




Regulatory Role of Nitric Oxide in Cutaneous Inflammation

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Abstract—Nitric oxide (NO), a signaling molecule, regulates biological functions in multiple organs/tissues, including the epidermis, where it impacts permeability barrier homeostasis, wound healing, and antimicrobial defense. In addition, NO participates in cutaneous inflammation, where it exhibits pro-inflammatory properties via the cyclooxygenase/prostaglandin pathway, migration of inflammatory cells, and cytokine production. Yet, NO can also inhibit cutaneous inflammation through inhibition of T cell proliferation and leukocyte migration/infiltration, enhancement of T cell apoptosis, as well as through down-regulation of cytokine production. Topical applications of NO-releasing products can alleviate atopic dermatitis in humans and in murine disease models. The underlying mechanisms of these discrepant effects of NO on cutaneous inflammation remain unknown. In this review, we briefly review the regulatory role of NO in cutaneous inflammation and its potential, underlying mechanisms.

KEY WORDS: nitric oxide; dermatitis; inflammation.

INTRODUCTION

NO takes on divergent roles in regulating a variety of cellular functions. Physiological levels of NO are required to maintain normal cellular function, while excessive NO can compromise cellular functions. For example, low levels of NO can increase cardiac output, while high levels decrease cardiac function [1]. Similarly, low concentrations of NO (5 to 50 $\mu\text{mol/l}$) increase, while

high concentrations (10 mM/l) decrease the beating rate of the sinoatrial node *in vitro*. [2] Deficiency in endothelial nitric oxide synthase (eNOS) increases blood pressure in mice [3, 4]. While knockout of eNOS alone lowers survival rate by 50%, knockout of all three NOS isoforms—inducible NOS (iNOS), neural NOS (nNOS), and eNOS—reduces the 10-month survival rate by 80% in mice [5]. In contrast, other studies showed iNOS deficiency increases survival rates and improves cardiac function in coronary ligated mice [6]. In the liver, NO produced by eNOS is required to maintain functional homeostasis and prevent the development of liver diseases. Stimulation by various stimuli, resulting in excess NO synthesized by iNOS, can provoke and/or exacerbate hepatic pathology [7]. Conversely, inhibition of iNOS activity alleviates damage to both the liver and the kidneys in bile duct-ligated rats [8]. Moreover, inhalation of NO improves lung function

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in both humans and animals [9–11]. Likewise, supplemental NO can improve tolerance to aerobic and anaerobic exercise in untrained or moderately trained humans [12]. Furthermore, inhibition of NO synthesis decreases T regulatory cells, worsens renal damage, and increases blood pressure in rats [13, 14]. Collectively, this evidence indicates that NO can diversely regulate the biological function of multiple cells/tissues.

Studies have also demonstrated a regulatory role for NO in cutaneous function, including stimulation of keratinocyte migration, proliferation, and improvement of cutaneous wound healing [15–19]. Previous studies showed that deficiency in iNOS delays cutaneous wound healing [20]. A requirement for NO in keratinocyte differentiation, lipid production, and epidermal permeability barrier has also been demonstrated, though a negative impact of NO on the epidermal permeability barrier has been shown [21, 22]. The antimicrobial properties of NO also have been well illustrated. For example, topical applications of NO-releasing nanoparticles for 2 days significantly accelerated the healing of wounds infected with *Acinetobacter baumannii* along with a marked reduction in bacterial burden [23]. Similarly, topical applications of NO-releasing nanoparticles for 3 days accelerated wound closure and decreased both inflammation and minimal bacterial burden in cutaneous wounds infected by methicillin-resistant *Staphylococcus aureus*. [24] Likewise, exogenous NO gas, used 8 h daily for 3 days, also reduces the bacterial count in *Staphylococcus aureus*-infected cutaneous wound [25]. Finally, NO also regulates cutaneous and extracutaneous inflammation [26–28], which is the subject of this review.

NO PRODUCTION AND REGULATION

NO is synthesized by 3 NO synthases (NOS) (EC 1.14.13.39)—nNOS (NOS1), iNOS (NOS2), and eNOS (NOS3), which are expressed in almost all tissues and various cell types. NOS converts arginine to citrulline, producing NO (Fig. 1). [29, 30] Flavin mononucleotide, flavin adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, and (6R-)-5,6,7,8-tetrahydro-L-biopterin serve as cofactors for NO synthase. However, the distribution of these three isoforms varies in different tissues. For example, nNOS is mainly expressed in the neurons and the brain, while eNOS is primarily expressed in endothelial cells, but both eNOS and nNOS are constitutively expressed in all tissues. [31–33] Likewise, iNOS is normally expressed at low levels in almost all tissues. Keratinocytes express all three isoforms of NOS, and macrophages, neutrophils, T cells, and fibroblasts also express various NOS. [33–35]

The expression and activity of NOS are regulated by a number of factors. eNOS and nNOS activity can be regulated by intracellular calcium via calmodulin-calcium interactions. High calcium level increases the binding of calmodulin to NOS, resulting in an increase in NO production. However, vascular endothelial growth factor-induced activation of eNOS can occur via both calcium-dependent and -independent manners [36]. Expression levels of mRNA for nNOS can be up-regulated by physical, chemical, and biological factors, such as heat, electrical stimulation, light exposure, colchicine, and allergic substances, as well as hypoxia [37]. Injuries and certain

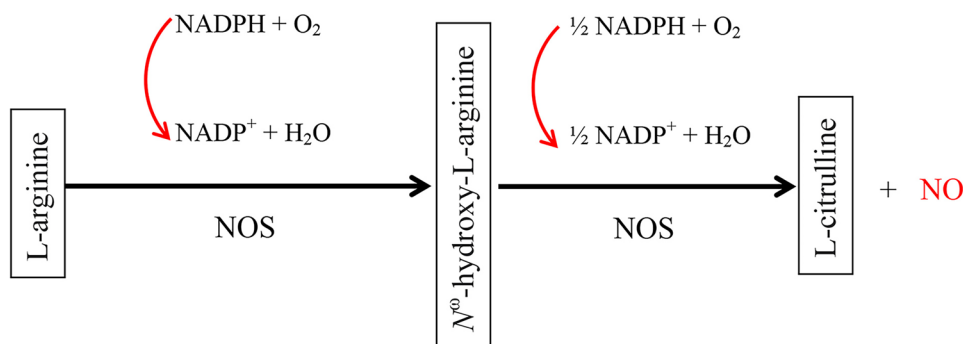


Fig. 1 Schematic diagram of enzymatic production of nitric oxide from L-arginine: Nitric oxide synthases first catalyze 5-electron oxidation of a guanidino nitrogen of L-arginine (L-Arg) to generate N^o-hydroxy-L-arginine (NOHLA), via activating oxygen at heme and transferring electrons from 1 molecule of nicotinamide-adenine-dinucleotide phosphate (NADPH) to flavin-adenine-dinucleotide and flavin-mononucleotide, followed by oxidation of N^o-hydroxy-L-arginine, consuming 0.5 molecules of NADPH and one molecule of oxygen, to produce citrulline and nitric oxide. This diagram is modified from previous publications [29, 30].

pathological conditions also increase nNOS expression in neural tissue [38–40]. Likewise, cutaneous wounding increases nNOS expression in keratinocytes [41]. In contrast, hypoxia and TNF- α down-regulate eNOS expression [37]. Interferon α/β (IFN α/β) lipopolysaccharide (LPS) and estrogen up-regulate eNOS expression and activity [42–45]. Moreover, mechanical stimulation of the skin increases cutaneous NO production by both nNOS and eNOS [46]. iNOS activity is also regulated by calcium-dependent and -independent signaling pathways, at least in some cells [47]. Estrogen and pro-inflammatory cytokines increase, while glucocorticoids decrease iNOS expression [48]. It is worth noting that some stimuli-induced iNOS expression in keratinocytes varies with the origin of the keratinocyte. For example, induction of iNOS expression by IFN γ is more profound in differentiating epidermal keratinocytes than in HaCat cells or mucosal keratinocytes [49]. Inhibitory effects of IL-10 and IL-4, but not IL-13, on NO production and iNOS expression have also been demonstrated, possibly by down-regulation of IL-1 production [50]. The mechanisms whereby Th1 and Th2 cytokines differentially regulate cutaneous NO production remain unknown. But studies show upregulation of NO production by Th1 cytokines, such as IL-2 and IFN γ is mediated by increased TNF- α production at least in macrophages because TNF- α antibody attenuates Th1 cytokine-induced increases in NO production [51]. Also, the p40 subunit of IL-12 is crucial for the induction of iNOS expression in mouse microglia [52]. Thus, the unique structure of some Th1 cytokines and the upregulation of TNF- α production can be ascribed to the upregulation of NO production by Th1 cytokines. Bacterial infection can increase iNOS expression and NO production, as well [53]. Additionally, either UVA or UVB irradiation increases NO production in the epidermis and the dermis. [54, 55] Our recent studies showed that disruption of the epidermal permeability barrier also increases iNOS mRNA expression in the epidermis [21].

REGULATION OF CUTANEOUS INFLAMMATION BY NO

The link between NO and inflammation in extra-cutaneous tissues has been well established. In inflammatory bowel diseases, such as Crohn's disease (CD) and ulcerative colitis, circulating levels of NO correlate positively with levels of Th17 cytokines (IL-17A, IL-23, IL-6, IFN- γ , and IL-12) [56, 57]. Pertinently,

inhibition of iNOS attenuated edema and neutrophil infiltration in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced acute colitis in rats [58]. The pathogenic role of NO in inflammation was further evidenced by the observation that inhibition of iNOS decreased, while an NO donor increased the levels of TNF- α and IL-6 in the culture medium of inflamed mucosa and renal epithelial cells [59, 60]. Similarly, inhibition of iNOS decreases IL-6 production in lung tissue infected by group B streptococcus [61]. Interestingly, inhibition of iNOS increases expression levels of IL-4 and IL-10 while decreasing IL-2 and IFN γ . [62] Other studies showed that inhibition of NOS with L-N^G-nitro arginine methyl ester (L-NAME) increased expression levels of TNF- α , IL-1 β , IL-6, MMP-2, and MMP-9 in a mouse model of osteoarthritis [63]. Studies have also demonstrated a regulatory role for NO in cutaneous inflammation *in vitro* and *in vivo* (Table 1). [64–93].

Pro-inflammatory Effects

NO has long been considered a key mediator in the development of cutaneous inflammation under various conditions. In both atopic dermatitis and allergic contact dermatitis, expression levels of eNOS and iNOS are increased in the dermis [94], although the absence of iNOS mRNA in the atopic epidermis was reported [95]. In psoriasis, another common inflammatory dermatosis, nNOS is expressed in all layers of the involved and uninvolved epidermis of psoriatic patients but only expressed in keratinocytes in the granular layer and eccrine sweat glands of normal skin. Expression of iNOS was also found in the epidermis of normal skin, while strong staining of iNOS was observed in both keratinocytes and in the papillary dermis of psoriatic skin. [95–97] Topical applications of an NO donor increased the number of CD3-, CD4-, and CD-68 positive cells in the skin [87]. Likewise, circulating levels of NO correlate positively with the severity of psoriasis [98]. All of these studies suggest a link between NO and inflammatory dermatoses in humans.

The link between NO and cutaneous inflammation is further supported by a number of *in vivo* and *in vitro* studies using NOS inhibitors and NOS knockout mice. In keratinocyte cultures, pre-treatment of keratinocytes with a NOS inhibitor (N^G-monomethyl-L-arginine, L-NMMA) decreased IgE-induced secretion of TNF- α and IL-6, while an NO donor increased cytokine production

Table 1 Regulatory Role of NO in Cutaneous Inflammation

Proinflammation		References
Models	Methods	Results
Keratinocytes stimulated with IgE	Pretreatment of keratinocytes with 1 mM L-NMMA, a NOS inhibitor, for 1 h, followed by stimulation with IgE for 48 h; or keratinocytes were cultured with 100 μ M SNP for 48 h	SNP increased IL-6 and TNF α L-NMMA inhibited IgE-induced increases in IL-6 and TNF α
Topical TPA-induced inflammation in mice	Topical application of aminoguanidine or LNMMA 30 min prior to TPA application. Skin samples were taken 4 h after TPA application. Or skin was treated with SNP, SNAP, or carboxy-PTIO for 2 h	NOS inhibitor decreased COX2 in TPA-treated skin; NO donors increased COX2 and PGE2 expression in normal mouse skin; NO scavenger (carboxy-PTIO) decreased COX2 expression
Inflammation induced by subcutaneous injection of carrageenin in male Wistar rats	Mouse hind paws were injected subcutaneously with 300 μ g carrageenin. In some experiments, animals were injected intraperitoneally with 5 mg L-NMMA 2 h before, and 24 and 48 h after the administration of carrageenin; the draining lymph node (DLN) was collected 48 h after the administration of carrageenin Paw edema was induced by subplantar injection of 0.1 ml of 1% A-carrageenin or 3% dextran. Carrageenin and dextran were given alone or in combination with L-arginine, D-arginine, L-NAME, or L-NMMA. The volume of the paw was measured with plethysmometry immediately after the injection. Subsequent readings of the volume of the same paw were carried out at 30- or 60-min intervals. In some experiments paw was treated with dexamethasone sodium phosphate (0.1 mg/kg) given s.c. 2 h prior to the induction of inflammation Paw edema was induced by subplantar injection of 0.1 ml of 1% carrageenin. Either L-NMMA or L-NAME was given intravenously (30–300 mg kg ⁻¹) 1 h before or after carrageenan administration	L-NMMA decreased the carrageenin-induced increase in skin swelling, without marked reduction in inflammatory infiltrates; L-NMMA did not affect the proliferation of T cells from DLN but inhibited cytokine production upon stimulation with concanavalin A Both L-NAME and L-NMMA dose-dependently inhibited the increase in vascular permeability and edema; L-arginine increased the inflammatory responses and reversed the inhibitory effects of L-NAME and L-NMMA; In dexamethasone-treated rats, L-arginine enhanced the dextran-induced edema and the early phase of carrageenin-induced edema but did not affect the inhibition by dexamethasone in the late phase of carrageenin-induced edema Both L-NMMA or L-NAME inhibited paw edema at all-time points; The selective iNOS inhibitors, L-NIL, or AG, did not inhibit paw edema during the first 4 h after carrageenan treatment, but inhibited paw edema at subsequent time points (from 5 to 10 h); All NOS inhibitors inhibited PGE2 production and neutrophil infiltration
Orally given L-NAME in the drinking water at a dose of approximately 75 μ M/rat/day for 2 and 4 weeks. Paw edema was induced by subplantar injection of carrageenin		L-NAME reduced carrageenin-induced paw edema; No changes in vascular permeability, as assessed by Evans blue extravasation, were observed in L-NAME-treated animals

Table 1 (continued)

Proinflammation			
	60 min prior to induction of inflammation with subcutaneous injection of carrageenin, L-NMMA was given by microdialysis	L-NMMA inhibited the increases in cutaneous PGE ₂ , 6-keto-PGF _{1α} , and COX2 induced by carrageenin	[70]
Substance p-induced edema in rats	Intradermal injection of substance P (0.03–1 nmol) with or without concurrent injection of L-NAME (0.1 μM) or L-NMMA (0.1 μM). Edema was assessed 15 min after	L-NAME and L-NMMA inhibited substance P-induced edema and blood flow; L-arginine (1 pmol) prevented the inhibitory effects of L-NAME	[71]
Mustard oil-induced inflammation in rat hind paws	L-NAME (43 μM/kg i.v.) 15 min prior to application of mustard oil. Edema was measured up to 2 h after mustard oil application	L-NAME decreased blood flow without changes in edema	[72, 73]
UVB-irradiated rat ears	Rat ears were irradiated with UVB at an intensity of 5.4 J/cm ² (each side of the ear) for 20 min. L-NAME (25 nM) was intradermally injected 24 h after irradiation	L-NAME had no effect on ear edema	[74]
UVB-irradiated mouse skin	Mice were irradiated with UVB at an intensity of 20 mW/cm ² for 9 min. Either L-NAME (100 nM/site) or L-arginine (10 μM/site) or L-NAME 100 nmol + L-arginine 10 μM was intradermally injected 17.5 h after irradiation	L-NAME abolished UVB-induced increase in blood flow. The effect of L-NAME was reversed partially by the co-injection of L-arginine	[75]
Complete Freund's adjuvant-induced paw inflammation in mice	30 min prior to induction of paw inflammation by intraplantar injection of complete Freund's adjuvant (CFA), 7-NINA (selective nNOS inhibitor), AG (selective iNOS inhibitor), L-NAME (a non-selective NOS inhibitor), but not L-NIO (selective eNOS inhibitor), at a dose of 50 mg/kg body weight was given intraperitoneally	Pretreatment with 7-NINA, AG, L-NAME, but not L-NIO, significantly attenuated thermal hyperalgesia induced by CFA; Pretreatment with the NOS inhibitors prevented the CFA-induced increases in TNF-α and IL-1β mRNA expression; 7-NINA and L-NAME increased while either AG or L-NIO decreased IL-10 mRNA expression	[76]
Complete Freund's adjuvant-induced paw inflammation in NOS KO (nNOS, iNOS, and eNOS) knockout mice	Paw inflammation was induced by intraplantar injection of 10 μl of complete Freund's adjuvant	Expression levels of TNF-α, IL-1β, and IL-10 mRNA in nNOS-, iNOS-, or eNOS-KO mice were lower than that in WT mice at 6 to 24 h, except for TNF-α in eNOS-KO and IL-10 in iNOS-KO mice at 24 h, where they were higher or equal to WT controls	[76]
Inflammation induced by intradermal injection of histamine or bradykinin in rabbits	Histamine (3 nM/site), bradykinin (0.1 nM/site), or PGE1 (0.1 nM/site) was co-injected with either SNP (0.4–400 nM/site), SIN-1 (0.4–400 nM/site) or L-NAME (0–400 nM/site)	NO donors did not affect vascular permeability induced by either histamine or bradykinin or PGE1; L-NAME inhibited plasma leakage induced by a combination of PGE1 and bradykinin or histamine; L-arginine or SNP reversed the inhibitory effect of L-NAME on plasma leakage	[77]

Table 1 (continued)

Proinflammation

Inflammation induced by intradermal injection of histamine, bradykinin, or zymosan-activated plasma in guinea pigs	Histamine, bradykinin, or zymosan-activated plasma was intradermally injected alone or with L-NAME. Inflammation was assessed 2 h after	Given L-NAME with bradykinin (10^{-10} M/site) caused a dose-dependent inhibition of bradykinin-induced edema formation; [78] At a dose of 10^{-6} M/site, L-NAME inhibited bradykinin-induced edema formation by 89%; SNP reversed the inhibitory effect of L-NAME on bradykinin-induced edema; L-NAME inhibited eosinophil infiltrate induced by zymosan-activated plasma, passive cutaneous anaphylaxis reaction, platelet-activating factor, and bradykinin
Reverse passive Arthus reaction in guinea pigs	Inflammation was induced by intradermal injection of antigen with or without L-NAME. Skin edema was assessed 4 h after induction of inflammation	L-NAME suppressed edema formation by 68%, whereas a cyclo-oxygenase inhibitor (ibuprofen) suppressed edema by 27% [79]
Inflammation in cutaneous wound of iNOS, eNOS, and NOS KO mice	A 6-mm full-thickness wound was created on the dorsal surface and covered with a semi-occlusive dressing. Wounds were treated daily for 7 days (d 0–6) with topical application of 50 μ l of either SP (10^{-7} M) or normal saline by infusion with a 26-gauge needle through the dressing onto the wound bed	NOS KO delayed wound healing. Densities of macrophage, leukocyte, and dendritic cells were lower in all NOS KO mice than in the controls at d 3 and d 7 post wound [80]
Inflammation in cutaneous wound of iNOS KO mice	A 2.5 cm longitudinal incision was created on the back of the mice	TGF- β 1 expression was increased by 50 to 100% in iNOS KO wounds on postoperative days 5 and 7; VEGF and IL-4 expression were elevated by 25 to 100% in wild type compared with iNOS-KO mice [81]
Allergic contact dermatitis in Balb/C mice	Dermatitis was induced by topical application of 0.4% DNFB to mouse ears. Intradermal injection of 10 μ l aminoguanidine (50 mM) or L-NMA (100 mM) into the ears	NOS inhibitors decreased ear thickness and inflammatory infiltrates [82]
Allergic contact dermatitis in iNOS KO and wild type mice	Dermatitis was induced by topical application of ovalbumin; the mice were intraperitoneally injected with 20 mg/kg L-NAME after sensitization	Ear swelling and the frequency of scratching for the OVA-sensitized mice decreased significantly after the administration of L-NAME; Ear swelling and the frequency of scratching in the sensitized animals were significantly suppressed in iNOS KO mice; Skin histamine content and number of mast cells were also lower in iNOS KO mice than in the controls [83]

Table 1 (continued)

Proinflammation	
Allergic contact dermatitis induced by pteryli chloride (PC1) in mice	<p>Ear swelling was observed at 2 h (early phase) and 24 h (late phase) after application of the antigen to PC1-sensitized CBA/J mice. L-NAME or L-arginine was intravenously injected at the time of the PC1 challenge [84]</p> <p>Low-dose (1 mg/kg) L-NAME inhibited the early-phase reaction, but not the late-phase reaction. High-dose (250 mg/kg) L-NAME inhibited both early- and late-phase reactions. High-dose (250 mg/kg) L-arginine increased both early and late phase reactions</p> <p>Injection of L-NAME (250 mg/kg) with PCI significantly decreased IL-2 and IFN-γ compared with PCI alone; Administration of L-arginine (250 mg/kg) significantly increased the production of IL-2 and IFN-γ by the lymph node cells</p>
Humans with atopic dermatitis	<p>15 patients with atopic dermatitis were topically treated with 1% NLA twice daily for 4 weeks [85]</p>
Normal human skin	<p>0.02 ml zeolite zinc (33% wt/wt) or 0.02 ml zeolite manganese NO (33% wt/wt) or 0.04 ml acidified NO₂⁻, was applied topically to the volar aspect of the forearm once every 8 h for 2 consecutive days [86]</p> <p>Topical Ze-NO induced a dermal CD4⁺ T cell to infiltrate and IFN-γ secretion. The acidified nitrite caused dermal infiltrate of CD3⁺, CD4⁺, CD8⁺, and CD68⁺ cells and neutrophils. Suction blisters were created in Ze-NO-treated and control skin. IFN-γ, but not IL-4, was detected in Ze-NO-treated skin</p>
Anti-inflammation	<p>NO increased staining intensity of CD3, CD4, CD8, CD68, VCAM-1 and ICAM-1, and neutrophil infiltration [87]</p>
Allergic contact dermatitis in mice	<p>Ear inflammation was induced by topical application of 20 μl of 0.3% (v/v) DNFB. iNOS was inhibited with an intraperitoneal injection of L-NIL (2.5 mg in 0.5 ml PBS twice daily) for 6 consecutive days starting 1 day before sensitization [88]</p> <p>iNOS inhibitor increased ear thickness and augmented FITC-induced migration of cutaneous DCs, including Langerin(+) LCs and Langerin(-) dermal DCs, to draining lymph nodes;</p> <p>iNOS inhibitor enhanced LC survival <i>in vitro</i></p>

Table 1 (continued)

Proinflammation

Irritant contact dermatitis in mice	Irritant contact dermatitis was induced by topical application of 5% benzalkonium chloride to mouse ears. Test products were applied either 15 min before or 5 min after benzalkonium chloride application	Topical NO-hydrocortisone (NCX 1022) (either pre or posttreatment) was more effective than hydrocortisone in reduction of ear thickness during the initial stages of inflammation (from 1 to 5 h); NCX 1022, but not hydrocortisone, significantly inhibited granulocyte recruitment and reduced the number of infiltrated cells and disruption of the tissue architecture compared to hydrocortisone-treated tissues; NCX 1022 was more effective than hydrocortisone in inhibiting benzalkonium chloride-induced leukocyte adhesion to the endothelium	[89]
Mouse model of atopic dermatitis	Atopic dermatitis was induced by sensitization with Ovalbumin. Berdazimer sodium (6%), a NO donor, was applied topically for 24 h	NO donor decreased <i>Staphylococcus aureus</i> colonization and expression of IL-4 and IL-13	[90]
Patients with atopic dermatitis	A NO donor, berdazimer sodium (2 or 6%), was applied topically twice daily for 2 weeks	NO donor decreased eczema area and severity index scores;	[90]
Nickel-induced inflammation in the mouse dermis	Allergic inflammation was induced by the intradermal injection of nickel chloride. An iNOS inhibitor, L-NIL (100 µM), was co-administrated with nickel	NO donor decreased expression levels of inflammation-related genes	[91]
iNOS KO mice	Inflammation caused by subcutaneous implantation	iNOS KO mice exhibited increased neutrophil and macrophage infiltration and collagen deposition; No changes in CXCL1 and CCL2 expression were observed	[92]
Nickel-induced inflammation in humans	Skin was topically treated with NOS inhibitor, L-NMMA, for 4 consecutive days, followed by nickel patch testing, then irradiated with a solar simulator	NOS inhibitor increased epidermal S-100 ⁺ dendritic cells and decreased dermal S-100 ⁺ dendritic cells; Erythema index and sunburn cells were decreased in NOS inhibitor-treated area	[93]

L-NMMA, N^G-monomethyl L-arginine; *L-NAME*, N^G-nitro-L-arginine methyl ester; *NLA*, N^ω-nitro-L-arginine; *L-MIL*, N-1-iminoethyl-L-lysine; *AG*, aminoguanidine; *L-NIO*, L-N(5)-(1-iminoethyl)-ornithine; *7-NINA*, 7-nitroindazole sodium salt; *SNP*, Sodium nitroprusside; *SIN-1*, 3-Morpholininosydnonimine; *TPA*, 12-O-tetradecanoylphorbol-13-acetate; *DNFB*, 2,4-dinitrofluorobenzene

[64]. *In vivo*, pretreatment of mice with an iNOS inhibitor prevented TPA-induced increases in COX2 expression [65]. Similarly, intraperitoneal injection of either nNOS or iNOS inhibitor (but not an eNOS inhibitor) lowered expression levels of TNF- α and IL-1 β in a mouse model of plantar inflammation induced by complete Freund's adjuvant [76]. In addition, intravenous injection of NOS inhibitor (L-NAME) decreased ear swelling as well as the contents of IL-2 and IFN γ in lymph nodes of mice with cutaneous inflammation induced by topical applications of picryl chloride [84]. In humans, topical application of 5% NO $^{-}_2$ solution increased NO content in the superficial dermis, accompanied by an increase in infiltrates of macrophages and neutrophils in both the epidermis and the dermis, along with increased dermal infiltration of T cells [86]. Likewise, topical applications of 5% nitrite cream markedly increased inflammatory infiltrates in both the dermis and the epidermis in humans.[87] Correspondingly, topical applications of an NOS inhibitor (N o -nitro-L-arginine) twice daily for 4 weeks reduced pruritus and erythema in patients with atopic dermatitis in subjects who responded poorly to topical steroids [85]. Direct evidence of NO in regulating cutaneous inflammation has been demonstrated in NOS knockout mice. In a mouse model of ovalbumin-specific immunoglobulin E-induced dermatitis, iNOS knockout mice displayed no increase in either cutaneous mast cell infiltration or circulating levels of pro-inflammatory cytokines, such as TNF- α , in comparison to wild-type controls [83]. Moreover, deficiency in either iNOS, nNOS, or eNOS decreased the densities of inflammatory cells, including dendritic cells, macrophages, and leukocytes in cutaneous wounds in mice [80]. Notably, the effects of NOS inhibitors on inflammation depend on their route of administration, at least in a rat model of carrageenin-induced pleurisy. For example, a single intrapleural injection of the iNOS inhibitors [S-(2-aminoethyl) isothioureia or N-(3-(aminomethyl)-benzyl) acetamidine] or eNOS inhibitor [1-N5(1-iminoethyl)-ornithine] exacerbated inflammation at early stages (1–6 h), while systemically administering NOS inhibitors ameliorated the severity of inflammation throughout the induction of carrageenin-induced pleurisy in rats [99]. Studies also demonstrated that inhibition of NOS increased vasodilation without changes in edema provoked by topical mustard oil [72, 73], suggesting regulation of NO in cutaneous inflammation varies in different inflammatory models. Nonetheless, these studies demonstrate a regulatory role for NO in cutaneous inflammation.

Although the precise underlying mechanisms of the pro-inflammatory effect of NO have not been fully clarified, several mechanisms could contribute to these effects. First, during the development of inflammation, vascular dilation and leukocyte migration are crucial events leading to inflammatory infiltration and edema. Studies showed that fewer migrated leukocytes and smaller vessel diameters were observed in iNOS-deficient mice than in the normal wild-type mice upon induction of inflammation with LPS [100]. NOS inhibitors such as L-NAME and L-NMMA inhibited the carrageenin-induced increase in vascular permeability and paw edema in rat skin [67]. The inhibitory effects of NO on inflammatory infiltration and edema are likely via prostaglandin E (PGE) because NOS inhibitors reduced, while NO donors increased PGE production and potentiated arachidonic acid-induced paw edema in rats [101, 102]. Moreover, inhibition of NOS attenuated cutaneous edema induced by either bradykinin or histamine [103] or zymosan-activated plasma-induced infiltration of eosinophil and neutrophils [78]. Thus, NO-induced increases in vascular permeability and leukocyte migration account in part for the pro-inflammatory effect of NO in cutaneous inflammation.

Secondly, NO can activate the promoter of the IL-8 gene and increase IL-8 mRNA expression in human melanoma cells and lung epithelial cells *in vitro*. [104–106] Correspondingly, NO donors enhance LPS-induced IL-8 production in neutrophils [107]. Likewise, NO donors and L-arginine increase expression levels of IL-6, IL-1 β , and TNF- α , as well as macrophage inflammatory proteins [59–61, 108]. Inhibition of iNOS decreases TNF- α , and IL-6 production by 66 and 27%, respectively, *in vitro*. [59] Similarly, nNOS deficiency decreases TNF- α , IL-1 β , and IL-6 production in macrophages stimulated with LPS [109]. Notably, nNOS, but neither iNOS nor eNOS, is involved in cytokine production in response to stimulation with LPS. Hence, stimulation of cytokine production can be an additional mechanism by which NO triggers/exacerbates inflammation.

Finally, NO can enhance proliferation and differentiation of Th1 cells, accompanied by an elevation in INF γ production [110], events that could also contribute to the pro-inflammatory effect of NO in cutaneous inflammation. In summary, the pro-inflammatory effects of NO can be collectively attributed to increased vascular permeability and cytokine production, as well as stimulation of inflammatory cell migration and T cell proliferation and differentiation.

Anti-inflammatory Effects

NO also exerts anti-inflammatory properties in cutaneous and extracutaneous tissues. For example, inhibition of NOS enhances the recruitment and extravasation of leukocytes in postcapillary venules [111]. Conversely, administration of an NO donor (3-morpholinopyridone, SIN-1) inhibits both platelet-activating factor- and integrin-induced leukocyte adhesion in venules [112, 113]. NO-releasing derivatives of mesalamine are more effective than mesalamine alone in the inhibition of colon inflammation and reduction of IL-1 β production by splenocytes [114]. Similarly, co-culture of peripheral blood monocytes with NO donor reduced secretion of IL-1 α , IL-6, IL-8, and TNF- α in comparison to the vehicle treatment [115]. Evidence indicates certain anti-inflammatory properties of NO are also demonstrated in the skin. For instance, acne is a common skin disorder accompanied by cutaneous inflammation. Preincubation of keratinocytes with NO donor for 1 h dose-dependently decreased *Propionibacterium (P.) acnes*-induced secretion of IL-6 and IL-8 as compared to those without NO donor treatment. Allergic contact dermatitis is another common cutaneous inflammatory disorder. Previous studies showed that intraperitoneal injections of an iNOS inhibitor for 6 days dramatically augmented ear thickness induced by topical dinitrofluorobenzene (DNFB) in mice [88]. Likewise, inhibition of iNOS enhanced nickel-induced ear thickness by over 70% as compared to vehicle-treated ears [91]. Consistent with these findings in murine models, topical applications of an NO donor twice-daily for two weeks lowered eczema area and severity scores by 23% from the baseline, along with suppression of gene expression related to innate immunity (Th2, Th17/Th22, Th9, and Th1) pathways in humans with atopic dermatitis [90]. Taken together, these studies demonstrate the anti-inflammatory benefits of NO in cutaneous inflammation.

The underlying mechanisms whereby NO attenuates cutaneous inflammation can be attributable to reductions in cytokine production and inflammatory infiltration, and stimulation of CD4+ T cells to differentiate into Treg cells. Previous studies showed that *P. acnes* increased expression levels of IL-1 β , IL-6, IL-8, and TNF *in vivo* and *in vitro* via activation of the NLRP3 inflammasome [115–119] and that an NO donor can inhibit NLRP3 inflammasome activity, leading to reductions in IL-8 and IL-1 β [120]. Likewise, an NO donor inhibited the secretion of IL-6 and other inflammatory proteins by monocytes by over 50% [121]. In contrast, inhibition of NO production increases expression levels of pro-inflammatory cytokines, such

as IL-1 β , IL-6, and TNF β , while an NO donor inhibited the expression of these cytokines in LPS-treated macrophages [122–125]. An NO donor (NOC-18) also inhibited proliferation and differentiation of Th17 cells, as well as the secretion of IL-17a and IL-22 [126], while increasing CLA⁺CD25⁺Foxp3⁺ regulatory T cells through the canonical soluble guanylyl cyclase–cyclic guanosine monophosphate (sGC–cGMP) signaling pathway [127], which negatively regulates inflammation. Moreover, either sodium nitroprusside or NOC12 (NO donors) can dose-dependently enhance T lymphocyte apoptosis and down-regulate expression levels of Bcl-2 protein, leading to reductions in T cell survivability [128]. The anti-inflammatory properties of NO can be ascribed to the enhancement of T cell apoptosis as well as inhibition of cytokine expression.

NO can also inhibit the migration and adhesion of inflammatory cells. Prior to sensitization with 2,4-dinitrofluorobenzene, daily intraperitoneal injection of iNOS inhibitor for 6 days dramatically increases lymphocytic infiltration into the dermis and dendritic cell migration into the lymph nodes in mice [88]. In a rat model of pleurisy, low doses of an NO donor (NOC-18 at a dose of 10 mg/kg) inhibited leukocyte infiltration by 20% 4 h after induction of pleurisy, while high doses of the same NO donor (30 mg/kg) increased leukocytes by 33% [129]. In a mouse model of irritant contact dermatitis induced by topical benzalkonium chloride, topical NO-hydrocortisone (NCX 1022) is more effective than hydrocortisone alone in inhibition of granulocyte recruitment and leukocyte adhesion to endothelia in addition to the reduction in the number of infiltrated cells [89]. Evidence indicates that NO-induced inhibition of neutrophil migration is mediated by cyclic GMP–intercellular adhesion molecule I [130]. Inhibition of migration and adhesion of inflammatory cells could therefore contribute to the anti-inflammatory properties of NO.

The exact underlying mechanisms for the divergent effects of NO on inflammation are unknown. Evidence indicates that NO is required in the induction of inflammation. Low levels of NO can increase endothelial permeability, facilitating the migration of inflammatory cells to the inflamed site and cytokine production. [131–134] Moreover, low levels of NO increase cyclic GMP and β 2 integrin, resulting in enhanced chemotaxis and neutrophil aggravation. Thus, either NOS deficiency or administration of NOS inhibitor attenuates inflammatory response to

stimuli. In contrast, high levels of NO inhibit inflammation. Previous studies showed that high levels of NO increase peroxynitrite production and ADP ribosylation of actin, leading to reductions in neutrophil infiltration [132]. High levels of NO also can induce neutrophil and T cell apoptosis. [132, 134]. In addition, NO donor inhibited histamine release and mast cell degranulation, while NOS inhibitor enhanced LPS-induced histamine release [135]. Hence, NO also exhibits anti-inflammatory properties, particularly in the case of inflamed skin. However, further studies are required to define which levels of NO are considered low or high.

CONCLUSIONS

NO exhibits both pro-inflammatory and anti-inflammatory properties via positive or negative regulation of cytokine expression, inflammatory cell proliferation, and adhesion, as well as T cell apoptosis. Although it appears that high levels of NO inhibit inflammation, further studies are needed to determine the optimal level of NO that can inhibit cutaneous inflammation and whether NO donors could improve cutaneous inflammation in clinical settings.

AUTHOR CONTRIBUTION

MQM originated the concept and drafted the manuscript; PME drafted the manuscript; JSW revised the manuscript and drafted responses to reviewers' comments; TMM critically reviewed the manuscript. All authors approved the final version.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

DECLARATIONS

Ethics Approval Not applicable.

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