Gastric injury induced by Non-steroidal Anti-inflammatory Drugs and therapeutic strategies for prevention

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Abstract

The toxicity of gastrointestinal (GI) tract associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is an important medical and socio-economic problem. The coprescription of traditional gastroprotective drugs such as proton pump inhibitors (PPIs) and H_2-receptor antagonist, to reduce gastric acid secretion are the common clinical therapeutically approach. However, these strategies are not effectively to reduce gastrointestinal adverse events of NSAIDs and recently have demonstrated their low safety in long-term use. In the search for new therapeutically approach, the use of selective COX-2 inhibitors and the use of prostaglandin analogue in order to maintain the local prostaglandins was considered. Unfortunately, their adverse events in cardiovascular or renal system provoked that their therapeutic use were discarded. Therefore, the search for new therapeutic strategies has been promoted. The current experimental and preclinical approaches includes very promising alternatives such as H_2S-NSAIDs, NO-NSAIDs and the possible use of Docosahexaenoic acid (DHA), an Omega-3 Fatty acid. In this regard, DHA is focused in face the prostaglandin independent mechanism of NSAID-induce gastric injury such as increment of proinflammatory molecules expression and neutrophil–endothelial adherence. However, large studies of these therapeutically approaches are still needed.

Keywords: Non-steroidal Anti-inflammatory Drugs, gastric injury, PPIs, omega-3

Introduction

For decades, damage of the gastric mucosa was regarded being caused by excessive gastric acid secretion [1]. Nowadays, it is known that under normal conditions the gastrointestinal (GI) tract, is continuously exposed to many noxious factors and substances that can alter its integrity [2]. However, GI tract is capable to face the damaging factors in a dynamic process termed “mucosal defense” [1], the appreciation of contribution of inflammatory process as key component of mucosal defense against exogenous and endogenous factors has been important [3]. On the other hand, it is well known that the use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) is associated with adverse GI events, such as gastric mucosal erosion, ulceration, bleeding, and perforation [4]. In addition to prostaglandins inhibition, inflammatory mechanism has been involved in the NSAID-induce gastric damage [5]. Furthermore, current therapies do not have the ability to protect the GI tract against NSAID-induce gastric damage, this fact has led the search for new agents to reduce side effects associated with NSAIDs and maintain their therapeutic efficacy.

Mucosal Defense

During digestive process the stomach is daily in contact to a wide range of microorganisms, nutrients and different substances which could trigger local and systemic inflammatory reactions to finally induce damage to the mucosa [2],[6]. Consequently, it has been proposed a complex network of components with the ability to prevent such injury as well as the possibility to repair the epithelium in a quickly manner, so it is termed “mucosal defense” [1], that finally set up a balance between the aggressive and protective factors of gastric mucosa, this term known as “gastroprotection” [7], [8].

The components of mucosal defense can be organized as a hierarchy, according to their anatomical disposition [9]. The first level of defense consists of factors secreted into the lumen, such as hydrochloric acid (HCl) which allow the activity of pepsin and also minimizes the bacterial colonization in the stomach [2], [9], [10]. Followed by the mucus gel, that serve as a lubricant to the gastric movements and restrict bacteria movements through the mucosa [2], [9]. This mucus gel contains phospholipids, and its luminal surface is coated with a film of surfactant phospholipids with strong hydrophobic properties [2], [11]. The secretion of bicarbonate ($HC0_3$ -) by the action of cotransporters and proton pumps, allows to maintain a neutral pH at the apical cell surfaces [2], [5], [11].

The second level of defense is formed by a continuous layer of surface epithelial cells interconnected by tight junctions, which form a “physical barrier” against harmful exogenous agents [7], [11], [12]. The epithelium is continually renewed from mucosal progenitor cells and maintains structural integrity of the mucosa in case of injury, through the formation of an appropriate microenvironment (mucoid cap) [7], [13]. The dense network of capillaries under the surface epithelium of the stomach, supplies nutrients and oxygen to the epithelium [1], [2]. The primary afferent sensory neurons and nerves directly affects the tone of submucosal arterioles, which regulate mucosal blood flow [1], [13]. The stimulation of gastric sensory nerves leads to the release