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Role of nitric oxide in gastrointestinal tract

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Nitric oxide is a gaseous free radical synthesized *via* L-arginine oxidation by a family of nitric oxide syntheses (NOS). Isomeric forms of NOS, representing at least three distinct and regulation. NOS isoforms are either calcium dependent and constitutively expressed in response to receptor stimulation in neurons and endothelial cells or calcium independent, inducible and expressed after exposure to diverse stimuli such as inflammatory cytokines.

NO is labile and its half life is < 15 s. In the presence of oxygen it is rapidly metabolized to nitrate and nitrite. NO reacts with superoxide anion to yield peroxynitrite which is not stable and following protonation produce the toxic hydroxyl radical.

The effects of NO in the gastrointestinal tract will be reviewed in this presentation.

NO AND NONADRENERGIC NONCHOLINERGIC (NANC) INHIBITION

NO is the mediator of NANC neurotransmission in the gut. NO is released from ileocolonic junction and stomach during nerve stimulation and induce smooth muscle relaxation in the LES, stomach, small intestine and internal anal sphincter. Its effects on longitudinal and circular muscles grossly mimic the effect of NANC nerve stimulation. Inhibition of NO synthesis attenuate the relaxing effect of electrical stimulation of NANC nerves in guinea pig colon, canine duodenum, rat gastric fundus and in circular muscle of LES, ileum and colon.

Its mechanism of action in the relaxation of gastrointestinal smooth muscle is probably mediated by induced levels of CGMP and may be linked to modulation of in tracellular calcium concentration. NO mimics the descending relaxation in the colon, proximal dilation of the stomach and the increase in gastric capacity-effects that are prevented by inhibition of NO synthesis. Decrease in neural NO production could direct to diseases in which there is sustained or vigorous non peristaltic contractions, such as in the aganglionic segment of Hirschsprung's disease or the non relaxing LES of achalasia. Increase NO production in the LES could play a role in reflux disease and imbalance of normal excitatory and inhibitory nerve activity as a result of disorders in the enteric NO system could lead to disease states such as a result of disorders in the enteric NO system could lead to disease states such as pseudo-obstruction or constipation.

NO AND GASTROINTESTINAL MUCOSAL PROTECTION

NO is an important vasodilator regulating mucosal blood flow and maintaining mucosal integrity in the gastrointestinal tract. Inhibition of NO synthesis reduces gastric mucosal blood flow and NO contributes to mechanisms that protect the gastric mucosa against ulceration.

Topical application of NO reduces the severity of ethanol induced hemorrhagic gastritis and inhibition of NO generation increase the severity-iodoacetamide in duced gastric damage. Recently, NO delivery systems combined to NSAIDs were reported to effectively decrease the extent of NSAIDs induced damage to the gastrointestinal tract. Endogenous formation of NO also maintains the microvascular integrity of the intestinal mucosa following acute endotoxin challenge and endogenous NO may be one of the mediators that help protect against the harmful effects o f endotoxic shock.

ROLE OF NO IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

In several models of experimental colitis-that induced by acetic acid, trinitro benzene sulfonic acid (TNB) and the sulphydryl blocker, iodoacetamide-colonic NO generation and NOS activity were found to be several-fold higher than in norm al colonic mucosa. Inhibition of NOS activity resulted in significant decrease in the extent of tissue injury in all these models. It is consequently suggested that in experimental colitis the enhanced NO generation by stimulated NOS activity contribute to the pathogenesis of tissue injury.

In inflammatory bowel disease (IBD), both in ulcerative colitis and in Crohn's disease, there is a marked increase in the activity of the inducible isoform and intestinal NOx generation is also significantly increased. Increases in the pro portion of citrulline, the coproduct of NOS activity, were found in active ulcer ative colitis. Direct measurement of rectal luminal NO detected NO in 4/8 ulcerative colitis patients but in none of the controls.

Immunostaining and *in situ* hybridization with an iNOS riboprobe identified in ulcerative colitis iN OS mRNA and translated protein in surface epithelial and crypt cells. The enhanced NO formation by stimulated iNOS may, therefore, have an important role in the pathogenesis of colonic inflammation in IBD. Moreover, since NO also induces muscle relaxation, it may also contribute to the altered motility in colitis. In T NB colitis the colonic perimeter is enlarged and intracolonic pressure is lower. In ulcerative colitis patients with toxic megacolon, iNOS activity in the muscularis propria is stimulated and immunostaining for iNOS is positive. In contrast, in colitis controls muscular iNOS activity is not detected. Local muscular generation of excessive NO in ulcerative colitis may be responsible for colonic dilation.

L-NAME, the L = arginine analog that inhibits NOS activity, effectively decreases the extent of colitis in capsaicin pretreated rats. Its protective effect was accompanied by significant decrease in colonic NOS activity and NOx generation. T he amelioration of experimental colitis by L-NAME supports the contention that enhanced NO generation promotes mucosal injury in these two models. In a similar way, L-NAME was shown also to ameliorate TNB-induced ileitis in guinea pigs.

Selective inhibition of iNOS, when and if appropriate drugs will be available, may be a novel therapeutic modality to decrease the inflammatory response in IBD patients.

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