Nitric oxide and the gut injury induced by non-steroidal anti-inflammatory drugs

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Abstract—Nitric oxide (NO) can protect the gastrointestinal tract from injury, including that provoked by non-steroidal anti-inflammatory drugs (NSAIDs). This protective profile of NO, which predominantly reflects actions on the microcirculation, is mimicked by NO donors. Moreover, the NO-donating agents known as the NO-NSAIDs or CINODs (cyclo-oxygenase-inhibiting nitric oxide-donating drugs) exhibit reduced gut injury in experimental models, which is considered to reflect these local beneficial actions of NO. NSAIDs cause chronic inflammatory lesions in the small intestine in experimental models. This injury results from initial COX inhibition and other local events, with translocation of indigenous luminal bacteria, leading to induction of NO synthase isoform, iNOS, and subsequent production of the cytotoxic moiety, peroxynitrite from NO and superoxide. Agents that inhibit iNOS or superoxide production can attenuate such intestinal injury. In the absence of reactive oxygen moieties, NO may play a beneficial role in the resolution of inflammatory damage to the gut, thus reconciling the potential opposing properties of NO in tissue inflammation and injury.

Key words: NSAIDs; gut damage; nitric oxide; NO-NSAIDs; CINODs; superoxide; iNOS; peroxynitrite.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have been known to cause extensive damage to the gastrointestinal tract ever since their introduction into clinical practice. Inhibition of cyclo-oxygenase (COX), particularly the predominant constitutive isoform COX-1, has been long considered to be one prime stage in the development of the gastro-intestinal pathology induced by NSAIDs (Whittle et al., 1980). More recent work suggest that inhibition of both the COX-1 and COX-2 isoforms are required for acute gastric injury to be provoked (Wallace et al., 2000).
Furthermore, these agents can provoke gut injury by multiple interactive mechanisms, with actions such as topical irritancy not directly reflecting the inhibition of COX (Whittle et al., 1980; Whittle, 2003).

The damage induced by NSAIDs can be attenuated by co-administration of acid-antisecretory agents such as histamine H₂ receptor antagonists or proton-pump inhibitors (Hawkey and Langman, 2003), or by mucosal protective agents such as the synthetic prostanoids or nitric oxide (NO) donors. Compounds chemically designed to attenuate topical irritancy, or have protective agents incorporated, particularly the NO-containing NSAIDs or CINODs (cyclo-oxygenase-inhibiting NO-donating drugs) show reduced acute mucosal injury in experimental models (Wallace et al., 1994; Kebble and Morre, 2002; Bargaud et al., 2002).

2. PROTECTIVE PROPERTIES OF NO

NO, which can be produced by vascular endothelial cells from a constitutive NO synthase isoform, eNOS, is a potent vasodilator, and is a key physiological modulator of vascular tone (Moilanen et al., 1999). NO can also modulate the permeability and integrity of the vascular endothelium. Thus, NO is a potent inhibitor of adhesion of white cells to the microvasculature, an early event in the initiation of many forms of gut injury, including that provoked by NSAIDs (Wallace and Miller, 2000). It is assumed that this action on microvascular cellular adhesion and integrity also reflects a physiological function, although this role may be more apparent under pathological conditions following initial challenge, such as low-grade trauma and inflammation.

NO derived from exogenous sources can likewise exert beneficial actions on the integrity of the gastric mucosa. Thus, early studies showed that intragastric application of NO donors used clinically as nitrovasodilators, glyceryl trinitrate, isoamyl nitrate or nitroprusside, protect against acute haemorrhagic mucosal injury provoked by topical irritants (MacNaughton et al., 1989). Local intra-arterial infusion low doses of glyceryl trinitrate and nitrosothiols were also shown to protect against gastric mucosal injury (Lopez-Belmonte et al., 1993; Laszlo et al., 1995). Furthermore, transdermal application of nitroglycerine prevented the mucosal damage caused by indomethacin, through effects on blood flow and leukocyte adhesion (Barrachino et al., 1995; Calatayud et al., 1999).

Clinical support for the concept that NO donors can protect against the damage induced by NSAIDs has come from convincing epidemiological studies showing that use of nitrovasodilators is associated with a reduced risk of upper gastrointestinal bleeding with NSAIDs (Lanas et al., 2000).

Such findings on the beneficial actions of NO donors have formed the basis for the development of the NO-containing NSAIDs. These agents exhibit a pharmacological profile distinct from the parent classical NSAIDs compounds from which they have been derived, as a result of the NO-bearing substituent, usually a nitroxybutyl ester (Bargaud et al., 2002). NO-NSAIDs have good efficacy in a