



Review Article:

## Statin Gastroprotective Mechanisms Independent of Gastric Acid Suppression

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### Abstract

**Background:** Statins have demonstrated various beneficial clinical outcomes, not only in patients with elevated cholesterol levels but also in those with normal levels, a collective phenomenon known as pleiotropic effects. In the cardiovascular system, statins exhibit numerous pleiotropic effects, including the improvement of endothelial function by enhancing nitric oxide synthesis, anti-inflammatory actions, and antioxidant properties. Similarly, within the gastrointestinal tract, statins confer advantageous pleiotropic effects. **Aim:** This review delves into the potential mechanisms underpinning the gastroprotective impact of statins against indomethacin-induced gastric ulcers. In particular, the administration of statins resulted in a notable elevation in the levels of NO and PGE2 in the mucosa of the stomach. These results substantiate the gastroprotective role of statin is attributed to scavenging of free radicals, elevation of nitric oxide levels, and enhancement of prostaglandin E2 levels. **Conclusion:** To sum up, the results indicate that statins could be a preferable therapeutic choice for individuals who are susceptible to developing gastric ulcers as a result of NSAIDs usage.

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## 1. Introduction

### 1.1 The pleiotropic effects of statins

Statins act by inhibition of the enzyme HMG-CoA reductase, they effectively reduce synthesis of cholesterol with consequent upregulation of liver LDL receptor with resultant decrease in plasma concentration of LDL, VLDL, and triglyceride with additional increase in HDL level (1). Statins have been proved to exert various beneficial clinical outcome in patients with elevated cholesterol level (2) and even in those with normal level collectively known as pleiotropic effects (3, 4). It still not completely understood whether statin have these effects depending on cholesterol reduction or attributed to a secondary mechanism that is independent on mevalonate pathway (5, 6). The pleiotropic effects have additional benefit in cardiovascular diseases,

like improvement in endothelial function with increased synthesis of nitric oxide (7, 8), anti-inflammatory and antioxidant effect (9). Similarly, statins have beneficial pleiotropic effect in the gastrointestinal tract (10, 11), they have protective effect in anti-inflammatory bowel diseases and gastric ulceration.

### 1.2 Mechanism of action as a pleiotropic agent

Statins competitively inhibit mevalonate pathway by potent inhibition of the enzyme HMG-CoA. By blocking the enzyme, they inhibit the formation of mevalonate, which is essentially required for the synthesis of cholesterol. Moreover, mevalonate also a building stone for synthesis of different variety of biologically active lipophilic intermediates called isoprenoid such as GGP, geranylgeranyl pyrophosphate, and FPP, farnesyl pyrophosphate (12). These intermediate by acting as anchor enable small molecule G-protein to attach to the cell membrane like Rho, Ras and Rac. The translocation of Ras is farnesylation- dependent while Rho translocation is geranylgeranylation-dependent. statin group by the inhibition of Rac activation, they have anti-inflammatory effect, they also scavenge the ROS generated from NADPH oxidase enzyme (13).

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### 1.3 Role of nitric oxide

Nitric oxide (NO) is a local signaling molecule produced naturally through the enzymatic reaction between the amino acid arginine and molecular oxygen (14, 15). This reaction is facilitated by the enzyme nitric oxide synthase (NOS). NO acts as a signaling molecule and play essential role in regulating muscle tone, muscle proliferation, angiogenesis (16). It also has important role in the inflammatory defense mechanism. Numerous studies have highlighted the significance of nitric oxide (NO) in providing protection against the development of gastric ulcer. The mechanism of such effect could be related to the increased blood flow to the ulcerated mucosa with additional increase in the thickness of the mucous (17), it also has antibacterial effect (18). Many evidence have suggested the protective role of NO against gastric ulceration, it keeps the lining intact (19). Topical application of nitric oxide (NO) donors to the stomach has been shown to lead to a reduction in gastric acid secretion (20). Previous study has shown that nitroglycerine transdermally could protect the lining of the stomach against the ulcerogenic effect of indomethacin (21). Results have shown that administration of LNAME together with NSAIDs provoke the hemorrhagic ulcer in the stomach and the small intestine (22).

Nitric oxide (NO) play a role in modulating neuron function within the gastrointestinal tract. This suggests that the application of NO donors could potentially lead to a decrease in acid secretion, which is mediated by the vagus nerves (23). This effect might be achieved by suppressing the neuronal activity linked to the vagus nerves. It's worth noting that NO-containing neurons have been identified not only in the gastrointestinal mucosa but also centrally within the CNS (24).

Moreover, Brown *et al.* (1993) conducted research that indicated high concentrations of NO donors have the capability to inhibit parietal cells acid secretion (25-28). Moreover, nitric oxide holds significant regulatory functions, particularly in modulating the adhesion of leukocyte to the endothelial layer of the vascular tissue in different inflammatory conditions. Elevated nitric oxide levels have been associated with reduced myeloperoxidase activity (29, 30), which serves as an indicator of neutrophil count, ultimately contributing to a mitigation of tissue damage. Prior research has indicated that the injection of Ach or nitroprusside reduce neutrophils infiltration in the mucosa of the stomach. Other investigations have highlighted NO's capability to impede superoxide production by neutrophils and directly inhibit NADPH oxidase—an enzyme responsible for superoxide generation. Furthermore, nitric oxide also impedes the production of superoxide and hydrogen peroxide during ischemic condition due to the use of NSAIDs (31). On the other hand, in peptic ulcers complicated by *H. pylori* infection, inducible nitric oxide synthase (NOS) expression is triggered. This elevation in inducible NOS has been associated with duodenal epithelial injury (32). However, the application of NOS inhibitors and superoxide dismutase inhibitors can curtail this effect. These findings underscore the interaction between NO and superoxide to generate peroxynitrite, which plays a role in gastric ulceration (33).

### 1.4 Role of prostaglandins

Numerous studies in human and lab animal have demonstrated that NSAIDs induces gastric ulceration (34). The mechanism underlying this effect is tied to the agent's

inhibition of cyclooxygenase activity, resulting in a reduction of prostaglandin (PG) biosynthesis. The latter was confirmed by the fact that exogenous PG have a protective effect against ulcer formation while the deficiency of PG is a contributing factor to the development of these lesions. Results have shown that statins gastro protective effect could be partially mediated by prostaglandin E2 (PGE2) (35). In fact, nitric oxide precursor enhanced the generation of PGE2 by statins (36, 37), this was confirmed by the enhancement of prostaglandin synthesis with L-arginine supplementation, by contrast, L-NAME administration inhibit PG synthesis (38). Prostaglandins have a comprehensive impact on various aspects of mucosal physiology, like secretion of bicarbonate and mucus, maintenance of blood flow, strengthen epithelial cells against injury, and inhibiting accumulation of leukocytes (39). Importantly, it has been demonstrated that NO can elevate PGE2 biosynthesis *in vivo* via a mechanism that is independent of cyclic guanosine monophosphate (cGMP)(35), suggesting that NO might have the capacity to modulate the release and/or production of PGE2 in the stomach subsequent to injury. The PG deficiency associated with nonsteroidal anti-inflammatory drugs (NSAIDs) arises from capacity to inhibit the enzyme cyclooxygenase (COX)(40). The latter is present in two forms, COX-1 constitutively active in many tissues and COX-2 which induced in response to growth factors and cytokines in most tissues (41). This isozyme specificity render COX-1 in maintaining gastrointestinal mucosa, while COX-2 becomes activated in inflammatory condition (42). Although the ulcer induced by NSAIDs have initially been attributed to COX-1 inhibition, further research involving has revealed that both isozymes play a role in the gastrointestinal ulcerogenic effects of NSAIDs [17-21]. Additionally, studies have demonstrated that inhibiting COX-1 can lead to mucosal COX-2 upregulation. Which in turn may contribute to maintaining the integrity of gastric mucosa (43).

### 1.5 Role ROS

As previously mentioned, the statin group exhibits the capability to inhibit the activation of Rac, resulting in an anti-inflammatory effect (9). Additionally, they act to scavenge reactive oxygen species (ROS) produced by the nicotinamide adenine dinucleotide phosphate oxidase (NADPH). Statins are well-documented for their anti-inflammatory and antioxidant properties (9), which are independent of their primary function in lowering lipid levels (44). By inhibiting the enzyme HMG-CoA, statins impede cholesterol biosynthesis, triggering a compensatory mechanism that increases the uptake of cholesterol through external receptors, consequently reducing its concentration in the bloodstream. Research has shown that statins possess the capacity to dampen inflammation by inhibiting cytokine production and curbing the recruitment of inflammatory cells (45). A growing body of evidence points to the statin antioxidant effect by inhibition of NADPH superoxide generation as well as the enhancement of antioxidants activity mediated by glutathione and catalase enzymes(46).

Drawing from the therapeutic advantages of statins, this study observes that treatment with statins can ameliorate NSAID-induced gastric damage (47-49). This improvement is evident through significant improvement in histological picture and improvement in oxidative status. The observed effects suggest that the anti-inflammatory and antioxidant properties of statins contribute to their potential for

mitigating the adverse gastric consequences induced by NSAIDs (9, 50).

### 1.6 Importance of Gastric Motility

Substantial evidences from animal studies indicate that the hypermotility induced by stress due to different reasons like cold stress or administration of irritating substances like NSAIDs caused temporary limitation of blood flow in the mucosa and decreased its resistance to damage (22, 51).

In animal studies, gastric hypermotility, induced by inhibiting COX-1, has been demonstrated to contribute to the development of ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs) (52, 53). The precise mechanism of injury remains uncertain, but it is thought to arise from a temporary reduction in blood flow to the mucosal lining due to high-intensity contractions, resulting in microvascular damage due to tissue oxygen deficiency, interactions between neutrophils and endothelial cells, and reduced mucosal resistance. This process eventually leads to the formation of gastric lesions. Studies have shown that the increased gastric motility may result in an increase in the permeability of the mucosa with accompanied increase in myeloperoxidase activity (53), ultimately result in gastric ulceration. Under microscopic examination, specifically the most affected parts are the upper or lower gastric foldings which undergo compression because of stomach contraction (52-54).

Interestingly, indomethacin increased gastric motility was successfully suppressed by the anticholinergic agents like hyoscine and prostaglandins type E2, however, PPIs have no significant protective effect. (52-54). Given that the anticholinergics have the capability to protect the gastric mucosa against the irritating effect of indomethacin, the effect of anticholinergics on gastric motility could be the reason behind this mechanism (53). Furthermore, indomethacin prompted the peroxidation of lipid and promote the generation of oxyradicals within the gastric mucosa due to the ischemic-reperfusion alterations stemming from increased contractility of the stomach (55, 56). The latter also significantly inhibited by atropine (57), once again highlighting the pivotal role increased gastric contraction in the pathogenesis of ulceration. Currently, the precise signal that enhance motility after NSAIDs administration is not fully understood. However, previous data suggest involvement of vagal stimulation. In addition, the central effects of indomethacin particularly at elevated doses suggest that the observed motility could be mediated through central actions rather than peripheral mechanisms (53). indomethacin (above 10 mg/kg) could breach the blood-brain barrier and attain concentrations substantial enough stimulate vagus nerve with resultant increased gastric motility. This hypothesis gains support from lab. data which showed the adverse effects of indomethacin were significantly reduced by nerve block or by the administration of anticholinergics. Suppression of gastric motility could provide protection against the disturbances in the microcirculation and reduction of superoxide generation. Consequently, this could prevent the development of band-like lesions associated with the folds, as observed following indomethacin administration. The hypothesis put forth by researchers is that NSAIDs induce gastric damage by inhibiting COX-1-dependent prostaglandin production, resulting in an amplified hypermotility response mediated by the central nervous system (53). This enhanced hypermotility causes microvascular disturbances promoting the adherence of neutrophils to endothelial cells and

subsequent damage caused by reactive oxygen species. The simultaneous blocking of COX-2 prevents the compensatory increase in prostaglandins derived from COX-2, which could counteract this damaging effect (58, 59). Whether gastric hypermotility also contributes to NSAID-induced ulcers in humans remains uncertain at present. Further experiments are recommended to fully understand the relation between increased gastric motility and the development of NSAID-induced ulcers in humans.

### 2. Conclusion

The initial mechanistic explanation attributing the side effects of NSAIDs due to inhibition of PG synthesis remains valid to a significant extent. However, it is evident that this explanation alone is insufficient to fully comprehend the complex process of ulceration. Actually the process involves intricate interplay of shortage of prostaglandins (PGs) and nitric oxide (NO), combined with the presence of gastric hypermotility. Particularly, the deficiency in endogenous PGs, as a result of cyclooxygenase (COX) inhibition, stands out as a key factor contributing to the formation of these lesions. In summary, has a protective effect in indomethacin-induced gastric ulceration. This effect involves various mechanisms, including elevation of nitric oxide and prostaglandin E2, it has antioxidant properties, and on the other hand statin by its ability to inhibit gastric hypermotility. They might have additional protective effect. which justify its safe co-administration with NSAIDs as an antihyperlipidemic medication. It's essential to note that these findings have been derived from animal studies, and their relevance to human gastric ulcers is not definitively established, thus continued research is necessary to bridge the gap between animal findings and their applicability to human conditions.

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## التأثير الوقائي لمجموعة الستاتين على المعدة بدون الاعتماد على تثبيط الحموضة

### الخلاصة

**المقدمة:** أظهرت الستاتينات نتائج سريرية مفيدة متنوعة، ليس فقط في المرضى الذين يعانون من مستويات مرتفعة من الكوليسترول ولكن أيضًا في أولئك الذين يمتلكون مستويات طبيعية، وهو ظاهرة جماعية معروفة باسم التأثيرات المتعددة. في الجهاز القلبي الوعائي، تظهر الستاتينات تأثيرات متعددة، بما في ذلك تحسين وظيفة الطبقة النهائية للأوعية عن طريق تعزيز تخليق أكسيد النيتريك، والتأثيرات المضادة للالتهاب، وخصائص مضادة للأكسدة. بالمثل، داخل الجهاز الهضمي، تمنح الستاتينات تأثيرات جماعية مفيدة. **الهدف:** تستكشف هذه المراجعة الآليات المحتملة التي تكمن وراء التأثير المحافظ للستاتينات على الجهاز الهضمي ضد قرح المعدة المستحدثة بواسطة الإندوميثاسين. على وجه الخصوص، أسفر إعطاء الستاتينات عن ارتفاع ملحوظ في مستويات أكسيد النيتريك PGE2 في المخاطة المعدية. هذه النتائج تؤكد أن الدور المحافظ للستاتينات على الجهاز الهضمي يُعزى إلى تصفية الجذور الحرة، وزيادة مستويات أكسيد النيتريك، وتعزيز مستويات البروستاغلاندين. **الاستنتاج:** تشير النتائج إلى أن الستاتينات يمكن أن تكون خيارًا علاجيًا مفضلًا للأفراد الذين يمكن أن يصابوا بقرح المعدة نتيجة استخدام مضادات الالتهاب غير الستيرويدية

**الكلمات المفتاحية:** الستاتينات, أكسيد النيتريك, بروستاغلاندين, E2 الحركة