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Research Article

Nebivolol prevents indomethacin-induced gastric ulcer in rats

Nahla E. El-Ashmawy, Eman G. Khedr, Hoda A. El-Bahrawy & Hend M. Selim

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Abstract

Gastric ulcer is a very common gastrointestinal disease that may lead to dangerous complica... prophylactic effect of ... Wistar rats were div... eprazole before I... meprazole was give... of ulcer by oral dosi... ized and their... d inflam... wed that a single or... of 2900 and significa... malondi... glandin E_2 (PGE_2), ... trol

resulted in a significant increase in GSH, PGE_2 and NO and a significant decrease in TNFα and MDA gastric levels, compared to ulcer control values. Results obtained with nebivolol were comparable to those with omeprazole: the preventive index in the nebivolol group was 90.7% compared to 94.5% in rats in the omeprazole group. These studies showed that nebivolol provided a valuable role in preventing gastric ulcers induced by INDO and provided a promise for potentially protecting hypertensive patients from experiencing gastric ulcer. Thus, it is possible that, pending further studies, nebivolol could be used for pre-exposure prophylaxis from gastric ulcer in these patients.

Keywords: Ulcer indomethacin nebivolol TNFα MDA GSH PGE2 NO

Introduction

Gastric ulcer is one of the most common disorders considering the gastrointestinal tract, it affects 5% of the population around the world, so its prevention and management are considered very important challenges (Boligon et al. 2014). Researchers have revealed several causes of gastric ulcer; these include an imbalance between aggressive and intrinsic defensive factors (Boligon et al. 2014). The aggressive factors include non-steroidal anti-inflammatory drugs (NSAID), alcohol, psychological stress and Helicobacter pylori infection; cytoprotective intrinsic factors include mucosal blood flow, bicarbonate, mucus, cell renewal, growth factors, NO and prostaglandins (Abbas &

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receptor blockers (Mejia & Kraft 2009). Presently, these therapies have a major disadvantage in that they cause many side-effects (Araujo et al. 2011).

Interestingly, it has been noted that patients with cardiovascular diseases have high gastric ulcer incidence rates (Morsy et al. 2012). Moreover, it was documented that adults with hypertension often suffer from peptic ulcer disease and are more likely to receive drugs for hypertension and peptic ulcer (Patil et al. 2012). Telmisartan, which is known as an anti-hypertensive drug, was documented to decrease gastric ulcer risk (Morsy et al. 2009). Considering this evidence, choosing an anti-hypertensive drug may be beneficial in the prophylaxis of gastric ulcer in hypertensive patients.

Nebivolol is an anti-hypertensive drug that is classified as a third-generation selective β_1-adrenoreceptor antagonist and β_3-adrenoreceptor agonist. It has been shown to stimulate the production of nitric oxide (NO) through stimulation of endothelial nitric oxide synthase, resulting in vasodilatation. Nitric oxide also plays an important role in gastro-protection in that it helps to maintain adequate blood flow in mucosal tissues (Morsy et al. 2012).

The current study was conducted to highlight the role of nebivolol as a gastro-protective agent (pre-exposure prophylactic) against INDO-induced gastric ulcer in male rats. In addition, the study also examined underlying biochemical pathways that were related to oxidative stress, inflammation and cyto-protection in the gut.

Materials and methods

Drugs

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study). The rats were housed in wire cages in a pathogen-free facility maintained at 24 ± 2 °C; 60–70% relative humidity and a 12-h light:dark cycle. All rats had ad libitum access to standard rodent chow and filtered tap water. All rats were acclimatized for 2 weeks before the experiments. This study was conducted in accordance with guidelines for the care and use of laboratory animals and approved by the Research Ethics Committee of Tanta University (Tanta, Egypt).

For the study design, the rats were randomly divided into four groups: Group 1 (control group, n = 20), Group 2 (ulcer group, n = 20), Group 3 (omeprazole group, n = 30) and Group 4 (nebivolol group, n = 20). The number of rats in Group 3 was higher (relative to that in other groups) as omeprazole affected gastric secretion to some extent; thus, the number of rats was increased to accommodate this effect. Note: From among the 20–30 rats/group, the stomachs of 2–4/group were randomly selected for histopathologic studies. Of the remaining rats in each group, the amount of tissue from a single stomach was not enough for chemical measures and so pooling of tissues from two rats each time (within each group) was required. Thus, the number of rats here used in statistical analyses of the non-histopathology end-points below yielded an n = 8/group (for Group 3 rats, tissues of 3–4 rats were randomly pooled to yield the same n = 8 value).

For induction of ulcer, INDO was given by a single oral gavage of 100 mg INDO/kg (Araujo et al. 2011). For rats in the drug pre-treatment groups, omeprazole (5 mg/kg) (Izzettin et al. 2012) or nebivolol (10 mg/kg) (Sorrentino et al. 2011) was given orally (gavage) daily for 10 consecutive days; on the final day, these rats were given INDO (by gava and 2 (that had bee with, respecti DO oral gavage; avoid coproph ing. Four hours af phyxiation and

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°C), the clear supernatant was recovered (Sivaraman & Muralidharan 2011) and used for pH measurement using a pH 211 meter (Hanna instruments, Bucharest, Romania).

Measurement of ulcer index

After gastric contents were removed, a board-certified pathologist then evaluated the total stomach under magnification (in a blinded manner). Based on these evaluations, the ulcer score for each group was calculated as the mean number of ulcers/stomach/rat in each group. From these values, an Ulcer Index (UI) was calculated by multiplying each group's ulcer score × 100. Subsequently, the net preventive index was calculated as 100% × (UI of ulcer only group − UI of treated group)/UI of ulcerated only group (Dawud et al. 2014). After these analyses, the tissues were then processed for use in the various assays outlined below.

Preparation of stomach tissues for analysis

Tissue preparation for assaying gastric levels of glutathione (GSH) and malondialdehyde (MDA), 250 mg tissue was homogenized in 2.5 ml potassium phosphate buffer (pH 7.5) using a Polytron homogenizer (PT 3100, Kinematica, Luzern, Switzerland) then tissue was centrifuged at 4000 rpm for 15 min at 4 °C. Tissue preparation for assaying stomach nitric oxide (NO) levels, 250 mg tissue was homogenized in 2.5 ml ice-cold normal (0.9%) saline. Afterwards, 1 ml absolute ethanol was added to 0.5 ml homogenate to precipitate the proteins and the samples were then centrifuged at 3000 rpm for 10 min at 4 °C. To prepare tissues for assaying gastric PGE_2 levels, 100 mg tissue was homogenized in 1 ml of phosphate-buffered saline (PBS, pH 7.4) usi

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(Unico 2100, Dayton, NJ). Values were then calculated using the kit-provided formula and presented as mg GSH/g starting tissue.

Determination of stomach malondialdehyde (MDA)

The gastric concentration of MDA was determined colorimetrically using a kit from Biodiagnostics. According to the protocol, thiobarbituric acid (TBA) reacts with MDA present in the sample (in acidic medium, at 95 °C for 30 min) to form TBA-reactive products (TBARS). The absorbance of these resultant pink products was then measured at 534 nm in the spectrophotometer. Values were then calculated using a kit-provided formula and presented as nmol MDA/g starting tissue.

Determination of nitric oxide (NO) content

The nitric oxide content in the stomach tissue was determined by measuring its nitrite (an indicator of original NO present). This method depends on reduction of nitrate to nitrite by vanadium trichloride (VCl3), which was followed by addition of Griess reagent (Miranda et al. 2001). In brief, homogenate supernatant (500 µl) was mixed with an equal volume of VCl_3 (400 mg dissolved in 50 ml 1 M HCl) and Griess reagent (0.1 g naphthylethylenediamine in 100 ml distilled water and 2 g sulphanilamide in 100 ml 5% HCl). After incubation at 37 °C for 30 min, the absorbance was measured at 540 nm in the spectrophotometer. Values were compared with those from sodium nitrite standards that were assessed in parallel and plotted in standard curve and the nitrite concentration in each sample was calculated. Results were presented as nmol NO/g starting tissue.

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hematoxylin and eosin solution. A board-certified pathologist then evaluated the materials under a light microscope (in a blinded manner).

Statistical analysis

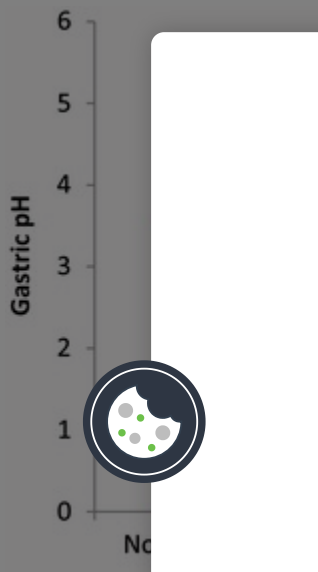
Analysis of data was performed using SPSS software (v.17.0, Armonk, NY, USA). All data are presented as mean ± SEM. Statistical comparisons among groups were performed using a one-way analysis of variance (ANOVA). Statistical significance was set at $p < 0.05$.

Results

Effect on gastric pH

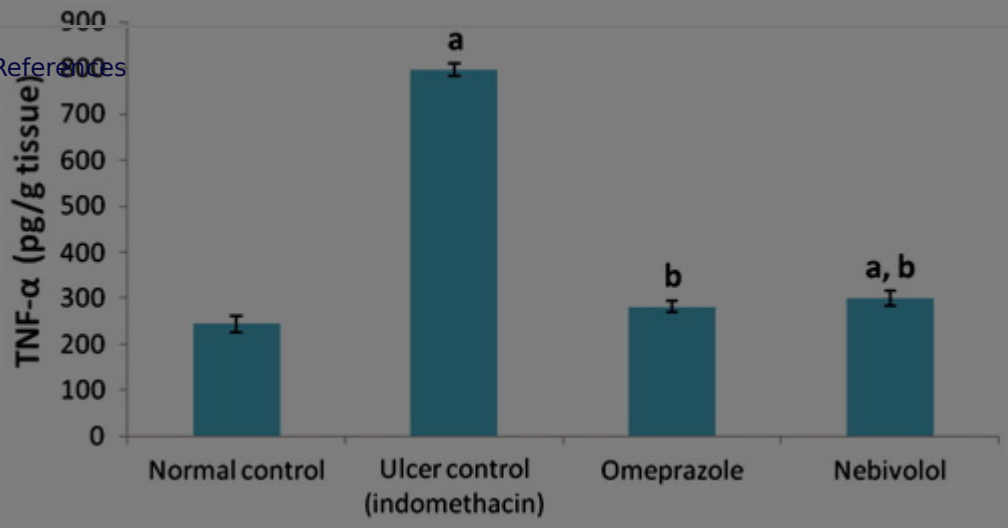
Administration of INDO caused a significant decrease in gastric pH (41.1%) as compared to the value in fluids from normal control rats (Figure 1). Values dropped from 3.58 ± 0.04 to 2.11 ± 0.05. Pre-treatment with nebivolol preserved gastric pH at the level of the control group (i.e. 3.50 ± 0.03), whereas pre-treatment with omeprazole significantly increased the gastric pH above the control value (to 5.13 ± 0.05).

Figure 1. Effect of treatments on gastric pH. Data shown are mean ± SEM (n = 8 rats/group). Value significantly different vs [a]normal control or [b]INDO only (ulcer control) ($p < 0.05$).



INDO alone caused a significant increase in gastric TNFα levels (3.26-fold increase; 796.5 ± 13.7 vs 244.0 ± 17.8) compared to values in samples from the normal control rats (Figure 2). Omeprazole or nebivolol pre-treatment significantly decreased gastric TNFα levels (by 64.7% and 62.5%, respectively, i.e. to 281.0 ± 12.2 and 299.0 ± 16.4) compared to levels seen in the ulcer (INDO only) rats (Figure 2).

Figure 2. Effect of treatments on gastric TNFα. Data shown are mean ± SEM (n = 8 rats/group). Value significantly different vs [a]normal control or [b]INDO only (ulcer control) ($p < 0.05$).



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Effect on ulcer index and preventive index

The ulcerated (INDO only) group had an ulcer score of 29.0 ± 1.7/stomach and a group UI of 2900 (Table 1). Rats that had been treated with nebivolol or omeprazole prior to INDO sh in the nebivolo omeprazole group ha e index, omepraz ith these rats hav arison, rats in the f 90.7%.

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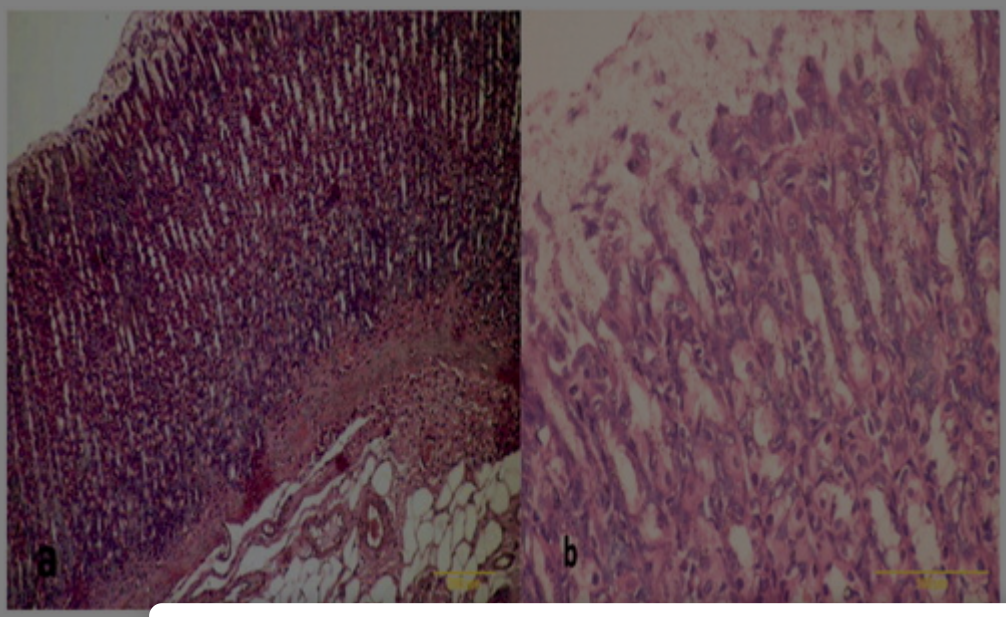
In line with the findings about the UI (and preventive indices), compared to the sections obtained from normal control rats (Figure 3), stomach sections from INDO only-treated rats showed gastric erosions with decreased gastric mucosa thickness, disruption of gastric mucosa and inflammatory cell infiltration (Figure 4). Sections from omeprazole and nebivolol pre-treated rats groups showed intact gastric mucosa and only slight congestion (Figures 5 and 6).

Figure 3. Sections of gastric mucosa of normal control rats. (a) Normal mucosal thickness with surface mucus layer covering gastric pits with intact mucosa and more gastric glands at the bottom (Magnification = 100×). (b) Parietal cells with central rounded nuclei are dispersed throughout the glands (Magnification = 400×). H&E stain. Representative images are shown.



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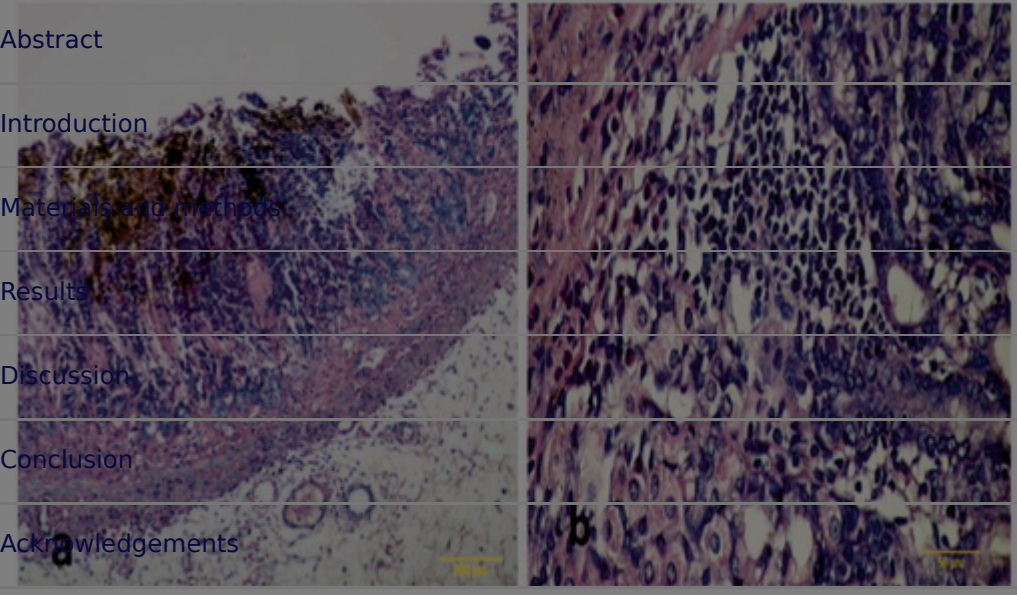

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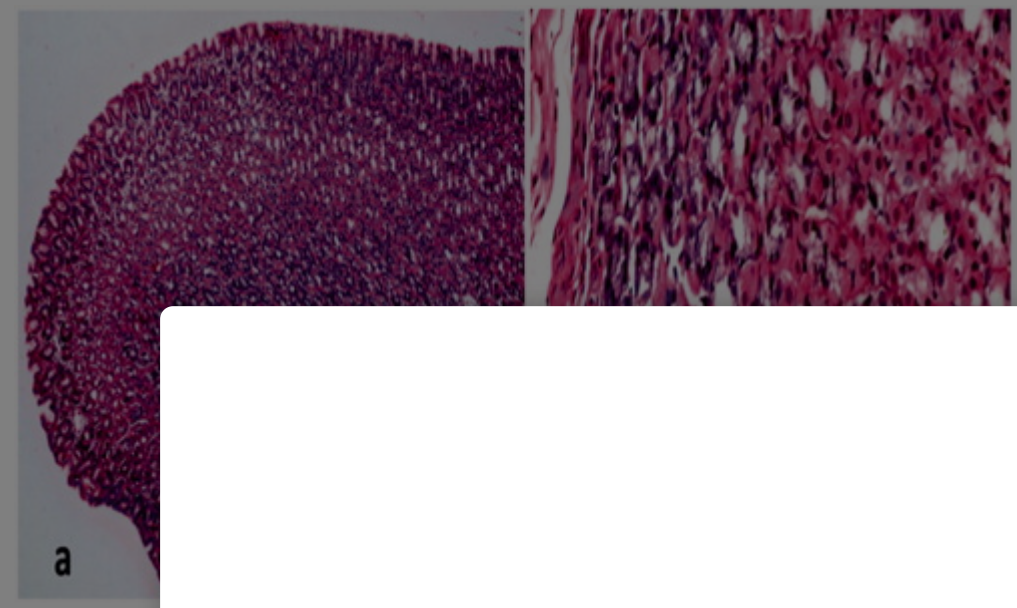
Figure 5. Sections of gastric mucosa of omeprazole-pre-treated rats. (a) Section indicates intact gastric mucosa (Magnification = 100×). (b) Gastric mucosa like normal and gastric glands with slight dilatation (Magnification = 400×). H&E stain. Representative images are shown. All of these tissues (and others from the group) were used by the pathologist to generate ulcer scores for each rat and, subsequently, the net protective index value for each group.



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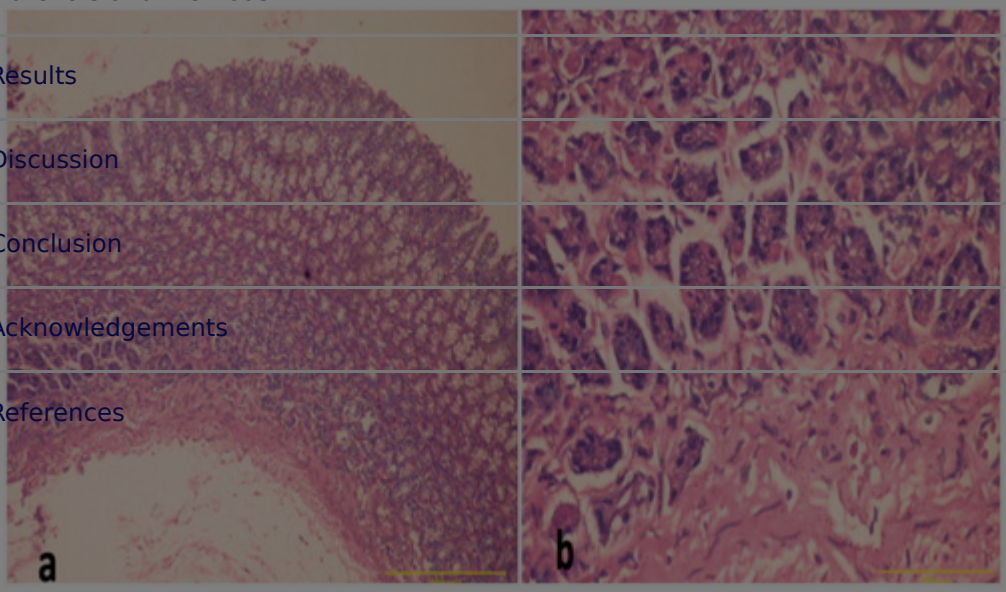
Representative images are shown. All of these tissues (and others from the group) were used by the pathologist to generate ulcer scores for each rat and, subsequently, the net protective index value for each group.



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Effect on gastric MDA and GSH

INDO caused a significant increase in gastric tissue MDA levels compared to values in tissues from the normal control rats (2.2-fold increase) (Table 2). Pre-treatment with omeprazole or nebivolol led to significant decreases in gastric MDA (50.5% and 48.2%, respectively) relative to that in the INDO only rats. On the other hand, GSH levels were significantly decreased by treatment with INDO (62.6% compared to control group). Pre-treatment with omeprazole or nebivolol partially corrected the gastric GSH levels (values were increased 2.48- and 2.29-fold, respectively) compared to levels in the INDO on

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respectively) compared to values in the INDO only ulcer rats. INDO also caused a significant decrease in gastric PGE_2 levels (44.1%) compared to values in the normal controls. Pre-treatment with omeprazole or nebivolol resulted in a significant increase in gastric PGE_2 level (1.71- and 1.69-fold increase, respectively) relative to the INDO only group value.

Table 3. Effect of treatments on stomach cytoprotective mediators.

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Discussion

Gastric ulcers often co-exist with hypertension and both diseases share some etiological factors (Morsy et al. 2012; Patil et al. 2012). An imbalance between endogenous gastroprotective and aggressive factors in the gastric mucosa leads to gastric injury and ulceration (Raji & Oloyede 2011). Endogenous gastroprotective factors include nitric oxide (NO) and prostaglandins (PGs), each of which is considered an important regulator of blood flow and mucus secretion (Suleyman et al. 2010; Morsy et al. 2012). Since NO, PGs and oxidative stress have been implicated in both hypertension and gastric ulcer (Abdel-Raheem 2010; Giles et al. 2012), one could hypothe might be helpful i ting ulcer develop ypertensive drug, ne is as a pre-exposur isms of any such e

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Increased gastric acid secretion plays an important role in gastric ulcer induction and is involved in its etiology as it decreases the process of restitution and ulcer healing via altering angiogenesis (Musumba et al. 2009).

The INDO only rats here also showed a significant decrease of gastric PGE_2 and NO. These results supported that of previous researchers (Abdallah et al. 2011; Abbas & Sakr 2013), who noted that gastric ulcers induced by INDO were accompanied by significant increases in gastric acidity and significant decreases in gastric PGE_2 and NO levels. This INDO effect on NO could be explained by an ability to up-regulate endothelin-1, a factor that leads to decreased release of endothelial NO, leading to an eventual loss of mucosal integrity (an event that is normally maintained by a presence of NO; Abdel-Raheem 2010).

The results of the present study also showed that nebivolol pre-treatment, before INDO, normalized gastric acidity, led to reductions in UI values and yielded a high preventive index. These outcomes could be explained, in part, by the ability of nebivolol to increase PGE_2 and NO levels since it is known that PGE_2 and NO increase mucus secretion and regulate gastric acidity via reduction in gastric acid secretion (Suleyman et al. 2010; Morsy et al. 2012; Rahim et al. 2014). This observed effect of nebivolol was significantly lower than that exerted by the proton pump inhibitor omeprazole (which had the greater preventive index value) that increased the pH value to one greater than normal. The results here indicated that gastric NO and PGE_2 levels were increased significantly in the nebivolol group when compared to the INDO only group. Nebivolol increases NO through activation of a β_3-adrenoreceptor that activates the NO synthase pathway a form of reactive not be involved wn to regulate nse via increasi g the repair proces e (Morsy et al tion betwee g the gastric t al. 2014).

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gastroprotective effect against ethanol-induced gastric ulcers in rats. Both omeprazole and nebivolol here caused comparable results and helped rats maintain gastric NO and PGE_2 to near-normal control values.

Oxidative stress is implicated in induction of gastric ulcers and is considered one of the mechanisms involved in INDO-induced ulcers (Adhikary et al. 2011). The present results supported this hypothesis as MDA levels were significantly elevated while GSH levels were significantly decreased in gastric tissues of the INDO only group when compared to normal values. Oxidative stress is produced as a result of increasing levels of reactive oxygen species (ROS) in gastric tissues; these ROS cause injury to the gastric tissue by damaging membranes and cellular biomolecules such as proteins, DNA and lipids (Suzuki et al. 2012; Badr & Al-Mulhim 2014). Further, increase in ROS levels could lead to uncoupling of (eNOS) and, thus, decreased NO synthesis (Landmesser et al. 2003; Kato et al. 2009). Hence, using drugs with anti-oxidant properties that decrease ROS formation and increase NO levels could protect gastric tissues from oxidant-mediated damage and be beneficial against ulcer formation/progression.

In our work, pre-treatment with nebivolol before INDO resulted in significant decreases in gastric MDA levels and significant increases in gastric GSH levels relative to those in the INDO only rats. Nebivolol is thought to possess anti-oxidant activity, possibly by inhibiting NADPH oxidase-induced free radical formation (Morsy et al. 2012), direct scavenging of ROS (Goel et al. 2009), decreasing free radicals pool (Gideroglu et al. 2008) and/or up-regulating hemoxygenase-1 (HO-1) enzyme expression (which augments GSH levels) (Morsy et al. 2012). Omeprazole pre-treatment, before INDO, here had
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2011). The present results confirmed the contribution of TNFα to the development of gastric ulcers induced by INDO. Platelet activating factor and TNFα are known to play the key roles in gastric injury induced by NSAIDs; these mediators induce inflammation and tissue damage through activation of adhering molecules, thus resulted in recruiting leukocytes. Neutrophil infiltration can cause injury by causing enhanced release of ROS that, in turn, damage gastric tissue (Musumba et al. 2009). In the current work, pre-treatment with nebivolol or omeprazole before INDO decreased gastric TNFα levels significantly compared to that in rats that received INDO only. It has been shown previously that nebivolol had the ability to decrease TNFα gene expression (Garbin et al. 2008). Further, omeprazole decreased serum TNFα levels and was protective against ethanol-induced gastric ulcers (Abood et al. 2014). Lastly, PGE_2 mitigates effects of TNFα and has been documented as a potent inhibitor of TNFα (Abood et al. 2014). Thus, it is plausible that each agent could have caused significant decreases in gastric TNFα via induced improvements in gastric PGE_2 levels.

Conclusion

The β_3-agonist nebivolol imparted a gastroprotective role (pre-exposure prophylactic) against INDO-induced gastric ulcer; the effect appeared to be mediated, in part, by reductions in oxidative stress and a preservation of gastroprotective mechanisms. Thus, nebivolol could possibly be used to maintain the required balance between aggressive and defensive forces and could be used as prophylaxis for patients suffering from hyperter o are hyperter

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