EDITORIAL

Novel Physiological and Pharmacological Avenues in the Mechanism of Gastrointestinal Integrity, Protection and Ulcer Healing

Peptic ulcer disease is a worldwide disease affecting 15-20% of the human population with an etiology that depends on regional and socioeconomic factors with the pathogenesis of this disorder remaining a mystery. In this issue of the journal, we have focused on the recent advances in the mechanism of gastrointestinal (GI) integrity, gastroprotection and ulcer healing that had recently triggered the attention of basic scientists and clinicians, due to the identification of novel and emerging pathways, thus shedding more light on the mechanism of protection, repair and ulcer healing within GI-tract. For a long time, it has been known that the gastric mucosa can withstand the natural attack of the acidified environment inside of the stomach. This is the so called mucosal barrier, a concept that was originally pioneered by Code and Davenport, and has resurfaced with the discovery of *Helicobacter pylori*, as well as other pathogenic and ulcer-causative mechanisms including the human ingestion of nonsteroidal anti-inflammatory drugs (NSAID). There are other risk factors of peptic ulcer disease such as smoking, alcohol, hiperosmolar solutions and bile salts refluxed from the duodenum. The physiological maintenance of the gastric mucosal integrity and the resistance to mucosal damage despite exposure to these factors is accomplished by the functional activity of the lines of mucosal defense such as the mucus-bicarbonate secretion, the undisturbed microcirculation, the presence of mucosal sulfhydryls and expression of heat shock proteins and defensines. Aside from Andre Roberts breakthrough principle that exogenous prostaglandins (PG) (direct cytoprotection) and endogenous PG (adaptive cytoprotection) are major gastroprotectants, there is now a consensus that CGRP/NO system together with PG represent a common final mechanism in gastroprotection against injury induced by various brain and appetite peptides such as TRH, ghrelin and leptin. In addition to stimulating or inhibit appetite, these peptides act locally to protect the gastric mucosa *via* increasing gastrointestinal microcirculation, as well as the activation of the brain-gut axis involving long a vagal loop to confer this protection. In contrast to short-term cytoprotection or gastroprotection, long-term ulcer healing is a complex process of tissue regeneration, which involves cell migration, proliferation from ulcer associated cell lineage (UCLA), re-epithalization, angiogenesis and vasculogenesis. Biochemistry of that process includes the comprehensive interplay between growth factors (EGF, bFGF, IGF-1) and the serum response factor (SRF) that activates early genes such as c-fos, egr-1/2, cyr 61 and cytoskeletal genes. The early microvascular damage due to hypoxia during the perpetuation of the gastric barrier triggers an expression of hypoxia inducible factor (HIF-1), which serves as hypoxia sensor and contributes to a compensatory and adaptive mechanism. A new promising avenues in the mucosal defense is gaseous mediators such as H_2S and CO, which together with NO contribute to both the protection and ulcer healing of the GI mucosa, by stimulating bicarbonate secretion in response to duodenal acid. The role of these new gaseous mediators from old gaseous mediators, namely H_2S and CO influencing the mechanism of mucosal protection and ulcer healing, constitutes a novel experimental approach that should be further elucidated and confirmed in humans. Hydrogen sulfide and CO combined with NSAID, which is similar to NO released from NSAID's seem to be the example of the preclinical utility of physiological gaseous mediators effective in counteracting adverse side effect such as gastric bleeding, and also those identified in the small intestine that were associated with the use of their parent NSAID. The incidence of small intestinal injury caused by NSAID supports the notion that NSAID-induced enteropathy cannot be considered exclusively as an acid-related disease. It also becomes evident that the bacterial flora and mitochondrial disorders may play a key role in small bowel injury induced by conventional NSAID. Since the injured gastric mucosa produces an abundant amount of Ang-(1-7), a novel concept is proposed that the local renin-angiotensin system could contribute to the mechanism of protection and to the mucosal recovery from gastric lesions due to the fast and excessive biosynthesis of active metabolites of angiotensin I such as Ang-(1-7). This mechanism may also play an essential role in ulcer healing due to prominent enhancement in the gastric circulation induced by vasodilatory Ang-(1-7) metabolite. The mechanism of the pathogenic action of cigarette smoke, one of the important risk factors of the peptic ulcer involves a disturbance in the cell proliferation, inhibition of protective mucus secretion and an impairment of the formation of new microvessels (angiogenesis). Moreover, cigarette smoke interferes with the innate immune response during the process of repair and healing of the GI mucosa. Recent advances revealed that cigarette smoke and its extract can deregulate the function and apoptosis of endothelial cells by inhibiting NO production, reducing gastric mucosal PGE_2 levels and impairing the angiogenic VEGF pathway. The involvement of physiological factors such as the specific GPCRs responsible for the chemosensing of proteins, L-amino acids, bile acids, fatty acids, and carbohydrates to the mechanism of GI-integrity should be further investigated. Taste receptors have a proposed role in the intestinal chemosensing, and there is an agreement that sweet, bitter, and *umami*

evoke their responses in the gut *via* GPCRs. The GPCRs family of protein seems not be fully explored scientifically, especially with regards to the mucosal integrity, but identification of nutrient receptor agonists and antagonists can provide novel therapeutic targets for metabolic diseases, obesity, acid reflux and mucosal injury. This latter seems to be of importance for GI integrity since free radical biology studies revealed that the concentration of the reactive oxygen metabolites (ROS) in the gastric mucosa is about 1000-fold higher than that in other tissues or plasma.

Generation of ROS contributes to exogenous injury to the gastric mucosa, including damage brought about by ethanol or nonsteroidal anti-inflammatory drugs (NSAIDs). Moreover, ROS play a major role in the multistep process leading to the development of gastric cancer. Interestingly, naturally occurring anti-oxidants called nutraceuticals including probiotics such as Lactobacilli, Saccharomyces bacteria or Bifidobacteria spp, were recently shown to exert a protective effect in the GI-tract mainly by the scavenging of oxygen and nitrogen free radicals breaking lipid chain peroxidation reaction. Beside probiotics this long list of protective nutraceuticals includes a variety of phytochemicals, flavonoids, curcumin, apple extracts, garlic and honey extracts. However, scientific validity of the use of a number of these products should be explored and rigorous research is warranted in order to identify the mechanism involved in the novel compounds to be used alone or in combination, perhaps as adjuvant therapy with standard drugs to treat gastrointestinal disorders. This issue of the journal prepared by experts in the field of gastroenterology gives an insight into the updated physiology and pharmacology of the exciting mechanisms by which GI mucosa can resist the injury, exerts protective response to noxious stimuli and heal in cases of ulcer development.

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