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Different Mechanisms in Formation and Prevention of Indomethacin-induced Gastric Ulcers

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Abstract—Indomethacin is an indol derivative, non-steroidal, anti-inflammatory drug with anti-inflammatory, analgesic, and antipyretic effects. Indomethacin became the first-choice drug to produce an experimental ulcer model as a result of having a higher ulcerogenic potential than other non-steroidal anti-inflammatory drugs (NSAIDs). There have been several conflicting reports about the ulcerogenic mechanism of indomethacin; the mechanism is still unclear. It has been suggested that indomethacin induces gastric damage via inhibiting the release of protective factors like cyclooxygenase-1 (COX-1), prostaglandin E2 (PGE2), bicarbonate, and mucus; increasing aggressive factors like acid; and increasing oxidant parameters while decreasing antioxidant parameters. Classic antiulcer drugs are known to produce antiulcer effects by activating against indomethacin (increasing PGE2, mucus, and bicarbonate production; inhibiting acid secretion; decreasing oxidant parameters; and increasing antioxidants). However, some antiulcer drugs have been shown to inhibit indomethacin-induced ulcers without affecting acid and mucus secretion or oxidant parameters, as well as to inhibit the production of protective factors like COX-1, PGE2, and bicarbonate, and to reduce antioxidant parameters. In order to resolve the contradictions in the abovementioned data, this review hypothesized a relationship between indomethacin-induced ulcers and α 2 adrenergic receptors. It is suggested that blockage of α 2 adrenergic receptors may be responsible for the increase in the aggressive factors induced by indomethacin, and stimulation of α 2 adrenergic receptors may be responsible for the increase of protective factors induced by antiulcer drugs.

KEY WORDS: indomethacin; ulcer; adrenergic receptors.

INTRODUCTION

Indomethacin is an indol derivative, non-steroidal, anti-inflammatory drug with anti-inflammatory, analgesic, and antipyretic effects [1]. It is used in the treatment of ankylosing spondilitis, osteoarthritis, rheumatoid arthritis, gout arthritis, bursitis, tendonitis, sinovitis, and other inflammatory diseases because of its effective suppression of pain, fever, color, and edema [2–4]. It is known that the inhibition potencies of non-steroidal anti-inflammatory drugs (NSAIDs) on cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes are different [5]. It is believed that while inhibition of COX-1 by NSAIDs causes side effects as a result of reduced prostaglandin (PG) synthesis, inhibition of COX-2 is related to their anti-inflammatory effect [5–7]. Indomethacin potently damages PG synthesis by inhibiting both the COX-1 and COX-2 enzymes [1, 8]. Inhibition of the COX-1 and COX-2 enzymes is necessary for gastric damage to occur [9]. Indomethacin and similar NSAIDs, which inhibit both isoforms of the COX enzyme, produce more severe damage in gastric tissue, even gastrointestinal bleeding when combined with antithrombotic agents [10]. Inhibition of the COX-2 enzyme is thought to be responsible for indomethacin's anti-inflammatory effect, while inhibition of COX-1 is responsible for its gastrointestinal system (GIS) side effects [10, 11].

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Indomethacin became the first-choice drug to produce an experimental ulcer model as a result of having a higher ulcerogenic potential than other NSAIDs [12]. The fact that nimesulide, which is less selective for COX-2, is able to inhibit NSAID-induced gastric damage [13, 14], while celecoxib and rofecoxib, which are more selective for COX-2 (350 to 800 times as selective), are unable to inhibit these ulcers [15], reveals that it is impossible to attribute the GIS side effects of indomethacin and other NSAIDs to the inhibition of only the COX-1 enzyme.

INHIBITION OF PROSTAGLANDIN SYNTHESIS

Prostaglandins are derived from arachidonic acid by phospholipase A2 and cyclooxygenase isoenzymes. Under basal conditions, prostaglandins are synthesized by constitutive cyclooxygenase (COX-1), which is expressed in most cell types [16]. For a better understanding of PG inhibition by indomethacin and other NSAIDs, it is necessary to give a detailed explanation of the COX enzyme system. COX enzyme catalyses the first step in the synthesis of arachidonic acid (AA) metabolites (PG, thromboxane A2, leukotrienes, prostacyclin) [16]. The COX enzyme was first discovered in 1971; later, COX-1, COX-2 (in humans), and COX-3 (in dogs) isoforms were found [17–19]. COX-1 is involved in the synthesis of PGs, which are responsible for platelet aggregation and gastric mucosal protection [20]. However, COX-2 is an inducible protein included in inflammatory reactions [21]. Gastric ulcers and other side effects related to NSAID usage occur as a result of COX-1 inhibition [10, 22]. It has been shown that indomethacin produces gastric damage by reducing PGE2 levels via COX-1 inhibition [23]. Ding *et al.* reported that indomethacin causes gastric damage by reducing PGE2 levels in stomach tissue [24]. Also, the exogenous administration of PGE2 prevented indomethacin-induced gastric mucosal damage [24, 25]. PGE2 and PGI2 are believed to expose gastroprotective effects by decreasing stomach acid secretion, increasing the thickness of mucus layers, and improving the blood flow of mucosa [26]. However, aspirin, which inhibits cytoprotective PGE2, was shown not to cause gastric damage, even in the case of preventing indomethacin-induced ulcers by intraperitoneal administration [27]. Aspirin may produce gastroprotection due to its effect on 15 epi-lipoxins. Lipoxins are potent anti-inflammatory lipid mediators [28]; their most interesting synthetic pathway is that associated with the acetylation of COX-2 by aspirin. Aspirin acetylates serine residues in both COX-1 and COX-2, leading to conformational changes in the enzyme that alters their ability to metabolize arachidonic acid [29–31]. With both isozymes, acetylation by aspirin leads to a complete blockade of the generation of PGH2. However, aspirin-acetylated COX-2 is still able to convert arachidonic acid to 15-R-Hydroxyeicosatetraenoic acid (15-RHETE), which can subsequently be metabolized via 5-lipoxygenase to 15-R-lipoxin A4 [30]. Lipoxins prevent further neutrophilic infiltration and stimulate local nitric oxide production. Wallace and colleagues have demonstrated this in several reports and have provided evidence for aspirin-triggered lipoxins in the protection of mucosal lesions [32]. However, lipoxin A4 generation is not observed following the administration of non-aspirin NSAIDs such as indomethacin. Moreover, the lipoxin generation is completely inhibited by co-administration of a selective COX-2 inhibitor [33]. Wallace and coworkers had also previously demonstrated [34] that NSAID-induced gastric damage required the inhibition of both COX-1 and COX-2; that is, the selective suppression of either isoform alone did not result in significant gastric damage in otherwise healthy animals. This observation was confirmed by other investigators [35, 36]. Furthermore, recent studies have demonstrated that the acetylation of the COX-1 dimer alters the substrate's specificity for the second dimer: COX-2 [37]. These data demonstrated that it is difficult to attribute the gastrotoxic effects of indomethacin to only one factor, specifically the inhibition of COX-1. In another study, naloxone could not improve indomethacin-induced PGE2 inhibition, despite increasing the mucosal PGE2 level [38], although morphine could not prevent indomethacin-induced mucosal lesions while it did inhibit aspirin-induced mucosal lesions [39]. Even so, morphine has been reported to increase indomethacin-induced ulcers [40]. This case shows that the ulcerogenic mechanisms of indomethacin and aspirin, which inhibit COX-1 enzymes, are different. Ketotifen, an anti-allergic agent, was found to exert an anti-ulcer effect by reducing the PGE2 level in rats [41]. Lansoprazole, an anti-ulcer agent, does not affect gastric PG production [42]. Although the chronic administration of NSAIDs significantly inhibited PGE2 production, reduction in mucosal lesions (cytoprotection) was observed [43]. These data indicate that there is no direct parallelism between NSAID-induced GIS damage and the degree of COX and/or PG inhibition. Glucocorticoids are also known to

suppress the production of arachidonic acid and its metabolites by blocking the induction of the phospholipase A2 enzyme [44, 45]. Thus, stomach damage occurring as a result of inhibited PG synthesis is one of the most prevalent side effects of glucocorticoids [46]. However, the fact that glucocorticoids are ulcerogenic in intact rats while being anti-ulcerogenic in adrenalectomized rats [47] clearly shows that there is no direct relationship between PG inhibition and GIS damage.

In addition to its effects on PG production, indomethacin has been shown to be a prostaglandin D2 (DP) receptor agonist [48, 49], and activation of these receptors promotes chemotaxis of Th2 cells, eosinophils, and basophils, as well as the degranulation of eosinophils and cytokine release from Th2 cells [50–53]. In addition, PGD2 has been demonstrated to be involved in indomethacin-induced gastric ulcer formation; specifically, PGD2 application reduced indomethacin-induced ulcer formation in experimental models [54]. It is unclear why indomethacin both induces ulcers via PGD2 inhibition and behaves like a PGD2 receptor agonist. The literature also suggests that the arachidonic acid pathway cannot be the sole factor in indomethacin-induced ulcers.

INCREASE OF ACID SECRETION

The importance of increased gastric acid secretion in the occurrence of severe indomethacin-induced stomach damage has previously been shown [55]. It has been suggested that increased gastric acid secretion results from the inhibition of PG synthesis via indomethacin [23]. Cytoprotective PGs exert their protective effect on GIS mucosa by reducing gastric acid secretion [1, 56]. Most of the anti-ulcer drugs presently used are produced with the aim of reducing gastric acid secretion. Treatment of gastric ulcers by proton pump inhibitors, H2 receptor antagonists, and anticholinergic and antiacid drugs as a result of gastric acid inhibition can be exemplified [1, 57].

Stimulation of muscarinic receptors (M) in stomach parietal cells increases gastric acid secretion [1]. Anisodamine, an atropine analogue that antagonizes M receptors, has been reported to prevent indomethacin-induced gastric mucosal damage by inhibiting gastric acid secretion [58]. Also, the anti-ulcer effect of diltiazem has been seen in the inhibition of gastric acid secretion [59]. A common property of the drugs used in ulcer treatment is that they are intended for the inhibition of gastric acid [1, 60]. However, morphine could not prevent indomethacin-induced ulcers despite reducing gastric acid secretion [39]. This indicates that the relationship between inhibition of acid secretion and gastroprotection is not convincing. The inability of morphine to prevent indomethacin-induced ulcers despite reducing acid secretion and the inhibition of this effect by naloxone [39, 40] indicate that gastric acid is not an aggressive factor. Atropine, known to be a muscarinic receptor antagonist, reduces gastric acid secretion by blocking M receptors in parietal cells [1]. Atropine significantly prevents indomethacin-induced mucosal ulceration where the cytoprotective effect has decreased after bilateral surgical vagotomy. This proves that atropine produces a gastroprotective effect without reducing gastric acid secretion [61]. Both oral and intraperitoneal (IP) administration of butoxamin reduced indomethacin ulcers; however, oral administration increased PGE2 levels, while IP administration did not affect PGE2 levels [62]. These data expose that there is no relation between either PG and acid secretion or PG-acid secretion and gastric damage.

INCREASE OF GASTRIC MUCUS PRODUCTION

Prostaglandins are found to produce a gastroprotective effect not only via decreasing acid secretion, but also by increasing the gastric mucus level [63]. The importance of protecting the gastric mucosal barrier in gastroprotection has been shown [64]. In addition to mucosal PG and bicarbonate, reduction of mucus secretion is responsible for indomethacin-induced gastric ulcers [65]. It has also been determined that clonidine produces an anti-ulcer effect by decreasing gastric acid and pepsin secretion and increasing mucus secretion [66]. In an experimental study on rats, Guzel *et al.* showed that fish oil protects stomach tissue from indomethacin-induced ulcers by increasing the mucus secretion of stomach mucosa [67]. Propranolol protects stomach tissue from indomethacin, ethanol, and stress-induced ulcers by preventing the reduction in mucus levels [68]. In addition, rebamipide, a new anti-ulcer drug, has been reported to increase the gastric levels of PGE2 and PGI2, which can increase gastric mucus concentration [69]. Omeprazole, a classic anti-ulcer drug, is known as not only a proton pump inhibitor, but also as a stimulator of gastric mucus secretion [70]. However, some herbal alkaloids (*Rhizoma coptis chinensis*) were shown to produce a gastroprotective effect

without affecting gastric mucus secretion [71]. These data demonstrate that the relationship between the increase of mucus secretion and gastroprotection is not considerable.

EFFECTS ON BICARBONATE SECRETION

Gastroprotective PGs (PGE2) are known to increase gastric bicarbonate content [72]. Classic drugs used in peptic ulcer treatment are thought to increase the production of gastrocytoprotective PGs [1, 73]. This information demonstrates the importance of the PG-HCO3 relation in gastroprotection. An example of this is the decrease in bicarbonate secretion in parallel with the reduction in PG amounts in indomethacin-induced ulcers [66, 74]. Drugs with a gastroprotective effect, as well as classic anti-ulcer drugs, increase the basal bicarbonate production of the stomach and the pH of the gastric content [1, 58]. However, Nimacih *et al.* demonstrated experimentally that nizatidine and ranitidine, classic anti-ulcer drugs, increase HCO3 secretion, while famotidine does not [75]. These data indicate that the relationship between the inhibition of HCO3 secretion and ulcers and/or the stimulation of HCO3 secretion and gastroprotection is not remarkable (Table 1). Thus, we can conclude that it is impossible to associate gastric ulcer formation and cytoprotection with only one factor.

EFFECTS ON OXIDANT AND ANTIOXIDANT PARAMETERS

The role of toxic oxygen radicals in the etiopathogenesis of indomethacin-induced gastric damage has been shown [76]. Research studies show that antioxidant parameters reduced in gastric tissue with indomethacin-induced damage [77–80]. Indomethacin produces gastric damage via increasing mucosal myeloperoxidase (MPO) and malondialdehyde (MDA) levels [81]. Two hours after indomethacin administration, an acute increase occurs in the production of toxic oxygen radicals (superoxide and hydrogen peroxide) in the gastric mucosa [82]. This shows that gastric damage results from toxic radicals. MPO, present in phagocytic cells (PNL), catalyses toxic hypochlorous acid (HOCl) production from hydrogen peroxide (H2O2) [83]. PNLs cause the excessive uncontrolled production of reactive oxygen species such as superoxide anions (O2-) and hydroxyl radicals (OH-) [84]. Excessive production of MPO and other reactive radicals bring about oxidative damage. Measurement of lipid peroxidation levels is used to determine oxidative damage [85]. Lipid peroxidation is an important reason for cell membrane damage; MDA is the end product of lipid peroxidation and used to indicate the level of lipid peroxidation [86]. Indomethacin-induced increases in mucosal MPO and MDA levels have been improved by classic anti-ulcer drugs like omeprazole and lansoprazole [81]. Diltiazem, a calcium channel blocker, produced an anti-ulcer effect via inhibiting the increase in mucosal MDA [59]. Taurine prevented the gastric damage that occurred as a result of the activation, numerical increase, and adhesion of PNLs after indomethacin administration [87]. This effect shows the importance of MPO and MDA inhibition in preventing indomethacin-induced gastric damage. These neutrophil derivative reactive oxygen species are involved in the formation of indomethacin-induced ulcers [88]. The anti-ulcer and gastroprotective effects of proton pump inhibitors are related to the mechanisms that are not dependent on acidity, such as the prevention of oxidative tissue damage and neutrophil infiltration [70, 81]. This group of drugs decreases various neutrophil functions, like the adhesion of neutrophils to endothelial cells and the acidification of phagocytes and phagolysosomes [89–91]. These data introduce the role of toxic oxygen radicals in ulcer formation. Furthermore, these data show the importance of the reduction of toxic oxygen products in the anti-ulcer activity of drugs, and indicates that the relationship between antioxidant activity and the anti-ulcer effect is more important. Cimetidine, a classic anti-ulcer drug, prevented indomethacin-induced ulcers, although it did not inhibit granulocyte elastase secretion, which depends on leukocyte activation, and it did not decrease the high MPO activity [92]. In another study, diethyl dithiocarbamate (DDC), a superoxide dismutase (SOD) enzyme inhibitor, was determined to prevent indomethacin-induced mucosal damage while inhibiting SOD activity, suggesting that the suppression of gastric motility is more important than antioxidant activity in ulcer healing [93]. While MPO and MDA levels increased in indomethacin administered to rat stomach tissue, enzymatic and nonenzymatic antioxidant parameters decreased, including GSH, glutathione S-transferase (GST), SOD, catalase (CAT), and glutathione peroxidase (GPX) [82, 94–96]. In addition, the inhibition of indomethacin-induced gastric lesions is thought to be related to the antioxidant effect [97]. Pantoprazole produces an anti-ulcer effect via preventing the decrease

Table 1. Effects of Indomethacin and Antiulcer Drugs on Gastric Mucosa, Mucosal PG, Acid, Mucus and Bicarbonate Secretion (+ increases, − decreases, ± not effect). (ADX: Adrenalectomized, PO: Per oral, IP: Intra-peritoneal)

Drugs	Gastric damage	COX-1	PGE2	Acid	Mucus	Bicarbonate
Indomethacin	+	−	−	+	−	−
PGE2	−			−	+	+
PGI2	−			−	+	+
Aspirin	−	−	−			
Naloxone	−		±			
Ketotifen	−		−			
Cortisole(intact)	+	−	−			
Cortisole (ADX)	−	−	−			
Lansoprazole	−		±	−	+	
Anisodamin	−			−		
Diltiazem	−			−		
Morphine	+			−		
Atropine	−			±		
Butoxamine (PO)	−		+			
Butoxamine (IP)	−		±			
Clonidin	−			−	+	
Fish oil	−				+	
Propranolol	−				+	
Rebamipide	−		+		+	
R.coptis chinensis	−				±	
Ranitidine	−		+	−	+	+
Nizatidine	−		+	−	+	+
Famotidine	−		+	−	+	−

in GSH levels in indomethacin or other NSAIDs administered to animal gastric tissue [98]. Lansoprazole was shown to produce similar effects to those of pantoprazole by Blandizzi *et al.* [94]. However, Robert *et al.* reported that DEM, a sulfhydryl blocker, produces gastroprotection via reducing GSH in gastric mucosa, and that gastric glutathione alone is not protective against stomach damage [99]. This particular study demonstrates that there is no significant relationship between GSH levels and ulcers.

After indomethacin administration, a decrease occurred in the GST and SOD activities in gastric mucosal tissue [95, 96]. However, ranitidine significantly prevented indomethacin-induced ulcers, despite decreasing GST levels more than indomethacin did [96]. The same study demonstrated that an herbal extract that increases GST levels significantly when compared to the control (intact) and indomethacin groups, exerted lower anti-ulcer effects than ranitidine. The prevention or reduction of the increase in SOD activity exacerbates gastric mucosal damage and increasing lipid peroxidation [100]. Improvement of gastric damage using ozonized sunflower oil (OSO) was a treatment found to be related to a significant increase in SOD activity in rat gastric tissue [101]. However, as mentioned above, DDC, which inhibits SOD activity, prevented indomethacin-induced ulcers [93]. This suggests that there are more important factors than antioxidant activity involved in ulcer healing. The CAT and GPX levels decreased in gastric tissue with indomethacin-induced damage [82, 95]. Some literature contradicts these data; specifically, while indomethacin produced ulcers by increasing the CAT level in rat gastric tissue, ranitidine showed an anti-ulcer effect via decreasing CAT and GST activity [96]. Nevertheless, in another study, the effects of ranitidine on CAT and GST activities were found to be insignificant [102]. Ranitidine significantly increased GPX activity, which was decreased by indomethacin [103]. Some research reported that ethanol, known as an ulcerogen agent, increases GPX activity [104]. In addition, in a study performed by Berenguer *et al.*, the anti-ulcer activity of a herbal extract was found to have less of an anti-ulcer effect at the dose that increases GPX activity more [105]. These data show that there is no direct relationship between GPX activity and ulcers.

Indomethacin was found to produce ulcers via increasing gastric acid secretion and decreasing nitric oxide (NO) synthesis [106]. NO is known to regulate

acid and gastric mucus secretion and blood flow in stomach tissue [107]. In addition, NO was reported to prevent peroxidation of membrane lipids [108]. A significant decrease was observed in the damaged stomach tissue when compared to healthy tissue; ranitidine produced an anti-ulcer effect by increasing the NO level significantly when compared to the control [102]. There are also data representing reduced NO levels in damaged stomach tissue [109]. Nevertheless, Morsy *et al.* demonstrated that indomethacin increased the NO level and that eugenol produced an anti-ulcer effect via reducing the NO level (Fig. 1) [110]. The abovementioned contradictory studies also demonstrate that oxidative stress and the antioxidant mechanism are directly responsible for indomethacin-induced ulcers.

EFFECTS ON OTHER PARAMETERS AND SYSTEMS

Mukarami *et al.* indicated the benefits of inhibiting granulocyte elastase, which is released from activated leukocytes, in preventing NSAID-induced gastric lesions; in this study, rebamipide, an anti-ulcer drug, and ONO-5046, an inhibitor of granulocyte elastase, was shown to inhibit indomethacin-induced ulcers, while cimetidine inhibited indomethacin-induced ulcers without inhibiting granulocyte elastase [92].

The prevention of indomethacin-induced ulcers has also been related to the opening of K (ATP) channels. While the K (ATP) channel opener diazoxide prevented indomethacin-induced ulcers, the K (ATP) channel antagonist glibenclamide ameliorated the gastric ulcer [111]. In another study, hydralazine was reported to have no effect on indomethacin-induced ulcers [112]. Hydralazine was reported to be a potassium channel opener [113]. These data cannot completely clarify the role of potassium channel activation in anti-ulcer activity.

Indomethacin produces gastric mucosal lesions with the reduction in the PGE2 level following neutrophil infiltration and an increase in the TNF-α levels in gastric mucosa; exogenous administration of PGE2 produced an anti-ulcer effect by preventing the indomethacin-induced TNF-α increase. In the same study, while pentoxifylline and PGE2 produced an anti-ulcer effect by preventing the increase in TNF-α levels, methotrexate produced an anti-ulcer effect without affecting TNF-α [24].

Indomethacin produces gastric mucosal damage by increasing the cAMP level in gastric mucosal tissue [73]. Also, naloxone was seen to improve indomethacin-induced ulcers by increasing the mucosal cAMP level [38]. These data also fail to explain the formation mechanism of indomethacin-induced ulcers.

A NEW HYPOTHESIS TO EXPLAIN INDOMETHACIN-INDUCED GASTRIC ULCERS: BLOCKAGE OF α 2 ADRENERGIC RECEPTORS

Presynaptic α 2 receptors have previously been reported to play a role in the inhibition of indomethacin-, aspirin-, ethanol-, stress-, and pyloric-ligation-induced ulcers [114–116]. α 2 adrenoreceptors have subtypes such as α 2A, α 2B, and α 2C. α 2A receptors have been shown to be responsible for the inhibition of gastric emptying and increased motor activity, while the α 2B and α 2C receptor subtypes are responsible for gastroprotection [117, 118]. α 2 Receptors produce gastroprotective effects through multiple mechanisms [117] that involve the stimulation of α 2 receptors to inhibit gastric acid secretion and motility. These effects occur with the activation of presynaptic α 2 receptors in the vagus nerve and the inhibition of acetylcholine release [118].

In previous studies, nimesulide, an anti-inflammatory drug, was surprisingly shown to prevent indomethacin-induced ulcers in intact rats [13]. However, nimesulide ameliorated indomethacin-induced ulcers in adrenalectomized rats and even produced gastric ulcers when used alone [119]. This situation made researchers hypothesize that there is an adrenal gland–derived factor that has a role in ulcer formation. Then, the authors exhibited the role of cortisol, an adrenal cortex hormone, and adrenaline, an adrenal medulla hormone, in the anti-ulcer effect mechanism of nimesulide [47]. In addition, Filaretova *et al.* showed that in adrenalectomized rat stomach, corticosterone can antagonize the gastric damage produced by celecoxib, an NSAID [120]. In light of the discovery that glucocorticoids can be gastroprotective in adrenalectomized rats, Suleyman et al. determined that in adrenalectomized rats, the anti-ulcer effect of prednisolone, a glucocorticoid, is antagonized by yohimbine, an α-2 adrenergic receptor blocker [47], suggesting a possible role of α-2 adrenergic receptors in the gastroprotective effects of glucocorticoids. This study also demonstrated that adrenalin prevented indomethacin-induced ulcers in both intact and adrenalectomized rats; however, prednisolone increased indomethacin-induced ulcers in intact rats and decreased indomethacin-induced ulcers in adrenalec-

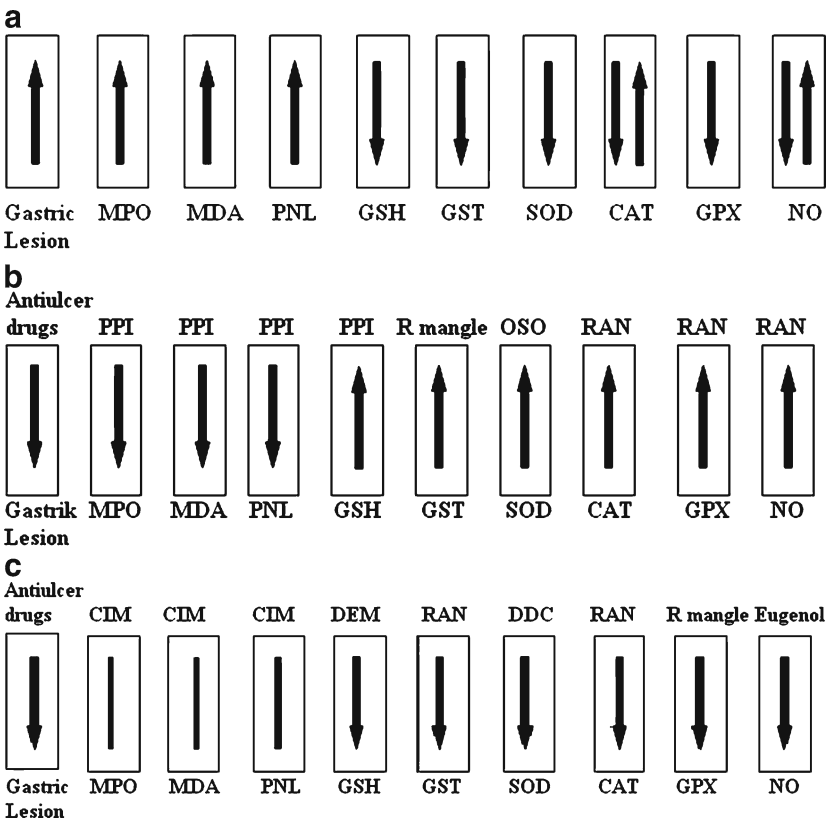

Fig. 1. **a** Effects of indomethacin on oxidant and antioxidant parameters in gastric tissue (↑ *increases*, ↓ *decreases*, ↑↓ *both increases* and *decreases*). **b** Effects of anti-ulcer drugs on oxidant and antioxidant parameters in gastric tissue of indomethacin given rats (↑ *increases*, ↓ *decreases*). **c** Effects of anti-ulcer drugs on oxidant and antioxidant parameters in gastric tissue of indomethacin given rats (↓ *decreases*, | *not effect*). RAN: ranitidine, CIM: cimetidine.

tomized and/or intact rats whose adrenalin level was decreased via metyrosine [47, 121]. These data demonstrate that increasing glucocorticoid levels when adrenalin presents in the body (at normal levels) produces gastric damage. Additionally, glucocorticoids may produce an anti-ulcer effect by binding α 2 adrenergic receptors in the absence or scarcity of adrenalin [47]. As we mentioned above, the α 2 adrenergic (α 2B, 2C) receptors have been reported to take roles in gastroprotection [117]. Suleyman *et al.* reported that nimesulide prevents indomethacin-induced ulcers by reducing adrenalin levels [47]. Because of the inhibition of indomethacin-induced ulcers via clonidine, an α 2 adrenergic receptor antagonist [122], we suggest that indomethacin produces gastric damage by blocking α 2 adrenergic receptors. Metyrosine, a thyroxine hydroxylase inhibitor, decreases cathecolamine synthesis by 35% to 80% [123, 124]. Prednisolone, a glucocorticoid, prevented indomethacin-induced ulcers in rats given metyrosine [47]. Furthermore, these data suggest that prednisolone produces an anti-ulcer effect via α 2 adrenergic receptors. L-dopa prevented indomethacin-induced ulcers; while haloperidol, a dopamine antagonist, failed to inhibit the gastroprotective effect of L-dopa, yohimbine successfully inhibited the effects of L-dopa [122]. When we reevaluate these latest data in combination with previous results, we can suggest that there is an extremely significant relationship between indomethacin-induced ulcers and α 2 adrenergic receptors.

CONCLUSION

In conclusion, this review argued that blockage of α 2 adrenergic receptors may be responsible for the increase of the mentioned aggressive factors induced by

indomethacin, and stimulation of α 2 adrenergic receptors may be responsible for the increase of the mentioned protective factors of antiulcer drugs.

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