Small Intestinal Injury Caused by NSAIDs/Aspirin: Finding New from Old

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Abstract: Small intestinal injury caused by non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin is an epoch making topic in clinical field with the aid of new devices, capsule endoscopy and double balloon enteroscopy to look at small intestine directly. However, the injury has been reported in animals since more than 40 years ago. Proposed mechanisms are impairment of mucosal defense through inhibition of cyclooxygenase (COX) resulting in deficiency of prostaglandins, and mitochondrial disorder. Possible aggressive factors are NSAIDs/aspirin themselves, bile, and enterobacteria. Translocation of enterobacteria through the mucosa impaired integrity may be the first step of the injury. Bacterial lipopolysaccharides stimulate toll-like receptor-4 in macrophages, which increases proinflammatory cytokines through MyD88 signaling pathway. Finally neutrophils are activated and the small intestinal mucosa is injured with the attacks of NSAIDs/aspirin themselves, bile, and proteolytic enzymes and active oxygen species released by neutrophils. Candidates of treatment tools are prostaglandin derivatives, mucoprotective drugs, probiotics, and mitochondrial protective drugs such as metronidazole and cyclosporin A. Further clinical studies are needed to elucidate the effect in humans.

Keywords: Aspirin, cyclooxygenase, injury, mitochondria, NSAID, prostaglandin, small intestine.

INTRODUCTION

Small intestinal injury caused by indomethacin, a non-steroidal anti-inflammatory drug (NSAID), has been at the first time published in 1966 [1] and since then, numerous such reports have been published. On the other hand, there have only been a few references to intestinal damage caused by aspirin [2]. The difference between NSAIDs and aspirin can be explained as the difference in pharmacodynamics. Namely, NSAIDs such as indomethacin is absorbed in upper gastrointestinal (GI) tract, excreted from biliary tract, and reabsorbed from small intestine [3]. This is called entero-hepatic cycle. Aspirin is, however, excreted from urinary tract after absorption from upper GI tract [4]. Therefore, NSAIDs is directly exposed to small intestine but not aspirin. Direct contact is needed for such agents to cause mucosal damage [5].

In spite of these valuable experimental data, possible small intestinal damage caused by NSAIDs has been ignored in humans for long time because there had not been useful tools to examine small intestine in clinical field. Recently, two important modalities have been available to look at the human intestine; video capsule endoscopy and double-balloon enteroscopy. Small intestinal injury caused by NSAIDs has been reported six years ago using capsule endoscopy, indicating high incidence of the lesions in chronic NSAIDs users [6]. Even low-dose aspirin has been reported to cause ulceration at human small intestine [7] in spite of the negative experimental results. To elucidate the underlying mechanisms of such small intestinal injury is important to find prevention and treatment for the lesions.

DAMAGING EFFECT OF NSAIDS/ASPIRIN IN SMALL INTESTINE - TOPICAL OR SYSTEMIC?

Considering difference in pharmacodynamics and small intestinal ulcerogenicity between NSAIDs and aspirin as mentioned above, direct exposure may be important for occurrence of injury. Ligation of bile duct prevents the increased permeability and mucosal injury at small intestine caused by NSAIDs suggesting its direct contact by entero-hepatic recirculation is important for the injury [8, 9]. Oral administration of aspirin does not cause small intestinal injury. This may be due to absence of aspirin exposure to small intestine not like NSAIDs because of its rapid absorption from stomach and duodenum under acidic condition and lack of entero-hepatic recirculation. Ivey *et al.* [5] have tested the effect of direct exposure of aspirin to jejuna mucosa in three obese patients with a small intestinal bypass that opened on the abdominal wall as a mucous fistula, showing the damaging effect of aspirin on direct contact. This direct toxicity has been reported using intestinal epithelial cell line *in vitro* [10, 11]. In such *in vitro* study, bile enhances the damaging effect of NSAIDs [11], suggesting involvement of bile in NSAIDs-induced small intestinal injury. Recently, Okabe's group established a new rat model of aspirin-induced small intestinal injury to introduce aspirin directly into duodenum [12]. This model may mimic small intestinal injury in humans who take enteric-coated aspirin. Incidence of small intestinal injury is relatively large in patients taking enteric-coated low-dose aspirin compared to those taking buffered one in a pilot study [13]. About 40 years ago, aspirin has been at the first time reported to cause small intestinal injury in fed rats being about 10 times more sensitive to fasted rats [14]. Mechanisms are unknown. Feeding may help aspirin for direct contact to small intestine. In humans, most people take aspirin with or after meal. This may be one of the reason why oral aspirin, even none-enteric-coated one, causes small intestinal injury in humans.

MECHANISMS OF NSAIDS-INDUCED SMALL INTESTINAL INJURY

Small intestinal injury may occur in the condition in which aggressive factors overcome defensive factors like stomach. NSAIDs impair intestinal mucosal integrity possible through cyclooxygenase (COX)-dependent and independent pathways (Fig. **1**). Candidates of aggressive factors are NSAIDs themselves, bile, and bacterial flora. The possible mechanisms of aspirin producing small intestinal injury are similar to those of NSAIDs in the limited condition that aspirin can be delivered to small intestinal lumen.

COX-Dependent Mechanism - Prostaglandins

Prostaglandins (PGs) exert strong protective action in gastrointestinal mucosa, which is called "cytoprotection" [15]. NSAIDs inhibit COX, the enzyme producing PGs from arachidonic acid, resulting in deficiency of endogenous PGs. Exogenous PGs inhibit small intestinal injury caused by indomethacin [16], suggesting PG deficiency produced by this agent may have an important role in this injury. Similarly to stomach [17], inhibition of both COX-1 and -2 is needed to induce small intestinal injury [18]. PG deficiency causes disruption of mucosal integrity, hence permit bacteria to invade into the mucosa. Takeuchi *et al.* [19] have demonstrated that intestinal hypermotility caused by NSAIDs-

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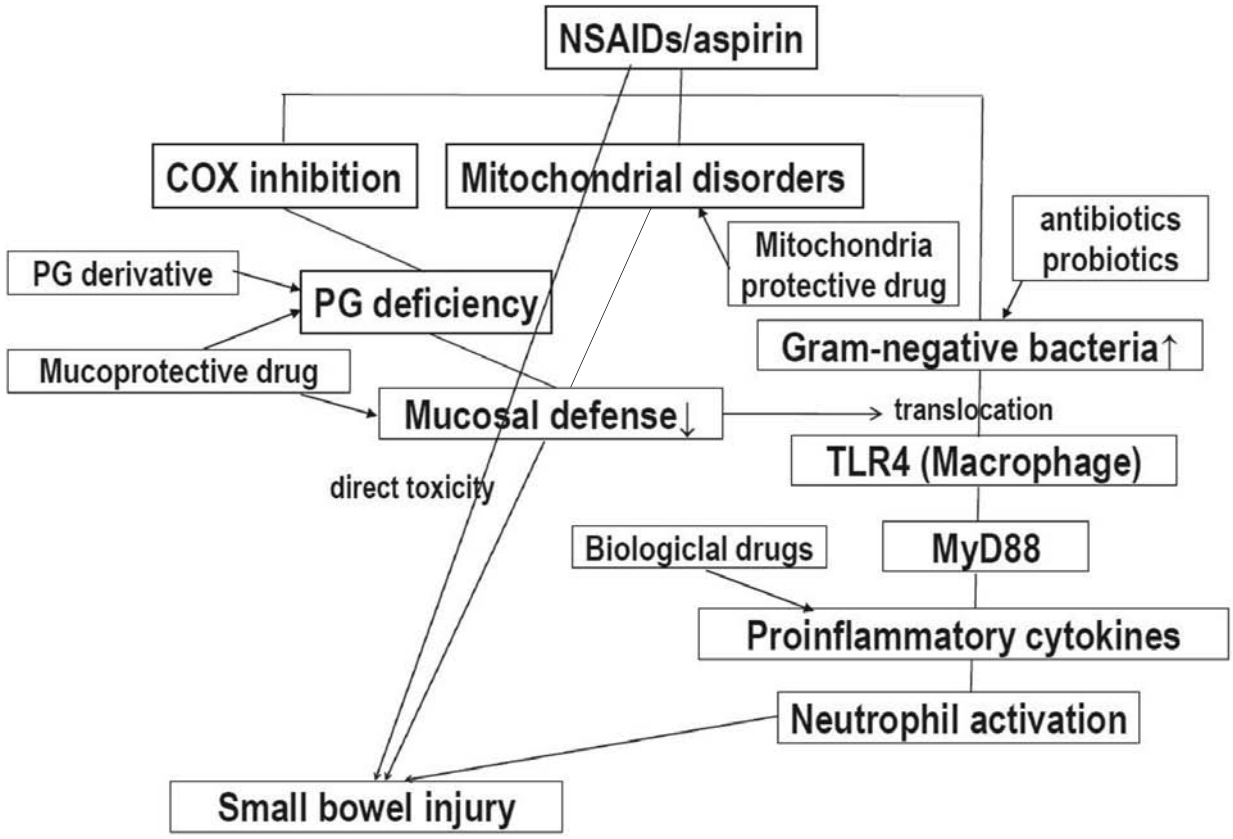

Fig. (1). Proposed mechanisms of small bowel injury caused by NSAIDs/aspirin and possible treatments.

induced PG deficiency has an important role in bacterial translocation.

However, several studies have demonstrated that unlikely to stomach, PG deficiency is not a major mechanism of small intestinal injury caused by NSAIDs. They pointed out that NSAIDs cause PG deficiency in small intestine, but it is not necessarily associated and not temporally synchronized with mucosal injury [20, 21].

COX-Independent Mechanism - Mitochondria

Mitochondria play an important role in energy production. Somasundaram *et al.* [22] have shown the ultrastructural morphological changes of mitochondria in rat small intestine at early phase after oral administration of NSAIDs: Vacuolation at one hour, and swelling and loss of cristae at two hours. These morphological changes are consistent with uncoupling of oxidative phosphorylation or inhibition of electron transport as effects of NSAIDs, which are not dependent on COX pathway. Inhibition of mitochondrial oxidative phosphorylation causes dysfunction of intercellular junctions and increases intestinal permeability, resulting in mucosal injury in the presence of aggressive factors such as NSAIDs themselves, bile, and enterobacteria [23].

Watanabe *et al.* [24] have demonstrated that both COX inhibition and mitochondrial disorders are needed to cause ulceration in small intestine from the study by Somasundaram *et al.* [10] (Table **1**).

Bacterial Flora

Broad-spectrum antibiotics prevent small intestinal injury caused by indomethacin in conventional rats [25, 26] and germfree rats are resistant to the injury [27], suggesting involvement of bacterial flora in this NSAID-injury. Invasion of enterobacteria into the mucosa may be the initial event resulting in the injury [26]. Watanabe *et al.* [28] have shown that indomethacin stimulates

Table 1. Effects of Drug Administration Routes on Onset of Small Bowel Ulcer

Drug and administration route	COX inhibition	Mitochondrial disorders	Ulceration
Oral treatment with indomethacin	+	+	+
Non-oral treatment with indomethacin	+	+	+
Non-oral indomethacin + bile duct ligation	+	-	-
Oral treatment with aspirin	+	-	-
Aspirin asministration into small bowel	+	+	+
Dinitrophenol administration into small bowel	-	+	-
Non-oral aspirin + dinitrophenol administration into small bowel	+	+	+

COX, cyclooxygenase.

overgrowth of both gram-negative and positive bacteria. Aztreonam, which is effective only for gram-negative bacteria, prevents the small intestinal injury while vancomycin, which is effective only for gram-positive bacteria, does not, suggesting involvement of gram-negative bacteria in the pathgenecity [29].

Proton-pump inhibitors (PPIs), which are potent strongest inhibitors of upper gastrointestinal injury caused by NSAIDs and aspirin, have been reported to exacerbate NSAID-enteropathy in experimental model [30]. This may be due to overgrowth of intestinal bacteria under suppression of gastric acid with PPI [31]. On the other hand, there are two reports indicating that omeprazole and lansoprazole are protective for small intestinal injury caused by NSAIDs in rats [32, 33]. The reasons are explained maybe due to their anti-inflammatory action, which is not associated with proton-pump inhibition. Human study is needed to elucidate whether PPIs are harmful for small intestine of patients who take NSAIDs or aspirin.

Toll-Like Receptor

Toll-like receptor 4 (TLR4) is the receptor to promote innate immunity. Its ligand is lipopolysaccharides (LPS), which is endotoxin of gram-negative bacteria. TLR4 is expressed mainly in monocytes/macrophages and a few epithelial cells in small intestine (29). Mice genetically lacking TLR4 are resistant to small intestinal injury caused by dicrofenac, an NSAID, suggesting the involvement of TLR4 in the injury [29]. Small intestinal ulcerogenic response to indomethacin is enhanced in arthritic rats that over-express iNOS and TLR4 in their intestine [34]. Aminoguanidine, an inhibitor of iNOS, suppresses the damage, suggesting that the upregulation of iNOS/NO through the increased expression of TLR4 in the small intestine is involved in the injury.

Proinflammatory Cytokines

LPS stimulate mRNA expression of tumor necrosis factor alpha (TNF-α), macrophage chemotactic protein-1 (MCP-1), and CINC-2α *via* MyD88 through TLR-4 in small intestine of mice given indomethacin [29]. Neutralising antibody against TNF-α or MCP-1inhibits small intestinal injury caused by indomethacin, suggesting involvement of these cytokines in the injury [29]. In addition, recent study has shown that the injury is less in TNF-α-/- mice than wild type mice [35]. In humans, infliximab, anti-TNF-α antibody, reduces incidence of small intestinal lesions assessed by capsule endoscopy in patients with rheumatoid arthritis or osteoarthritis, who are taking NSAIDs [36].

Antiserum against neutrophils prevents small intestinal injury caused by indomethacin [29]. The result may indicate that neutrophils are final mediators of the injury, which produce injurious substances such as proteolytic enzymes and active oxygen species.

PREVENTION AND TREATMENT

PPIs are most effective in acid-dependent area, namely upper GI tract. These drugs, however, do not prevent or heal small intestinal injury [37]. There is no tool for prevention and treatment of the injury. New idea is needed to resolve this problem. Candidates of the treatment tools are as follows.

Prostaglandin Derivative

Misoprostol, PGE derivative, prevents small intestinal injury caused by dicrofenac given 2-weeks in healthy subjects given omeprazole assessed by capsule endoscopy [38]. This drug also exerts healing effect on the lesions caused by low-dose enteric-coated aspirin in patients with cardiovascular disease [39]. PG derivatives are, however, difficult to use because of side effects such as diarrhea, abdominal discomfort, and so on.

Mucoprotective Drug

Rebamipide, a mucoprotective, antiulcer drug, inhibits the injury caused by dicrofenac in healthy subjects given omeprazole [40, 41]. Rebamipide has been developed in Japan and is available in 10 countries mainly of Asia. There are a lot of papers indicating its basic action such as stimulation of PG production, scavenge of active oxygen species, increase in growth factors, heat-shock proteins, and nitric oxide, and inhibition of inflammation [42, 43]. There are also numerous human studies regarding its anti-inflammatory and ulcer healing effect [42, 43].

Importance of COX-2 is known for acceleration of ulcer healing in chronic ulcer model [44]. Rebamipide stimulates the induction of COX-2 and production of PGE2 in rats [45]. Interestingly, this drug accelerates ulcer healing in COX-2 deficient mice [46], suggesting that rebamipide exerts mucoprotective action *via* COX-2-dependent and –independent pathways. Downregulation of 15-hydroxyprostaglandin dehydrogenase may be one of COX-2-independent action of this drug [47].

Similar study on small intestinal injury has been done in healthy subjects taking low-dose enteric-coated aspirin and teprenon, another mucoprotective, did not prevent the injury [48]. More clinical data with mucoprotective drugs are needed to determine the adequate treatment for small intestinal injury caused by NSAIDs/aspirin.

Probiotics

Lactobacillus strains protect small intestinal mucosa against NSAIDs both supernatant of culture and live bacteria, but not dead one in rats [28, 49]. Lactic acid produced by the bacteria may have a key role in the protection, which is not dependent on TLR-4 [28]. We need data of clinical trial using probiotics. Antibiotics may be effective for clinical use although side effects may be much larger than expected advantage.

Mitochondria Protective Drug

Leite *et al.* [50] for the first time have demonstrated that metronidazole prevents small intestinal injury caused by indomethacin in rats consistent with inhibition of uncoupling of mitochondrial oxidative phosphorylation. Cyclosporin A, a cyclophilin D inhibitor, is another candidate for mitochondrial protection against NSAIDs, because cyclophilin D is a key regulator of the mitochondrial permeability transition, which increases permeability of mitochondrial membrane, resulting mitochondria-mediated cell death. LoGuidice *et al.* [51] have demonstrated that small intestinal injury caused by dicrofenac is less in mitochondrial cyclophilin D-deficient mice and cyclosporin A inhibits the injury in wild-type mice. A c-Jun-N-terminal kinase (JNK) regulates mitochondria-mediated apoptosis and also is a key node where many of the proximal stress signals converge. Ramirez-Alcantara *et al*. [52] have shown that an inhibitor of JNK protect small intestine from injury caused by dicrofenac.

CONCLUSION

Regarding mucosal injury caused by NSAIDs/aspirin, most of all attention has been paid in upper gastrointestinal tract. Recent reports showing small intestinal injury caused by these drugs indicate that NSAIDs/aspirin-induced injury is no more only acid-related disease. Mechanisms are somehow different from the injury of upper gastrointestinal tract. Bacterial flora and mitochondrial disorder may be key factors for the small bowel injury. Method of prevention and treatment for the small intestinal injury is not

established yet. Possible candidates proposed in animal experiments should be tested in clinical trials as soon as possible.

ABBREVIATIONS

NSAIDs = non-steroidal anti-inflammatory drugs

COX = cyclooxygenase

PGs = Prostaglandins

PPIs = Proton-pump inhibitors

TLR4 = Toll-like receptor 4

LPS = lipopolysaccharides

TNF-α = tumor necrosis factor alpha

MCP-1 = macrophage chemotactic protein-1

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