric levels of total reduced glutathione, glutathione peroxidase activity and lipid peroxidation

<table>
<thead>
<tr>
<th>Group</th>
<th>GSH (nmol/mg protein)</th>
<th>GPx activity (U/mg protein)</th>
<th>MDA (nmol/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (saline)</td>
<td>48.9 ± 1.3</td>
<td>0.492 ± 0.001</td>
<td>3.00 ± 0.1</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>20.6 ± 1.2</td>
<td>0.301 ± 0.001</td>
<td>9.30 ± 0.3</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (12.5 mg/kg)</td>
<td>34.6 ± 1.1†</td>
<td>0.371 ± 0.003†</td>
<td>5.80 ± 0.20†</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (25 mg/kg)</td>
<td>39.2 ± 1.4†</td>
<td>0.403 ± 0.002†</td>
<td>4.60 ± 0.10†</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (50 mg/kg)</td>
<td>44.7 ± 2.3†</td>
<td>0.451 ± 0.001†</td>
<td>3.30 ± 0.09†</td>
</tr>
</tbody>
</table>

Data are the mean±SEM of six rats. *P < 0.05 compared with control; †P < 0.05 compared with H$_2$O$_2$; ‡P < 0.05 compared with 12.5 mg/kg melatonin (MT); §P < 0.05 compared with 25 mg/kg MT.

### Table 3: Effect of melatonin on H$_2$O$_2$-induced changes in gastric levels of prostaglandin E$_2$, nitric oxide and tumour necrosis factor-α

<table>
<thead>
<tr>
<th>Group</th>
<th>PGE$_2$ (ng/g tissue)</th>
<th>NO (µmol/g protein)</th>
<th>TNF-α (pg/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (saline)</td>
<td>92.0 ± 6.3</td>
<td>9.20 ± 0.22</td>
<td>10.3 ± 0.1</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>33.0 ± 4.2†</td>
<td>5.50 ± 0.16†</td>
<td>22.1 ± 0.3†</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (12.5 mg/kg)</td>
<td>42.0 ± 2.1†</td>
<td>8.30 ± 0.34†</td>
<td>17.2 ± 0.3†</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (25 mg/kg)</td>
<td>58.0 ± 3.2†</td>
<td>12.6 ± 0.7†</td>
<td>14.4 ± 0.3†</td>
</tr>
<tr>
<td>H$_2$O$_2$ + MT (50 mg/kg)</td>
<td>75.0 ± 5.3†</td>
<td>16.8 ± 1.1†</td>
<td>10.6 ± 0.2†</td>
</tr>
</tbody>
</table>

Data are the mean±SEM of six rats. *P < 0.05 compared with control; †P < 0.05 compared with H$_2$O$_2$; ‡P < 0.05 compared with 12.5 mg/kg melatonin (MT); §P < 0.05 compared with 25 mg/kg MT.

PGE$_2$, prostaglandin E$_2$; NO, nitric oxide; TNF-α, tumour necrosis factor-α.
observed oxidative stress, which was claimed to partially inactivate COX-1 and reduce the generation of gastroprotective prostaglandins in the GIT. The NO content of gastric tissue was significantly reduced following administration of H$_2$O$_2$. This can be explained by the consumption of NO during H$_2$O$_2$-induced oxidative stress to form the damaging species peroxynitrites. Pretreatment with MT restored normal NO content of gastric tissues. This is linked to the vasodilating actions of NO and enhanced blood supply can lend additive support to the putative gastroprotective effects of MT.

Tumour necrosis factor-α is a pro-inflammatory cytokine that has many biological effects, including the induction of other inflammatory cytokines and activation of neutrophils. It is also involved in the pathogenesis of a variety of gastric injuries, such as those caused by NSAIDs,59 the pathogenesis of a variety of gastric injuries, such as those caused by NSAIDs,59 and activation of neutrophils.58 It is also involved in the inflammatory responses induced by H$_2$O$_2$ that eventually lead to gastric mucosal damage.

In conclusion, MT protects rat gastric mucosa against H$_2$O$_2$-induced damage. The observed protective effects of MT can be attributed, at least in part, to its anti-oxidant properties, preservation of PG_E$_2$ and NO levels, as well as inhibition of TNF-α induction in gastric tissues.

REFERENCES


