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Modulation of Oxidative Stress and Inflammation by Nitric Oxide Modulators in a Rat Model of Bronchial Asthma

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Abstract

Bronchial asthma is a chronic inflammatory airway disease that primarily involves IgE-mediated mast cell activation and cytokine-driven inflammation, resulting in bronchospasm, mucus hypersecretion, and airflow obstruction. Although conventional therapies offer symptomatic relief, they neither reverse airway remodelling nor prevent its progression and are associated with long-term adverse effects. These limitations have driven the search for alternative therapeutic targets, with nitric oxide being investigated as a potential candidate.

Enzyme nitric oxide synthase (NOS) generates nitric oxide (NO) from L-arginine, whereas arginase metabolizes L-arginine, thereby reducing the availability of L-arginine for NO synthesis. NOS are present in constitutive and inducible form and synthesize NO in differential manner under various conditions and determine state of health and disease. Dysregulation of these pathway contribute to airway inflammation and tissue injury in asthma.

The present study aimed to evaluate the effects of an NO donor (isosorbide dinitrate, ISDN), NO precursor (L-arginine), and arginase inhibitor (2(S)-amino-6-boronohexanoic acid hydrochloride, ABH) in an ovalbumin (OVA)-induced rat model of bronchial asthma. Wistar rats were sensitized and challenged with OVA, followed by either of the NO modulator treatments to assess the effect on inflammatory and oxidative markers in serum and bronchoalveolar lavage (BAL) fluid.

Results showed that OVA immunization and challenge significantly increased leukocyte, eosinophil, and neutrophil counts, OVA-specific IgE, TNF-α, and malondialdehyde (MDA) levels, while decreasing IL-10 and reduced glutathione (GSH), confirming airway inflammation and oxidative stress. Treatment with ISDN, L-arginine, or ABH markedly reduced inflammatory cell infiltration and IgE, TNF-α, and MDA levels, while elevating IL-10 and GSH concentrations. The combination of L-arginine and ABH showed the greatest improvement in the markers of oxidative stress and inflammation.

These findings suggest that enhancing endogenous NO through L-arginine supplementation or preventing its depletion via arginase inhibition may restore redox balance, reduce oxidative stress, and mitigate airway inflammation. Overall, modulation of the L-arginine–NO–arginase pathway provides a promising strategy to attenuate airway inflammation and oxidative injury in asthma, indicating that NO donors and arginase inhibitors may serve as effective adjunctive therapies to conventional treatments.

Keywords: *Airway Inflammation; Oxidative Stress; Bronchial Asthma*

Introduction

Bronchial asthma is a chronic inflammatory disease characterized by airway remodelling, hyperresponsiveness, and infiltration of inflammatory cells such as eosinophils, neutrophils, and mast cells [1]. The cellular mechanism of asthma involves an early sensitization phase during which allergen-specific immunoglobulin E (IgE) and T-cell responses are initiated, followed by an effector phase comprising immediate and late-phase responses [2]. Th2 lymphocytes play a central role by releasing cytokines such as IL-4, IL-5, IL-13, and GM-CSF, which promote inflammatory signalling and sustain airway inflammation [3,4]. TNF-α contributes by inducing histamine release from mast cells, promoting cytokine production by T cells, acting as a chemo attractant, and stimulating myocyte proliferation [5]. In contrast, IL-10 functions as an anti-inflammatory cytokine that maintains immune homeostasis and limits tissue damage caused by excessive immune responses [6]. The mainstay of treatment of bronchial asthma includes inhaled corticosteroids, β agonists, leukotriene antagonists and muscarinic antagonists. However, despite the general success in symptomatic relief, current asthma treatment primarily causes no change in reversal of remodelling. This, along with numerous side effects of long-term treatment with conventional agents, necessitated further study into the pathophysiology of asthma emphasizing the need for alternative targets such as nitric oxide (NO).

NO is a ubiquitously present physiological messenger activating soluble guanylate cyclase (sGC) by binding to the haem group/moiety of the enzyme and leads to increase in cyclic GMP which further activates cyclic GMP dependent protein kinase and causes phosphorylation of respective protein kinases (myosin). This in turn results in reduced smooth muscle contraction and causes reduction in muscle tone. Such effects explain NO effects on vascular, bronchial and gastrointestinal smooth muscles [7]. NO is obtained from L-arginine by enzyme nitric oxide synthase (NOS), which is present in two forms i.e. constitutive form in endothelium (eNOS) and neuronal (nNOS) cells produces low, protective levels of NO that maintain airway tone and vascular integrity, whereas inducible NOS (iNOS) generates high amounts of NO during inflammation, leading to oxidative and nitrosative stress through peroxynitrite formation [8].

The site and concentration specific effects of NO may have beneficial or detrimental effects on airway inflammation and bronchospasm in asthma [9].

In this study ovalbumin (OVA)-induced model of asthma in rats was employed to evaluate the effects of NO modulators viz. NO donor (isosorbide dinitrate, ISDN), NO precursor (L-arginine), and arginase inhibitor (2(S)-amino-6-boronohexanoic acid hydrochloride, ABH) on ovalbumin specific IgE, markers of inflammation (TNF- α, IL-10) and oxidative & nitrosative stress.

Materials and Methods

Ethical approval and animals

All animal studies were performed in accordance with the recommendations of the Committee for Control and Supervision of Experiments on Animals (CCSEA) and approved by the Institutional Animal Ethics Committee. Experiments were performed on Inbred Wistar rats of either sex (180 - 250g). Wistar rats were kept under stable environment of temperature (21°C - 25°C with twelve hr light and dark cycle). Drinking water and rodent food was easily accessible to rats.

Drugs and chemicals: Ovalbumin (OVA), aluminium hydroxide, L-arginine, arginase inhibitor ABH hydrochloride, nitric oxide donor isosorbide dinitrate (ISDN), and prednisolone were used. Cytokine and immunoassay kits (TNF-α, IL-10, OVA-IgE) were obtained from standard suppliers.

Experimental design: Rats were divided into seven groups with 6 rats/group: 1) normal group rats, 2) disease control, 3) ISDN, 4) L-arginine, 5) ABH, 6) L-arginine + ABH, and 7) prednisolone. All groups except Normal rats were sensitized by intraperitoneal administration of OVA (40 μg/rat) adsorbed onto aluminium hydroxide (2 mg/rat) on day 1 and thereafter, daily exposed to aerosolized OVA (1% in normal saline) for 20 minutes for 08 days, starting from day 15 [9]. The challenge was carried out in a Plexiglas chamber by using ultrasonic nebulizer (Aeroneb Lab Nebulizer System, Ireland). Drugs were administered intraperitoneally 30 minutes prior to each challenge.

Rats of normal and disease control groups were treated daily with isotonic saline. Rats in group ISDN were given NO donor ISDN 50 mg/ kg, i.p/day in isotonic saline. Rats in L-ARG group received NO precursor L-Arginine 500 mg/kg, i.p/day. Rats in group ABH were administered with Arginase inhibitor ABH-400 ug/kg, i.p. in isotonic saline. Rats in L-ARG + ABH group were administered combination of L- Arginine 500 mg/kg and ABH-400 ug/kg, i.p in isotonic saline from 15 - 22 day of OVA immunisation. Rats treated with prednisolone 10 mg/kg, i.p., served as positive control. The doses for L-arginine, ABH and ISDN have been selected on the basis of doses mentioned in existing literature and earlier studies conducted in our laboratory (Mitani., *et al*. 1997; Krause., *et al*. 2018; Gulati., *et al*. 2007). On day 23, the animals were anesthetized by intraperitoneal administration of α-chloralose (100 mg/kg body weight). Bronchoalveolar lavage (BAL) fluid and blood samples were collected for cytological and biochemical analyses. Following sample collection, the rats were euthanized by cervical dislocation under deep anesthesia. Total and differential leukocyte counts were performed using a Neubauer chamber and Wright–Giemsa staining.

Biochemical assays

OVA-specific IgE assay

Antigen specific IgE antibodies are extremely important in the initiation as well as progression of asthma pathology. OVA-specific IgE levels were measured using commercially available ELISA kit manufactured by Qayee Bio-Technology Co. Ltd., China (Cat. No. - QY-E11195). The assay was performed as per the manufacturer's instructions. Standard curve was generated for 0-100 µg/ml concentrations of OVA-specific IgE. The result was expressed in µg/ml.

TNF-α assay

TNF-α is a pro inflammatory cytokine that plays a major role as in the pathogenesis of bronchial asthma by increasing chemotaxis, leukocyte adhesion, diapedesis and T-cell activation. Serum and BAL fluid samples were assayed for TNF-α levels using commercially available ELISA kit manufactured by Diaclone SAS, France (Cat. No. - 865.000.096), as per the manufacturer's instructions. Briefly, 100 µl of sample and standard diluent were added to appropriate number of wells, followed by the addition of 50 µl of biotinylated anti-Rat TNF-α to all wells. The microtiter plate was then covered and incubated at room temperature (24°C) for 3 hours. The liquid from each well was then aspirated and washed using 0.3 ml of the washing solution provided in the kit. Following three wash cycles, 100 µl of Streptavidin-Horseradish peroxidase solution was added to each well and the microtiter plate incubated at room temperature for 30 minutes. Wash step was repeated. Further, 100 µl of TMB Substrate Solution was added into all wells. The plate was then covered with aluminium foil and incubated in the dark for 15 minutes at room temperature. Further, 100 µl of H_2SO_4: Stop Reagent was added to each well and absorbance at 450 nm was immediately read using a spectrophotometer. Results were expressed in pg/ml.

Interleukin-10 assay

IL-10 has numerous immunomodulatory functions and predominantly plays an anti-inflammatory role by inhibiting the expression of NF-kB. Serum and BAL fluid samples were assayed for IL-10 levels using commercially available ELISA kit manufactured by Qayee Bio-Technology Co. Ltd., China (Cat. No. - QY-E11536), following manufacturer's instructions. The absorbance was read at 450 nm using a spectrophotometer and results were expressed in pg/ml.

Oxidative stress markers

Malondialdehyde (MDA) assay

Malondialdehyde is a product of lipid peroxidation therefore it acts as a marker of oxidative stress. MDA was measured using the method described by Ohkawa., *et al*. [10]. In a 0.2 ml serum sample, 1.5 ml of acetic acid (20%, pH adjusted to 3.5 with NaOH), 1.5 ml of thiobarbituric acid (0.8%) and 0.2 ml of sodium lauryl sulfate (8.1%) were added. The mixture was heated at 100°C for 1 hour in boiling water bath and cooled with tap water. 5 ml of butanol: pyridine (15:1% v/v) and 1 ml of distilled water were added in the mixture. The

mixture was then centrifuged at 4000 rpm for 10 minutes. Thereafter, absorbance of the separated organic layer was measured at 532 nm using a spectrophotometer and concentration expressed as nmol/ml. 1, 1, 3, 3-tetramethoxypropane (TMP) was used as the standard.

Reduced glutathione levels

Reduced Glutathione (GSH) provides thiol group to scavenge reactive oxygen species thereby it is used as an indicator of antioxidant status. Reduced glutathione (GSH) levels were estimated by the method described by Ellman [11]. This assay is based on the enzymatic recycling procedure in which glutathione is sequentially oxidised by the DTNB and reduced by NADPH in the presence of glutathione reductase. An equal quantity of sample was mixed with 10% trichloroacetic acid (TCA) and centrifuged to separate the proteins. To 0.1 ml of this supernatant, 2 ml of phosphate buffer (pH 8.4), 0.5 ml of DTNB [5'5-dithiobis (2-nitrobenzoic acid)] and 0.4 ml of double distilled water were added. The mixture was then vortexed and absorbance read at 412 nm within 15 minutes. The concentration of GSH was expressed as μmol/L.

Statistical analysis

All the data for the markers of inflammation, oxidative stress in both serum and BAL i.e. TLC, DLC, OVAs-IgE, TNF-α, IL-10, MDA, GSH is expressed as Mean ± SEM. The data was analysed using one-way Analysis of Variance (ANOVA) followed by Dunnett's test (Post hoc test) for multiple intergroup comparisons using Graph pad Prism software (Version 8.4.3 (686)). $P < 0.05$ has been considered statistically significant for all the parameters.

Results

Effect of NO donor (ISDN), NO Precursor (L-arginine) and arginase inhibitor (ABH) on inflammatory cell counts in BAL of OVA induced model of bronchial asthma in rats

Ovalbumin challenge significantly increased leukocyte, eosinophil, and neutrophil counts in disease control rats. The L-arginine + ABH combination showed the greatest decrease (41% WBC, 65% eosinophils). Only ISDN significantly reduced neutrophils, indicating NO donor's distinct anti-inflammatory effect. These results are shown in figure 1.

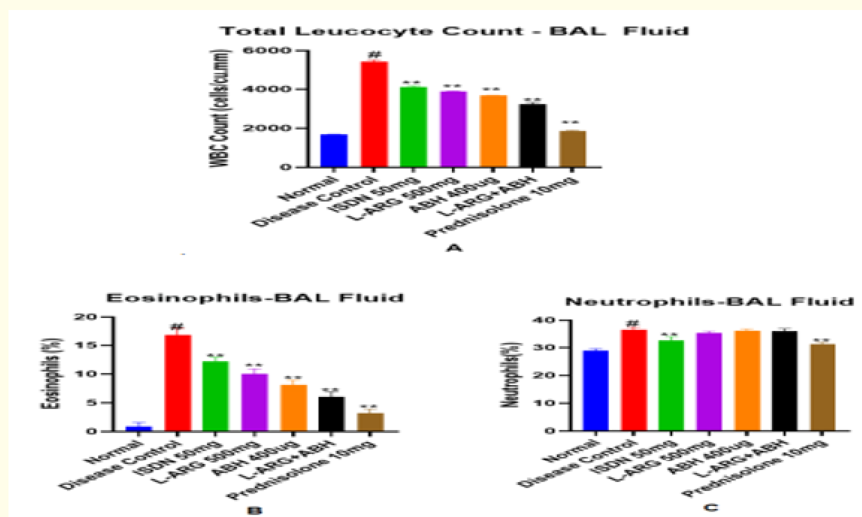

*Figure 1: Effect of NO donor (ISDN), NO Precursor (L-arginine) and arginase inhibitor (ABH) on total leucocyte count, Eosinophil (%) and Neutrophil (%) in BAL of ovalbumin immunized and challenged rats. Results are shown as Mean ± SE, no of rats = 6 in every group; #p < 0.01 compared to Normal group of rats; *p < 0.05; **p < 0.01 compared to Disease control group. ISDN: Isosorbide di nitrate, L-ARG: L-arginine, ABH: 2(S)-Amino-6-boronohexanoic acid hydrochloride. The mentioned doses are in mg/kg of respective drugs and ABH is in μg/kg.*

Effect of NO donor (ISDN), NO Precursor (L-arginine) and arginase inhibitor (ABH) on markers of Inflammation in OVA induced model of bronchial asthma in rats

OVA specific IgE levels

Ovalbumin immunization elevated OVA-specific IgE in serum and BAL fluid of disease control rats ($p < 0.01$). Pretreatment with ISDN, L-arginine, or ABH significantly reduced IgE levels, comparable to the positive control, prednisolone. Combined L-arginine and ABH further lowered serum IgE by 41% and BAL IgE by 32%, without significant additive effect. These results are depicted in table 1.

TNF-α levels

OVA challenge significantly increased TNF-α levels in serum and BAL fluid of disease control rats ($p < 0.01$). Pretreatment with ISDN, L-arginine, or ABH markedly reduced TNF-α, comparable to prednisolone. Combined L-arginine and ABH produced the greatest reduction (47% in BAL), showing enhanced anti-inflammatory efficacy. These results are shown in table 1.

IL-10 levels

OVA challenge significantly reduced IL-10 levels in serum and BAL fluid of disease control rats ($p < 0.01$). Pretreatment with ISDN, L-arginine, or ABH increased IL-10, with the combination of L-arginine and ABH showing the highest rise (76% serum, 105% BAL), comparable to prednisolone's anti-inflammatory effect. These results are presented in table 1.

	OVAs IgE		TNF-α Levels		IL-10 Levels	
	Serum (µg/ml)	BAL (µg/ml)	Serum (pg/ml)	BAL (pg/ml)	Serum (p g/ml)	BAL (p g/ml)
Normal	3.53 ± 0.31	5.67 ± 0.38	7.56 ± 0.12	9.55 ± 0.13	61.67 ± 0.66	71.61 ± 0.55
Disease control	6.38 ± 0.39#	8.77 ± 0.20#	18.93 ± 0.24#	38.93 ± 0.26#	29.83 ± 0.69#	25.99 ± 0.17#
ISDN (50)	4.73 ± 0.23**	7.45 ± 0.21*	17.56 ± 0.16**	27.56± 0.17**	34.33 ± 1.97*	29.17± 0.79*
L-ARG (500)	5.02 ± 0.24**	7.75 ± 0.15*	16.10 ± 0.16**	26.10± 0.16**	41.01 ± 0.36**	41.5 ± 0.36**
ABH (400 µg/kg)	4.01 ± 0.15**	6.95 ± 0.24**	16.43 ± 0.41**	26.93 ± 0.26**	39.21± 0.36**	44.14 ± 0.21**
L-ARG (500) + ABH (400 µg/kg)	3.78 ± 0.23**	5.98 ± 0.14**	13.89± 0.13**	21.22 ± 0.28**	52.50 ± 0.42**	53.32 ± 0.77**
Prednisolone (10)	3.51 ± 0.32**	5.87± 0.28**	11.17 ± 0.27**	15.62 ± 0.13**	60.10 ± 0.36**	67.50 ± 0.42**

Table 1*: Effect of NO donors (ISDN), NO Precursor (L-Arginine) and arginase inhibitor (ABH) on OVAs IgE, TNF-α, and IL-10 levels in serum and BAL fluid of OVA induced model of bronchial asthma in rats. All data is expressed as Mean ± SEM, n = 6 per group; #: p < 0.01 vs Normal rats; *: p < 0.05, **: p < 0.01 vs Disease control group. ISDN: Isosorbide Di Nitrate, L-ARG: L-arginine, ABH: 2(S)-Amino-6-boronohexanoic acid hydrochloride. The doses mentioned in brackets are in mg/kg of respective drugs and ABH is in µg/kg.*

Effects of NO donors (ISDN), NO precursor (L-arginine) and arginase inhibitor (ABH) on markers of Oxidative stress

MDA levels

OVA-challenged disease control rats showed significantly elevated MDA levels in serum and BAL fluid ($p < 0.01$), indicating oxidative stress. Pretreatment with ISDN, L-arginine, or ABH reduced MDA levels, with the greatest reduction seen in the L-arginine + ABH group (58% serum, 60% BAL), showing enhanced antioxidant protection. The results are depicted in table 2.

GSH levels

OVA challenge significantly decreased GSH levels in serum and BAL fluid ($p < 0.01$). Pretreatment with ISDN, L-arginine, or ABH increased GSH, indicating improved antioxidant status. The L-arginine + ABH combination showed the greatest rise (60% serum, 51% BAL), closely matching prednisolone's effect, and demonstrating enhanced antioxidant protection. The results are shown in table 2.

	MDA		GSH	
	Serum (nmol/ml)	BAL (nmol/ml)	Serum (μmol/l)	BAL (μmol/l)
Normal	3.55± 0.04	1.53± 0.14	70.64 ± 0.14	55.01 ± 0.13
Disease control	7.69 ± 0.52#	4.61 ± 0.21#	31.89 ± 0.20#	32.33 ± 0.20#
ISDN (50)	6.87 ± 0.33	4.33 ± 0.34	44.18± 0.25**	39.14 ± 0.29**
L-ARG (500)	5.06 ± 0.31**	3.46 ± 0.32*	41.97 ± 0.27**	41.91 ± 0.30**
ABH (400 μg/kg)	4.49 ± 0.08**	2.87 ± 0.21**	48.66 ± 0.16**	42.98 ± 0.21**
L-ARG (500) +ABH (400 μg/kg)	4.10 ± 0.22**	1.85 ± 0.19**	51.34 ± 0.15**	49.04 ± 0.22**
Prednisolone (10)	4.09± 0.24**	1.66 ± 0.16**	64.99 ± 0.25**	52.63 ± 0.31**

***Table 2**: Effect on MDA and GSH levels seen with donors of NO (ISDN), Precursor (L-arginine) also arginase inhibitor (ABH) in serum and BAL fluid of ovalbumin sensitized and challenged rats. Data represented as Mean ± Standard error of mean, number of rats= six in every group; #: p value< 0.01 versus Normal rats; **: p value < 0.01 versus disease control group.*

Discussion

Bronchial asthma is characterised by inflammation of the airways, remodelling, airway hyperresponsiveness with an abnormal accumulation of inflammatory cells in the bronchioles [12]. There is increased expiratory resistance as well as bronchospasm, mucosal oedema, and mucus plugging leading to air trapping, increased dead space, and hyperinflation. Asthma, if treated inadequately can result in airway damage, including smooth muscle hypertrophy, epithelial hyperplasia, and airway connective tissue deposition due to chronic airway inflammation and remodelling [13]. The conventional treatment consisting of bronchodilator and corticosteroids are quite symptomatic in management and combative to some extent only and is expensive. Moreover, their continuous use is associated with various side effects and refractoriness of the responses; thus, there is a growing concern for exploration of novel targets for developing new therapeutic strategies, acting through different mechanisms.

The role of nitric oxide in the pathophysiology of asthma has been elusive. The complex interaction of intermediates of L-arginine metabolism through the arginase and nitric oxide synthase pathways, has generated multiple questions about the role of NO in asthma. Asthma pathophysiology involves complex cellular and molecular interactions, causing airway infiltration by various cells, cytokines, and mediators. One of such cells are eosinophils, very prominent in allergic inflammation. They release mediators like major basic protein (MBP), reactive oxygen species, cytokines (e.g. GM-CSF and IL-8), and lipid mediators (e.g. cysteinyl leukotrienes) [14].

In this study we therefore determined the effects of NO donor (ISDN), NO precursor (L-arginine), arginase inhibitor (ABH) and co-treatment with L-arginine and ABH on airway inflammation and oxidative stress in an experimental model of asthma. Further, pre-treatment with the NO precursor, L-arginine and Arginase inhibitor ABH, reduced the total cell count, the eosinophil count and the neutrophil count. These results are in accordance with Arıkan., *et al*. [15] who showed that there was a reduction in BAL- eosinophilia with L-arginine administration and arginase inhibition. Pre-treatment with NO donor (ISDN), NO precursor (L-arginine), and arginase inhibitor (ABH) significantly reduced inflammatory cell infiltration, TNF-α, malondialdehyde (MDA) levels, while elevating IL-10 and GSH in both serum and BAL fluid. These results corroborate the earlier findings reported by Ray., *et al*. [16]. The combination of L-arginine

and ABH provided greater reductions in TNF-α and oxidative markers, though not always additive. These results suggest that enhancing endogenous NO through administration of NO precursor, L-arginine or preventing its depletion via arginase inhibition (ABH) restores redox balance and reduces inflammation.

Overall, modulation of the L-arginine–NO–arginase pathway attenuated airway inflammation and oxidative stress in asthma. The study highlights NO modulators as potential adjunctive therapies in asthma management, though further research is required to clarify their complex, context-dependent roles.

Conclusion

In this study, ovalbumin-induced asthmatic rats exhibited increased leukocytes, eosinophils, IgE, TNF-α and oxidative stress markers, and decreased IL-10 and GSH, confirming airway inflammation. Pretreatment with NO donor (ISDN), NO precursor (L-arginine), and arginase inhibitor (ABH) significantly reduced inflammatory cell infiltration, TNF-α and Malondialdehyde while elevating IL-10 and GSH in both serum and BAL fluid. The combination of L-arginine and ABH provided greater reductions in TNF-α and oxidative markers. These results suggest that enhancing endogenous NO through L-arginine or preventing its depletion via arginase inhibition restores redox balance and reduces inflammation.

Taken together it is concluded that nitric oxide (NO) modulators-NO donor (ISDN), precursor (L-arginine), and arginase inhibitor (ABH)-significantly reduced airway inflammation and oxidative stress in ovalbumin-induced asthmatic rats. The results suggest that the effects of NO depend on its concentration and source, highlighting NO donors and arginase inhibition as potential asthma therapies. Administration of L-arginine and ABH in combination showed greater efficacy, suggesting crucial role of NO and the modulation of NO bioavailability and source may serve as a potential therapeutic approach for asthma.

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