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Forum Review Article

Role of Nitric Oxide in the Regulation of Acute and Chronic Inflammation

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ABSTRACT

Recent studies by a number of different laboratories have implicated nitric oxide (NO) as an important modulator of a variety of acute and chronic inflammatory disorders. A hallmark of inflammation is the adhesion of leukocytes to post-capillary venular endothelium and the infiltration of leukocytes into the tissue interstitium. Leukocyte adhesion and infiltration is known to be dependent on interaction of the leukocytes with the endothelial cell surface via a class of glycoproteins collectively known as endothelial cell adhesion molecules (ECAMs). Several recent studies suggest that NO may modulate cytokine-induced ECAM expression in cultured endothelial cells *in vitro* by regulating the activation of nuclear transcription factor kappa B (NF-κB). This discussion reviews some of the more recent studies that assess the role of the different NOS isoforms on the inflammatory response *in vivo*. Antiox. Redox Signal. 2, 391–396.

INTRODUCTION

SINCE THE LANDMARK DISCOVERIES by the Ignarro, Furchott, Moncada, and Murad laboratories (Murad *et al*., 1978; Palmer *et al*., 1987; Ignarro *et al*., 1987; Furchgott and Zawadzki, 1980), nitric oxide (NO) has been shown to function as a key mediator in several physiological processes ranging from maintenance of vascular tone to control of neuronal and immune function. To date, three isoforms of nitric oxide synthase (NOS) have been identified: Two of the isoforms, endothelial cell NOS (eNOS; NOS 3) and neuronal NOS (nNOS; NOS 1), are expressed constitutively whereas the inducible isoform (iNOS; NOS 2) is expressed in response to a host of inflammatory stimuli such as bacterial products, cytokines, and lipid mediators. Recent studies by a number of different laboratories have implicated NO in the modulation of a variety of acute and chronic inflammatory disorders (Grisham *et al*., 1999). By definition, inflammation is the normal physiological response of the microcirculation designed to wall off, dilute, or destroy injured tissue. A hallmark of inflammation is the adhesion of leukocytes to post-capillary venular endothelium and the infiltration of leukocytes into the tissue interstitium. Leukocyte adhesion and infiltration is known to be dependent on interaction of the leukocytes with the endothelial cell surface via a class of glycoproteins collectively known as endothelial cell adhesion molecules (ECAMs). ECAMs

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such as P-selectin have been shown to promote leukocyte rolling along the endothelial cell surface whereas intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), or E-selectin allow the rolling leukocytes to adhere firmly to vascular endothelium, which ultimately facilitates their extravasation into the interstitium (Fig. 1). Several recent studies suggest that NO may act as an endogenous anti-inflammatory agent by virtue of its ability to down-regulate cytokine-induced ECAM expression in cultured endothelial cells *in vitro* (Peng *et al.*, 1995a,b; Khan *et al.*, 1996; Spiecker *et al.*, 1997; Spiecker and Liao, 1999). The mechanisms by which exogenous NO exerts this apparent anti-inflammatory effect have not been fully delineated, however, it is thought that NO inhibits the activation of nuclear transcription factor kappa B (NF-κB) by: (i) scavenging reactive oxygen species (ROS) thought to be important in the signaling events upstream of NF-κB activation, (ii) enhancing expression and/or stabilization of its inhibitor I-κB, and/or (iii) inhibiting the binding of the p50/p65 heterodimer to its consensus sequence in the promoter/enhancer region upstream of ICAM-1, VCAM-1, or E-selectin (Fig. 2). Although an attractive hypothesis, there has been little information reported that has assessed the roles of iNOS, eNOS, or nNOS-derived NO in modulating ECAM expression and leukocyte-endothelial interaction *in vivo* in different models of acute or chronic inflammation. The importance of different isoforms of NO in inflammatory tissue damage has recently been reported by Jones *et al.*, who demonstrated that ischemia and reperfusion injury in the mouse myocardium is dramatically enhanced in eNOS-deficient mice compared to wild-type (Jones *et al.*, 1999). This discussion will review some of the recent studies that test the modulatory role of the different NOS isoforms on the inflammatory response *in vivo*.

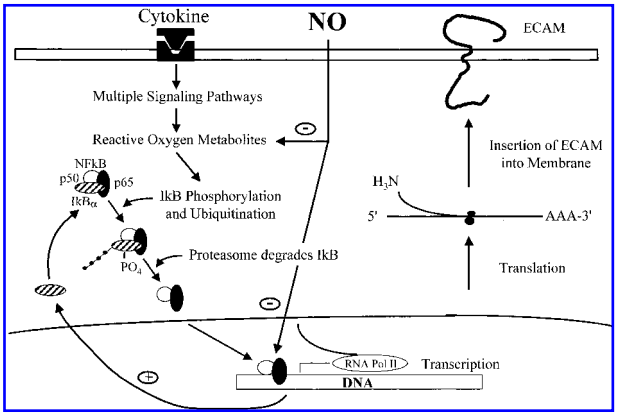

FIG. 2. Potential role of NO in inhibiting NF-κB activation and ECAM transcription. NO has been proposed to: (i) scavenge reactive oxygen species (*e.g.*, superoxide, hydroxyl radical, lipid hydroperoxyl radical) thought to be important in signaling events upstream of NF-κB activation, (ii) inhibit binding of the p50/p65 subunit to its consensus sequence in the promoter/enhancer regions upstream of the different ECAM genes, and/or (iii) induce the synthesis and/or stabilization of IκB.

ROLE OF NO IN LEUKOCYTE ROLLING AND ADHESIONS *IN VIVO*

The advent of genetic engineering technology has allowed the production of mice selectively deficient in one of the three isoforms of NOS (Huang *et al.*, 1993; 1995; MacMicking *et al.*, 1997). This development has provided investigators the unique opportunity to delineate the role of each NOS isoform in normal as well as pathophysiological conditions. Furthermore, NOS-deficient animals offer an advantage over the use of traditional NO inhibitors, such as analogs of L-arginine, in that these animals have a targeted deficiency in one isoform whereas traditional NOS inhibitors are not absolutely selective for one specific isoform nor can they be easily administered over a period of several weeks or months.

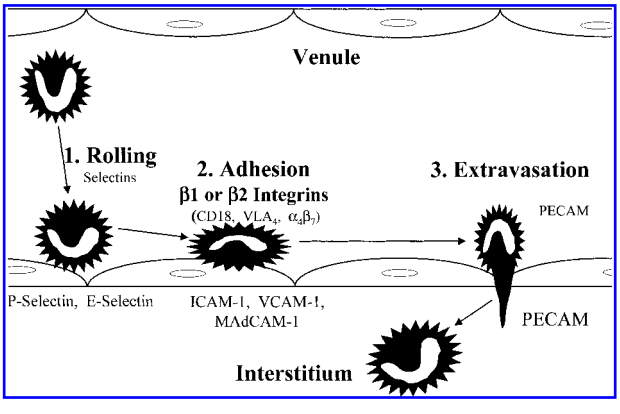

FIG. 1. Leukocyte–endothelial cell interactions. The multistep model of leukocyte rolling, adhesion, and extravasation.

In a recent series of studies, using intravital microscopy, basal and stimulated leukocyte rolling and adherence of leukocytes to the post-capillary venular endothelium in mesenteric venules was investigated in iNOS-, eNOS-, and nNOS-deficient mice (Lefer *et al*., 1999). Under basal conditions, the number of rolling leukocytes in iNOS-deficient ($iNOS^{-/-}$) animals was unchanged compared to wild-type controls. Interestingly, both $nNOS^{-/-}$ and $eNOS^{-/-}$ mice exhibited significant increases in the number of rolling cells/min of approximately two- and six-fold, respectively (Lefer *et al*., 1999). Examination of leukocyte adhesion to mesenteric venules in these same animals revealed that, as with rolling, $iNOS^{-/-}$ mice exhibited no change in the number of adherent cells/100-μm vessel whereas $nNOS^{-/-}$ and $eNOS^{-/-}$ animals showed significant increases in numbers of adherent leukocytes. These data suggest that eNOS and nNOS-derived NO play an important role in modulating leukocyte-endothelial cell interactions and homeostasis.

As stated earlier, leukocyte rolling is dependent upon expression of P-selectin on the vascular endothelial cell surface. Modulation of P-selectin expression would therefore be expected to influence leukocyte rolling and subsequent adhesion of circulating leukocytes. The role of NO in modulating P-selectin expression was assessed by examining the number of P-selectin-positive staining vessels in the mesentery of the different NOS-deficient mice. Not surprisingly, under basal conditions both $nNOS^{-/-}$ and $eNOS^{-/-}$ mice exhibited significant increases in P-selectin expression whereas $iNOS^{-/-}$ animals did not under basal conditions (Lefer *et al*., 1999). When wild-type $nNOS^{-/-}$, and $eNOS^{-/-}$ mice were pretreated with a specific anti-P-selectin monoclonal antibody (RB40.34 Pharmingen), both leukocyte rolling and adhesion were reduced below control values in both the $eNOS^{-/-}$ and $nNOS^{-/-}$ mice as compared to their IgG_1 isotype controls (Lefer *et al*., 1999). To confirm these results, wild-type, $eNOS^{-/-}$, and $nNOS^{-/-}$ were pretreated with the P-selectin ligand PSGL-1. As with the RB40.34 monoclonal antibody blockade, pretreatment with PSGL-1 markedly reduced both rolling and adhesion of leukocytes in $nNOS^{-/-}$ and $eNOS^{-/-}$ mice, confirming that NO regulates P-selectin expression under basal conditions and that this selectin plays a key role in leukocyte–endothelial interactions (Lefer *et al*., 1999). Taken together, these data clearly demonstrate a role for constitutively produced NO in the modulation of both selectin expression and leukocyte–endothelial cell interactions under basal conditions.

To assess the role of NO in modulating leukocyte rolling during acute inflammation, wild-type as well as NOS-deficient mice were examined following superfusion of the mesentery with the pro-inflammtory mediator thrombin (Lefer *et al*., 1999). Thrombin treatment for 30 min induced significant increases in leukocyte rolling in all mice with $eNOS^{-/-}$ and $nNOS^{-/-}$ mice exhibiting an exaggerated response compared to wild-type mice. Leukocyte adhesion was, however, significantly increased in all study groups compared to their baseline values in response to thrombin, and differences between groups were observed. In both studies, the most dramatic increase in leukocyte rolling and adherence was observed in $eNOS^{-/-}$ mice, suggesting that this source of NO is the most important source for modulating the response to this acute inflammatory stimuli. Surprisingly nNOS-derived NO also appears to be an important modulator of the inflammatory response to thrombin stimulation in the mouse mesentery.

ROLE OF NO IN MODULATING LEUKOCYTE EXTRAVASATION *IN VIVO*

Leukocyte rolling and adhesion may ultimately lead to extravasation of the leukocytes out of the circulation and into the tissue interstitium. Several reports have suggested that NO may influence leukocyte extravasation as well (Granger and Kubes, 1994, 1996; Lefer and Lefer, 1999). Recently, we have addressed the role of NO in the migration of leukocytes into peripheral tissue during acute inflammation by using mice selectively deficient in the three different isoforms of NOS as well as using selective iNOS inhibitors such as L-*N* imnoethyl-lysine (L-NIL) in rats (Cockrell *et al*., 1999). In one study, peritonitis was induced in rats by intraperitoneal administration of a 1% solution of oyster glycogen. One group of animals was given L-NIL orally immediately prior to oyster

glycogen and again at 2 and 4 h following oyster glycogen injection for a total L-NIL dose of 100 mg/kg. This amount of L-NIL has been shown to inhibit NO production from iNOS by >80% as assessed by plasma nitrate/nitrite levels (Cockrell *et al.*, 1999). At 6 hr post injection, extravasated neutrophils were harvested by peritoneal lavage, counted, and examined for the presence of iNOS. Animals treated with L-NIL exhibited no difference in the number of extravasated neutrophils when compared to vehicle-treated controls. Neutrophils harvested from both vehicle- and L-NIL-treated rats expressed similar levels of iNOS protein as assessed by Western blotting. These data suggest that inhibition of iNOS activity in stimulated rat PMNs has no effect on their ability to extravasate into peripheral tissues from the circulation in an oyster glycogen model of acute inflammation. A similar study utilized mice deficient in the different isoforms of NOS to elucidate further the role of NO in PMN extravasation. In this study, wild-type mice as well as mice deficient in each isoform of NOS were injected intraperitoneally with 1 ml of thioglycollate medium 135-C (Cockrell *et al.*, 1999). At 6 hr following stimulation, extravasated PMNs were harvested and counted. As with the oyster glycogen/L-NIL study in rats, $iNOS^{-/-}$ mice showed no difference in the number of extravasated PMNs when compared to wild-type controls. However, both $nNOS^{-/-}$ and $eNOS^{-/-}$ mice exhibited an increase in the number of leukocytes in the peritoneal cavity with $eNOS^{-/-}$ animals exhibiting an almost two-fold increase in extravasated PMNs. These data correlate well with the observations of increased leukocyte rolling and adhesion in $nNOS^{-/-}$ and $eNOS^{-/-}$ versus wild-type mice, suggesting that NO does indeed play a role in the modulation of acute inflammation when produced from nNOS and eNOS but not from iNOS. The molecular mechanisms responsible for this isoform-specific modulatory role are not clear at the present time.

ADHESION MOLECULE EXPRESSION AND iNOS

As discussed earlier, NO is able to modulate the basal expression of certain ECAMS, such as P-selectin, which in turn may influence leukocyte rolling and adhesion. On the basis of these observations, studies were conducted to ascertain the role that NO has on ECAM expression in models of acute and chronic inflammation. Using the thrombin-induced model of acute inflammation in $NOS^{-/-}$ mice, it was shown that P-selectin expression is significantly increased in $eNOS^{-/-}$ animals compared to wild type and $iNOS^{-/-}$ mice (Lefer *et al.*, 1999). P-selectin expression in $iNOS^{-/-}$ mice stimulated with thrombin was unchanged compared to wild-type mice, supporting previous studies that suggest the lack of a role for iNOS-derived NO in leukocyte–endothelial cell interactions. In a separate series of studies, the influence of NO on VCAM-1 expression in both acute and chronic inflammation was addressed (Kawachi *et al.*, 1999). Wild-type and $iNOS^{-/-}$ mice were given a single i.p. injection of either 10 or 25 μg/kg recombinant tumor necrosis factor-α (TNF-α) and VCAM-1 expression assessed *in vivo* using the dual radiolabeled monoclonal antibody technique at 5 hr post-stimulation. Injection of 10 μg/kg TNF-α has been shown to produce half-maximal expression of VCAM-1 *in vivo*, whereas 25 μg/kg produces maximal expression. VCAM-1 expression in the colon and cecum of wild-type mice injected with 10 μg/kg TNF-α was increased by two- to three-fold compared to saline-injected controls. Surprisingly, $iNOS^{-/-}$ mice injected with an equal dose of TNF-α showed a further enhancement of VCAM-1 expression in the colon and cecum (Kawachi *et al.*, 1999). Wild-type mice injected with 25 μg/kg TNF-α exhibited an approximately two-fold increase in VCAM-1 expression in the colon when compared to mice receiving only 10 μg/kg; however, $iNOS^{-/-}$ mice stimulated with 25 μg/kg showed no further enhancement of VCAM-1 expression over wild-type controls. In addition to the colon and cecum, a number of different tissues have been assayed in wild-type and $iNOS^{-/-}$ mice injected with TNF-α. Approximately 50% of all tissues respond with an exaggerated VCAM-1 response to 10 μg/kg TNF-α in $iNOS^{-/-}$ mice. This tissue specificity remains the subject of active investigation. The fact that thrombin-stimulated rolling and adhesion or thioglycollate-elicited PMN recruitment was not altered in $iNOS^{-/-}$ mice suggest that either VCAM-1 is not involved in these processes, the

mesentery tissue is devoid of iNOS-mediated regulation, or that the pro-inflammatory mediators produced upon stimulation with thrombin or oyster glycogen produce maximal upregulation of VCAM-1 and thus is no longer regulated by NO. We know that the mesentery in mice is one of the tissues that does indeed respond to 10 μg/kg TNF-α with enhanced expression of VCAM-1 in iNOS$^{-/-}$ mice compared to their wild-type control, suggesting that the latter possibility is more likely.

A second study was carried out to examine the role of iNOS derived NO in modulating VCAM-1 expression in a chronic model of gut inflammation (Kawachi *et al.*, 1999). In this study, severe combined immunodeficient mice (SCID) mice were reconstituted with CD4^{+}, CD45RB^{high} T cells, producing a progressive and chronic inflammation of the large bowel at 6–8 weeks post injection. Recent studies demonstrated that colonic VCAM-1 expression was elevated by approximately four-fold in SCID/CD45RB^{high} mice compared to their CD45RB^{low} reconstituted controls. In addition, one group of the colitic animals received continuous inhibition of iNOS via oral administration of L-NIL at a dose of 25 mg/kg per day beginning at 4 weeks post-injection when there is little or no inflammation of the colon and continuing until week 8 when maximal colitis is observed. Expression of VCAM-1 in the colon of reconstituted L-NIL-treated was also elevated approximately four-fold compared to untreated mice, suggesting that iNOS-derived NO is unable to modulate VCAM-1 expression during chronic inflammation. These data are not surprising in view of the fact that TNF-α, interleukin-1 β (IL-1β), and interferon-γ (IFN-γ) levels in the inflamed colon are very high and most probably produces maximal up-regulation of VCAM-1.

Taken together, these studies show that NO can play a role in the modulation of ECAM expression and subsequent leukocyte–endothelial interaction under basal conditions as well as during certain acute inflammatory responses. However, this modulation is dependent upon the source of NO, the tissue involved, and both the type and dose of stimulus used to induce acute inflammation. Both nNOS and eNOS appear to play key roles in the modulation of P-selectin expression and subsequent leukocyte rolling and adherence under basal conditions as well as PMN extravasation into surrounding tissue in response to inflammatory stimuli. In addition, we have found that iNOS-derived NO had little or no effect on P-selectin expression under basal or inflammatory conditions but appears to play a role in the modulation of VCAM-1 expression in response to a submaximal stimulation of this ECAM in some but not all tissue. However, iNOS does not appear to play a role in PMN extravasation into the peritoneum in response to thioglycollate or oyster glycogen, nor does there appear to be any modulatory effect of iNOS-derived NO on VCAM-1 expression in an immune-based model of chronic inflammatory bowel disease. In summary, these data suggest that the involvement of NO in the modulation and regulation of ECAM expression as well as leukocyte–endothelial interactions in both acute and chronic inflammation is a complex process that is dependent upon many factors, such as the source of NO, stimulus used, ECAM being examined, and degree of stimulation.

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ABBREVIATIONS

ECAMs, Endothelial cell adhesion molecules; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL-1β, interleukin-1β; L-NIL: L-*N*6-iminoethyl lysine; NF-κB, nuclear transcription factor kappa B; NO, nitric oxide; NOS, nitric oxide synthase; TNF, tumor necrosis factor; ROS, reactive oxygen species; SCID, severe combined immunodeficient; VCAM-1, vascular cell adhesion molecule-1.

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