ANIMAL MODELS TO EVALUATE THE CAUSE BEHIND GASTRIC ULCERS

Saini Amita*, Sharma Nidhi, Sharma Ramica
Rayat Institute of Pharmacy, Railmajra, S.B.S. Nagar, Gujarat, India

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*Email: amita.bpharma@gmail.com

ABSTRACT
Peptic ulcer is the major cause of mortality and morbidity in developing countries, characterised by imbalance between aggressive gastric luminal factor and defensive mucosal barrier. This disease is mainly associated with increase in gastric acid secretion. Numerous factors like diet, smoking, drugs like aspirin and infection are responsible for augmentation of ulcers. Still, no therapeutic intervention has been found successful. So, this review has been designed to explore various animal models to find out a suitable medication. Various synthetic Omeprazole, cemitidine and herbal drugs like tulsi, Areca catechu are employed in the management of the ulcers but still no curative treatment is available due to unknown mechanism behind ulceration. So this review has been designed to explore various animal models that depict the signalling pathway involved in ulcers and have open vista for the development of the new drugs.

KEY WORDS: peptic ulcers, therapeutic intervention, animal models.

INTRODUCTION
Ulcers are deep lesions penetrating through the entire thickness of the gastrointestinal tract (g.i.t) mucosa and muscularis mucosa. Generally ulcers occur in the stomach or duodenum. Ulcers develop due to exposure of stomach lining to the acids produced in the digestive juices. Further, the basic cause of ulceration is imbalance between gastric offensive factors (pepsin, lipid Peroxidation, nitric oxide) and defensive factors (mucin secretion, glycoprotein and glutathione). Various factors are implicated that play a pivotal role in the pathogenesis of ulcers like, sedentary life style, alcohol intake, spicy food, drugs and various bacterial infections like Helicobacter pylori. It has been reported that during ulceration various mediators like tumour necrosis factor-α (TNF-α), nitric oxide (NO), reactive oxygen species (ROS), oxidative stress are implicated in the pathogenesis of ulceration. During gastric and duodenal ulceration there is decrease expression of inducible Nitric oxide synthase (iNOS). Decreased activity of iNOS results in decrease generation and bioavailability of Nitric oxide (NO) and results in oxidative damage. Nitric oxide is endothelial derived relaxing factor. Nitric oxide include a reduction in the acid secretion and have gastroprotectant action. Moreover, Oxidative stress is a one of the major factors that indirectly impaired cell function, promote cellular organelles damage in the cells. Due to the generation of the ROS could causes directly disrupt in the mitochoandrial membrane that leads to membrane rupture of the lysosomes, causing the release of cathepsins which than activate the caspases and finally leads to the cell death by apoptosis. Further, ROS has been found to causes peroxidation of lipid and protein along with DNA damage. Moreover, in inflamed gastric mucosa there is increased level of Tumour necrotic factor-α (TNF-α) and various cytokines like Interlukin-8(IL-8). Further, drugs like Non steroidal anti-inflammatory drugs (NSAID) are too responsible for the progression of ulceration. Cyclooxygenase-1(COX-1) inhibition by the NSAIDS leads to the significant release of the endothelin-1(ET-1) which is a potent vasoconstriction which has been shown to induce mucosal injury. NSAIDS by Inhibiting the cyclooxygenase-1 (COX-1) causes marked reduction in Mucosal blood flow, impaired platelet aggregation, increased leukocyte adherence and mucus secretion that are responsible for pathogenesis of ulceration. Moreover, with COX inhibition there is inhibition of prostaglandins (PG) which are reported as ulceroprotective as they stimulate mucus and bicarbonate secretion in the stomach. H. pylori infection is an interaction of the host cells with the bacteria. And have been reported to be implicated in the various gastrointestinal (g.i.t) diseases such as gastric ulcer, adenocarcinoma and lymphoproliferative disorders. Gastric mucosa infected with the H. pylori induced inflammation is implicated in the development of the mucosal damage and is characterised by the strong granulocytic and lymphocytic infiltration. H. Pylori induces a three fold increase in the serum gastric concentration. Certain cytokines released in the H. Pylori gastritis such as TNFα and specific products of H. Pylori such as ammonia. Further, IL-1 beta is too overexpressed in the H. Pylori induced gastritis. Various methods are available for inducing ulcers experimentally like ethanol, ceramide, indomethacin. So this review has designed to study various models for ulcers which include signalling pathway involved in the progression of the ulcers.

VARIOUS ULCER MODELS
Ceramide-induced gastric ulcer
Ceramide are the highly bioactive sphingolipids, involved in the diverse cell processes, including cell-cell interactions, adhesion, cellular proliferation, differentiation and oncogenic transformation. Phorbol 12-myristate 13-acetate (PMA) is a derivative of ceramide when injected subserosally in rats with a dose of 50 µg leads to the ulcer formation. Ceramide have emerged as key participants in the signalling pathway of the cytokines and apoptosis. Ceramide participate in the mediation of the tumour necrosis factor-α (TNF-α) and interferon-γ. Ceramide has also been reported to induce IL-6 production in fibroblast and IL-2 secretion in lymphocytes and IL-1-induced E-selectin expression in the endothelial cells. Ceramide also activate the transcription factor nuclearfactor-kB(NF-kB) and Nuclear factor-kB (NF-Kb) is an ubiquitous rapid response factor in cells involved in immune and inflammatory reactions. Nuclear factor-Kb exerts its effect by expressing cytokines, chemokines, cell adhesions molecules, growth factor and immunoreceptor. Activation of the TNF-α by the ceramide triggers the release of stress activated kinases like...
Indomethacin belongs to the category of the NSAIDS plays an important role in the progression of the gastric ulcers. Ulcer formation induced by indomethacin is known to be related the inhibition of the cyclooxygenase (COX), that in turn inhibit the release of the mucus. It has been reported that indomethacin also accounts for the activation of the neutrophil, generation of the free radicals in response to the oxidative stress, which than contribute to the lipid peroxidation. Indomethacin induced ulcers. Indomethacin exerts its anti-inflammatory effects by the suppression of PG synthesis. Suppression of PG have a negative impact upon the secretion of the mucus and bicarbonate by gastric acid, the function of immunocytes (eg: mast cells) . Cyclooxygenase, a primary enzyme responsible for PG synthesis, exists in two forms COX-1 and COX-2. COX-2 has been shown to play pivotal role in ulcer healing, such that its inhibition leads to significant impairment of ulcer healing and angiogenesis . Neutrophils have implicated as playing crucial role in induction of endothelial injury. NSAIDS administration results in rapid and significant increase in the number of neutrophils adhering to the vascular endothelium . The adherence of the neutrophils to the vascular endothelium depends upon the β integrins and intercellular adhesion molecule-1 (ICAM-1) on the vascular endothelium . Leukotrienes are the another group of mediators that might contribute to the increase in neutrophil adherence to the vascular endothelium and the mucosal injury that occurs after NSAIDS administration. Leukotrienes are derived from arachidonic acid. They have been shown to increase the susceptibility of the gastric mucosa to injury and also have stimulatory effects on the neutrophils adherence to the vascular endothelium . Fig 2 shows indomethacin induced ulcers

HCl-induced ulcers

Oral administration of 1.5ml of HCl contribute to the significant increase in the number of the gastric mucosa, volume of gastric juice. Oxidative stress also play pivotal role in the progression of the ulcers induced by HCl. Further, this oxidative stress leads to the generation of the free radicals and lipid peroxidation. The administration of the HCl leads to the sodium (Na) and potassium (K) flux into the lumen and increase the release of histamine and pepsin . It also depresses the level of DNA, RNA and protein synthesis

Reserpine-induced ulcers

Reserpine is derived from the roots of the rawolphia serpentine. reserpine is an indole alkaloid having antipsychotic, antihypertensive and post sympathetic blocking property that impairs the storage of biogenic amine by interfering with an uptake mechanism. It has been reported that reserpine play pivotal role in the progression of ulcers. Various reports indicates that administration of 8mg/kg reserpine causes the degranulation of mast cells with increase in the gastric acid secretion by sympathetic activation. Reserpine is documented to generate free radicals and inhibit the prostaglandin synthesis. Inhibition of the mucus release and surface mucus breakdown by the β – adrenoreceptor have also been attributed to the ulcerative potentials of the reserpine

Cysteamine-Induced Ulcers

Cysteamine is low molecular weight amino thiol and natural product of coenzyme A. It has been reported that cysteamine leads to the progression of the duodenal ulcers by elevating the levels of the gastrin and also increase the level of gastric acid secretion. Activation of the hypoxia inducible factor 1α (transcription factor) play important role in the pathogenesis of the ulcers induced by the cysteamine. This aminothiol generate hydrogen peroxide in the presence of transition elements, producing oxidative stress which may contribute to organ specific damage. Cysteamine induced duodenal ulcer in the presence of pretreatment with the fe2+ and fe3+ compounds which elevated iron concentration in the duodenal ulcers. Moreover cysteamine also enhanced the activation of mucosal regulatory protein1. Transferring receptor 1 protein expression also increased, which leads to the expansion of the intracellular labile iron pool in the duodenal mucosa, which causes lipid peroxidation.

CONCLUSION

This review concluded that numerous factors and signalling pathways are implicated in the pathogenesis of ulceration. So, with this review various new interventions are developed for the management of ulcers by studying various animal models.

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TABLE 1: NOVEL TARGETS IN THE MANAGEMENT OF THE ULCERS

<table>
<thead>
<tr>
<th>MAPK</th>
<th>SPECIFIC INHIBITORS</th>
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<tbody>
<tr>
<td>1)</td>
<td>PD98059</td>
</tr>
<tr>
<td></td>
<td>Specific inhibitors of MAPK/MEK</td>
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<tr>
<td>2)</td>
<td>SB203580</td>
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<tr>
<td></td>
<td>Specific inhibitors of P38 MAPK</td>
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<tr>
<td>3)</td>
<td>SB202190</td>
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<tr>
<td></td>
<td>Potent and selective inhibitors of P38 MAPK</td>
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<tr>
<td>TNF-α INHIBITORS</td>
<td></td>
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<tr>
<td>Rtitumab</td>
<td>Lukenia treatment</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Treat autoimmune response by interfering with TNF-α</td>
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<tr>
<td>JNK</td>
<td>SPECIFIC INHIBITORS</td>
</tr>
<tr>
<td>1)SP600125</td>
<td>JNK inhibitor</td>
</tr>
<tr>
<td>NF-Kb</td>
<td>SPECIFIC INHIBITORS</td>
</tr>
<tr>
<td>1) IFRD1</td>
<td>NF-Kb inhibitor</td>
</tr>
<tr>
<td>2) OLMESARTAN</td>
<td>NF-Kb P65 inhibitor</td>
</tr>
<tr>
<td>3) DITHICARBAMATES</td>
<td>NF-Kb inhibitor</td>
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FIG 2: INDOMETHACIN INDUCED ULCERS
INDOMETHACIN

DECREASED COX

REDUCED MUCOSAL BLOOD FLOW

DECREASED PG

IMPAIRED ANGIOGENESIS

REDUCED MUCUS SECRETION

IMPAIRED DEFENCE

IMPAIRED DEFENCE

GASTRIC ULCERS