INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Review Article

ANIMAL MODELS TO EVALUATE THE CAUSE BEHIND GASTRIC ULCERS

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Article Received on: 08/04/12 Revised on: 29/06/12 Approved for publication: 20/07/12

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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[1]. 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)[1]. Various factors are implicated that play a pivotal role in the pathogenesis of ulcertions 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[2]. During gastric and duodenal ulceration there is decrease expression of inducible Nitric oxide synthase (iNOS)[3]. Decreased activity of iNOS results in decrease generation and bioavailability of Nitric oxide (NO) and results in oxidative damage[3]. Nitric oxide is endothelial derived relaxing factor[4]. Nitric oxide include a reduction in the acid secretion and have gastroprotectant action[2]. Moreover, Oxidative stress is a one of the major factors that indirectly impaired cell function, promote cellular organelles damage in the cells[5]. Due to the generation of the ROS could causes directly distrupt in the mitrochondrial membrane that leads to membrane rupture of the lysosome, 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[5]. Moreover, in inflamed gastric mucosa there is increased level of Tumour necrotic factor- α (TNF-α) and various cytokines like Interlukin-8(IL-8)[6].Further, drugs like Non steroidal anti-inflammatory drugs (NSAID) are too responsible for the progression of ulceration[7] .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 [7]. 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 [8] 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, adrenocarcinoma and lymphoproliferative disorders[9]. 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 infilteration[9]. 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[9].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, cell proliferation, differentiation and oncogenic transformation[10]. 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[11]. Ceramide have emerged as key participants in the signalling pathway of the cytokines and apoptosis[10]. Ceramide participate in the mediation of the tumour necrosis factor-α (TNF-α) and interferon-y[12].Ceramide has also been reported to induce IL-6 production in fibroblast[13], IL-2 secretion in lymphocytes[14] and IL-1-induced E-selectin expression in the endothelial cells. Ceramide also activate the transcription factornuclearfactor-kB(NF-kB)[15]

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

C-JUN (janus kinase), leads to the apoptosis due to oxidative damage.

Ethanol-induced ulcers

Administration of 1ml of ethanol leads to the ulceration via penetrating in the gastric mucosa. It has been documented that ethanol increases the vascular permeability and causes the release of vasoactive products[16]. Further, Ethanol causes severe damage to the gastrointestinal mucosa with microvascular injury results in increase vascular permeability. Moreover, ethanol decreases the secretion of biocarbonate (HCO_3^-) and mucus damage. Various evidences indicates that during ethanol-induced ulceration there is increase neutrophil infiltration in the gastric mucosa that results in increase oxidative stress with increased generation of free radicals [17], that is reported as major hallmark in the pathogenesis of ulceration. Further Ethanol also has been reported to activate TNF-α and mitogen activated protein kinases (MAPK)[16]. Further, ethanol has been reported to initiate apoptosis which lead to cell death[16].Cell death is mainly responsible for progression of ulcers. Further ethanol generate the ROS which leads to the induction of the ulcers. Protein tyrosine phosphtase (PTP) has been reported to play important role in the induction of ulcers[18]. Figure 1 illustrates mechanism involved in the progression of ethanol induced ulcers.

Indomethacin-induced gastric ulcers

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[19]. It has been reported that indomethacin also accounts for the activation of the neutrophil, generation of the free redicals 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 biocarbonate by gastric acid, the function of immunocytes (eg: mast cells) [20]. 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 impairement of ulcer healing and angiogensis[20]. 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[19]. The adherence of the neutrophils to the vascular endothelium depends upon the β_2 integrins and interacellular adhesion molecule-1(ICAM-1) on the vascular endothelium[21]. Leukotrines 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. Leukotrines are derived from arachidonic acid. They have been shown to increase the succeptibilty of the gastric mucosa to injury and also have stimulatory effects on the neutrophils adherence to the vascular endothelium[20]. 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 redicals 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[22]. It also depresses the level of DNA, RNA and protein synthesis

Reserpine-induced ulcers

Reserpine is derived from the roots of the rawolfia serpentine. reserpine is a 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[23] with increase in the gastric acid secretion by sympathetic activation. Reserpine is documented to generate free redicals and inhibit the prostaglandin synthesis. Inhibition of the mucus release and surface mucus breakdown by the β – adrenoreceptor [24] 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 [25]. 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 pathogensis of the ulcers induced by the cysteamine[26]. This aminithiol 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 fe^{3+} and fe^{2+} 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 managment of ulcers by studying various animal models.

ACKNOWLEDGEMENT

I am very thankful to the management of Rayat institute of pharmacy, my director Dr. AC Rana and my guide for guiding me and providing us the scientific facilities that helped me a lot in completing my literature survey.

REFERENCES

1. Jones MK, Kawanaka H, Baatar D, Szabó IL, Tsugawa K, Pai R, Koh GY, Kim I, Sarfeh IJ, Tarnawski AS. Gene therapy for gastric ulcers with single local injection of naked DNA encoding VEGF and angiopoietin-1. Gastroenterol 2001;121:1040-1047.
2. Ma L, wallance JL. Endothelial nitric oxide synthase modulates gastric ulcer healing in rats. Am. J physiol Gastrointest. Liver physiol 2000;279:4341-4346.
3. Yamasaki K, Edington HD, McClosky C, Tzeng E, Lizonova A, Kovesdi I, Steed DL, Billiar TR. Reversal of impaired wound repair in iNOS deficient mice by topical adeno viral mediated iNOS gene transfer. J clin invest 1998;101:967-971.
4. Takeuchi K, Mizoguchi H, Araki H, Komoike Y, Suzuki K. Lack of gastric toxicity of nitric oxide releasing indomethacin. NCX-530 in experimental pharmacology. Dig Dis Sci 2001;43:1805-1878.
5. Dotan Y, Lichtenberg D, Pinchuk I. Lipid peroxidation cannot be used as universal criterion of oxidation stress. Prog Lipid Res 2004;43:200-227.
6. Crabtree JE, Peichl P, Wyatt JI, Stachl U, Lindley IJ. Gastric interleukin-8 and IgA IL-8 autoantibodies in Helicobacter Pylori infection. Scand J immunol 1993;37:65-70.
7. Toshiyuki F, Koji C, Takuya H, Yoshihiro K, Aishi K, Masao S. Mucosal acid causes gastric mucosal microcirculatory disturbance in

nonsteroidal anti-inflammatory drug treated rats. Eur J Phramacol 2007;554:53-59.
8. Allen A, Flemström G, Garner A, Kivilaakso E. Gastro duodenal mucosal protection. Physio Lev 1993;73:823-857.
9. Martin J. Not all Helicobacter pylori strains are created equal; should all be eliminated. Blases in Lancet 1997;349:1020-22.
10. Kolesnick RN, Kronke M. Regulation of ceramide production and apoptosis. Annu Rev Physiol 1998;60:643-65.
11. Uehara K, Miura S, Takeuchi T, Taki T, Nakashita M, Adachi M, Inamura T, Ogawa T, Akiba Y, Suzuki H, Nagata H, Ishii H. Significant role of ceramide pathway in experimental gastric ulcer formation in rats. The Journal of pharmacology and Experimental Therapeutics 2003;305:232-239.
12. Dbaibo GS, Obeid LM, Hannun YA. Tumour Necrosis Factor-α (TNF-α) Signal Transduction through ceramide dissociation of growth inhibitory effects of TNF-α from activation of nuclear factor-κB. J Biol Chem 1993;268:17762-17766.
13. Laulederkind SJ, Bielawska A, Raghow R, Hannun YA, Ballou LR. Ceramide induces interlukin 6 gene expression in human fibroblast. J Exp Med 1995;182:599-604
14. Mathias S, Younes A, Kan CC, Orlow I, Joseph C, Kolesnick RN. Activation of Sphingomyelin Pathway in intact EL4 cells and in a cell free system by IL-1β. Science (Wash DC) 1993;259:519-522.
15. Verma IM, Stenenson JK, Schwarz EM. Rel / NF-κB /IκB family initates tales of association and dissociation. Genes Dev 1995;9:2723-2735
16. Mahmood AA, Al-Bayaty FH, Salmah I, Nor Syuhada AB, Harita H and Mughrabi F. F3Enhacement of gastric ulcer of gastric ulcer by areca catechu nut in ethanol induced gastric mucosal injuries in rats. Journal of medicinal plant Research 2011;5(12):2562-2569.
17. Bogdanova OV, Kot LI, Lavrova KV, Bogdanov VB, Sloan EK, Beregova TV, Ostapchenko LI. Modulation of protein tyrosine phosphorylation in gastric mucosa during re-epithelization processes. WJBC 2010;1:338-347.
18. Dengiz GO, Gursn N. Effects of momordica charantia L (cucurbitaceae) on indomethacin induced ulcer model in rats. Turk J Gastroentrol 2005;16(2):85-88
19. Roberta GC, Leônia MB, Lourdes CDS, Alba RMDSB; Wagner V. Phytochemical study and antiulcerogenic activity of syngonathus bisulcatus (Eriocaulaceae). Brazilian Journal of Pharmaceutical Scinces 2006;42:3
20. Wallance JL. Pathogensis of NSAID induced gastroduodenal mucosal injury. Best practice & Research gastroenterology 2001:5(15):691-703.
21. Andrew FJ, Malcontenti- Wilson C & O'brien PE. Effect of non-steroidal anti-inflammatory drugs on LFA-1 and ICAM-1 expression in gastric mucosa. American journal of physiology 1994; 266:657-664
22. Hung CR, NEU SL. Acid induced gastric damage in rats is aggravated by starvation and prevented by several nutrients. Nutrient requirements and interactions 1996.
23. Cho CH, Ogle CW, Dai S. A Study on the etiology of reserpine ulceration and the antiulcer action of soleoseryl in rat stomach. Journal of Pharmacy and Pharmacology 1985;37:823-825.
24. Sadiq Y, Alexander BA, Andrew JN, Danladi AA and Emmanuel OB. Effect of acute bilateral adrenalectomy andreserpine on gastric mucus secretion and mucosal injury in pyloric ligated rats. African Journal of Biotechnology 2007;7(17):3143-3148.
25. Miller SL, Schlesinger G. Prebiotic Synthesis Of vitamin coenzyme. Cysteamine and 2-Mercaptoethanesulfonic acid (Conenzyme M). J Mol Evol 1993;36:302-307.
26. Khomenko T, Szabo S, Deng X, Ishikawa H, Anderson GJ, McLaren GD. Role of iron in the pathogensis of the cysteamine induced duodenal ulcers. Amj Physiol Gastrointest Liver Physiol 2008;296:G1277-G1286.

TABLE1: NOVEL TARGETS IN THE MANAGEMENT OF THE ULCERS

MAPK	SPECIFIC INHIBITORS
1) PD98059	Specific inhibitors of MAPKK/MEK
2) SB203580	Specific inhibitors of P38 MAPK
3) SB202190	Potent and selective inhibitors of P38 MAPK
TNF-α INHIBITORS	
Rituximab	Lukemia treatment
Etanercept	Treat autoimmune response by interfering with TNF-α
JNK	SPECIFIC INHIBITORS
1)SP600125	JNK inhibitor
NF-Kb	SPECIFIC INHIBITORS
1) IFRD1	NF-κB P65 inhibitor
2) OLMESARTAN	NF-κB inhibitor
3) DIITHICARBAMATES	NF-KB inhibitor

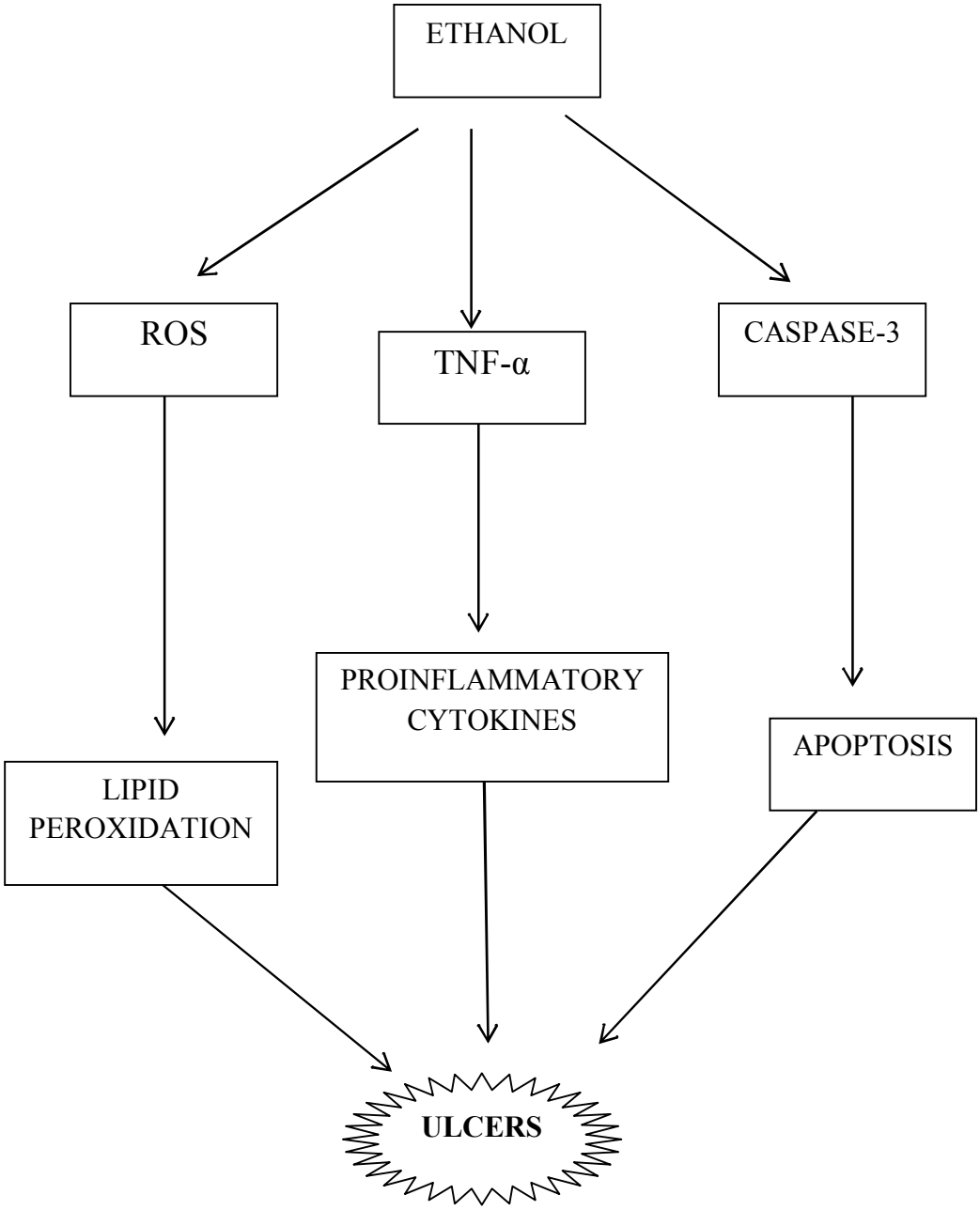

FIG 2: INDOMETHACIN INDUCED ULCERS