

Inhibition of NADPH Oxidase as a Strategy for Managing Asthma

Activation of NADPH oxidase plays a mediating role in many phases of asthmatic inflammation: activation of mast cells (enabling secretion of histamine and production of leukotrienes),¹⁻³ VCAM-mediated migration of eosinophils into lung tissue,⁴ pro-inflammatory activity of eosinophils and neutrophils,⁵⁻⁷ and the hyperproliferation of airway smooth muscle cells that contributes to lung remodeling in chronic asthma.^{8,9} NADPH oxidase would also be expected to play a role in the fibrotic response to chronic asthma.¹⁰⁻¹² Patients with asthma appear to be under increased oxidant stress, with reduced plasma levels of oxidant scavengers.¹³⁻¹⁸ Bilirubin, recently revealed to function as a physiological inhibitor of NADPH oxidase,¹⁹⁻²² has been shown to inhibit the migration of eosinophils and lymphocytes into lung parenchyma in asthmatic mice,²³ and to inhibit proliferation of airway smooth muscle cells in vitro.²⁴ Remission of severe chronic asthma was noted in a patient during an episode of hyperbilirubinemia associated with hepatitis.²⁵ Inhalation of apocynin, another inhibitor of NADPH oxidase, suppresses the hyperreactive response to methacholine induced by ozone inhalation.²⁶ Many authorities suggest that antioxidants may have potential in the management of asthma.^{15-17, 25} All of these considerations suggest that bilins (biliverdin, phycocyanobilin),²² as well as ingestion of spirulina (the richest natural source of phycocyanobilin),²⁷ may be useful for treating both the acute and chronic phases of asthma.

References

- (1) Suzuki Y, Yoshimaru T, Matsui T, Inoue T, Niide O, Nunomura S, Ra C. Fc epsilon RI signaling of mast cells activates intracellular production of hydrogen peroxide: role in the regulation of calcium signals. *J Immunol* 2003 December 1;171(11):6119-27.
- (2) Kim JY, Lee KH, Lee BK, Ro JY. Peroxynitrite modulates release of inflammatory mediators from guinea pig lung mast cells activated by antigen-antibody reaction. *Int Arch Allergy Immunol* 2005 June;137(2):104-14.
- (3) Suzuki Y, Yoshimaru T, Inoue T, Niide O, Ra C. Role of oxidants in mast cell activation. *Chem Immunol Allergy* 2005;87:32-42.
- (4) bdala-Valencia H, Earwood J, Bansal S, Jansen M, Babcock G, Garvy B, Wills-Karp M, Cook-Mills JM. Nonhematopoietic NADPH oxidase regulation of lung eosinophilia and airway hyperresponsiveness in experimentally induced asthma. *Am J Physiol Lung Cell Mol Physiol* 2007 May;292(5):L1111-L1125.
- (5) Bankers-Fulbright JL, Kita H, Gleich GJ, O'Grady SM. Regulation of human eosinophil NADPH oxidase activity: a central role for PKCdelta. *J Cell Physiol* 2001 December;189(3):306-15.
- (6) Kilpatrick LE, Jakobovics E, McCawley LJ, Kane LH, Korchak HM. Cromolyn inhibits assembly of the NADPH oxidase and superoxide anion generation by human neutrophils. *J Immunol* 1995 April 1;154(7):3429-36.

- (7) DeChatelet LR, Shirley PS, McPhail LC, Huntley CC, Muss HB, Bass DA. Oxidative metabolism of the human eosinophil. *Blood* 1977 September;50(3):525-35.
- (8) Hoidal JR, Brar SS, Sturrock AB, Sanders KA, Dinger B, Fidone S, Kennedy TP. The role of endogenous NADPH oxidases in airway and pulmonary vascular smooth muscle function. *Antioxid Redox Signal* 2003 December;5(6):751-8.
- (9) Sturrock A, Huecksteadt TP, Norman K, Sanders K, Murphy TM, Chitano P, Wilson K, Hoidal JR, Kennedy TP. Nox4 mediates TGF-beta1-induced retinoblastoma protein phosphorylation, proliferation, and hypertrophy in human airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 2007 June;292(6):L1543-L1555.
- (10) Manoury B, Nenan S, Leclerc O, Guenon I, Boichot E, Planquois JM, Bertrand CP, Lagente V. The absence of reactive oxygen species production protects mice against bleomycin-induced pulmonary fibrosis. *Respir Res* 2005;6:11.
- (11) Wang CL, Kang J, Li ZH. [Increased expression of NADPH oxidase p47-PHOX and p67-PHOX factor in idiopathic pulmonary fibrosis]. *Zhonghua Jie He He Hu Xi Za Zhi* 2007 April;30(4):265-8.
- (12) McCarty MF. Administration of bilins and high-dose biotin may replicate the beneficial impact of heme oxygenase-1 induction on pathogenic fibrosis. *Medical Hypotheses* 2007;submitted for publication.
- (13) Antczak A, Nowak D, Bialasiewicz P, Kasielski M. Hydrogen peroxide in expired air condensate correlates positively with early steps of peripheral neutrophil activation in asthmatic patients. *Arch Immunol Ther Exp (Warsz)* 1999;47(2):119-26.
- (14) Joseph BZ, Routes JM, Borish L. Activities of superoxide dismutases and NADPH oxidase in neutrophils obtained from asthmatic and normal donors. *Inflammation* 1993 June;17(3):361-70.
- (15) Nadeem A, Chhabra SK, Masood A, Raj HG. Increased oxidative stress and altered levels of antioxidants in asthma. *J Allergy Clin Immunol* 2003 January;111(1):72-8.
- (16) Mak JC, Chan-Yeung MM. Reactive oxidant species in asthma. *Curr Opin Pulm Med* 2006 January;12(1):7-11.
- (17) Misso NL, Brooks-Wildhaber J, Ray S, Vally H, Thompson PJ. Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma. *Eur Respir J* 2005 August;26(2):257-64.
- (18) Liao MF, Chen CC, Hsu MH. Evaluation of the serum antioxidant status in asthmatic children. *Acta Paediatr Taiwan* 2004 July;45(4):213-7.
- (19) Lanone S, Bloc S, Foresti R, Almolki A, Taille C, Callebort J, Conti M, Goven D, Aubier M, Dureuil B, El-Benna J, Motterlini R, Boczkowski J. Bilirubin decreases nos2 expression via inhibition of NAD(P)H oxidase: implications for protection against endotoxic shock in rats. *FASEB J* 2005 November;19(13):1890-2.
- (20) Matsumoto H, Ishikawa K, Itabe H, Maruyama Y. Carbon monoxide and bilirubin from heme oxygenase-1 suppresses reactive oxygen species generation and plasminogen activator inhibitor-1 induction. *Mol Cell Biochem* 2006 October;291(1-2):21-8.

- (21) Jiang F, Roberts SJ, Datla S, Dusting GJ. NO modulates NADPH oxidase function via heme oxygenase-1 in human endothelial cells. *Hypertension* 2006 November;48(5):950-7.
- (22) McCarty MF. "Iatrogenic Gilbert syndrome" - a strategy for reducing vascular and cancer risk by increasing plasma unconjugated bilirubin. *Medical Hypotheses* 2007;accepted for publication.
- (23) Keshavan P, Deem TL, Schwemberger SJ, Babcock GF, Cook-Mills JM, Zucker SD. Unconjugated bilirubin inhibits VCAM-1-mediated transendothelial leukocyte migration. *J Immunol* 2005 March 15;174(6):3709-18.
- (24) Taille C, Almolki A, Benhamed M, Zedda C, Megret J, Berger P, Leseche G, Fadel E, Yamaguchi T, Marthan R, Aubier M, Boczkowski J. Heme oxygenase inhibits human airway smooth muscle proliferation via a bilirubin-dependent modulation of ERK1/2 phosphorylation. *J Biol Chem* 2003 July 18;278(29):27160-8.
- (25) Ohrui T, Yasuda H, Yamaya M, Matsui T, Sasaki H. Transient relief of asthma symptoms during jaundice: a possible beneficial role of bilirubin. *Tohoku J Exp Med* 2003 March;199(3):193-6.
- (26) Peters EA, Hiltermann JT, Stolk J. Effect of apocynin on ozone-induced airway hyperresponsiveness to methacholine in asthmatics. *Free Radic Biol Med* 2001 December 1;31(11):1442-7.
- (27) McCarty MF. Clinical potential of spirulina as a source of phycocyanobilin. *J Medicinal Food* 2007;in press.