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Review

Inflammatory Mechanisms in Bronchial Asthma and COPD

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ICHINOSE, M. *Inflammatory Mechanisms in Bronchial Asthma and COPD.* Tohoku J. Exp. Med., 2003, **200** (1), 1–6 —— Both bronchial asthma and chronic obstructive pulmonary disease (COPD) are recognized as inflammatory diseases, although the inflammatory process for each disease is different. In this review, I describe some inflammatory molecules that seem to be involved in the inflammatory process in each disease. ———— asthma; COPD; neuropeptides; reactive nitrogen species

Bradykinin and bronchial asthma

Bradykinin causes a variety of responses via two kinds of cell surface specific receptors, namely bradykinin B_1 and B_2 receptors (Barnes et al. 1998). B_1 receptors may be expressed in some chronic inflammatory conditions. At present, the effects of bradykinin on airways have been reported to be mediated by B_2 receptors, because selective B_2 but not B_1 receptor antagonists inhibit the effect of bradykinin on the airways including that of bronchoconstriction (Ichinose and Barnes 1990a). Further, B_1 selective agonist does not cause a bronchoconstrictor response in asthma (Polosa and Holgate 1990). B_3 receptors have been proposed in sheep airways, but there are doubts regarding its existence because it has been examined with weak antagonists (Farmer et al. 1991).

Bradykinin inhalation causes a potent bronchoconstrictor response in asthmatic patients but not in healthy subjects (Fuller et al. 1987; Polosa and Holgate 1990), indicating the increased hyperresponsiveness of airway smooth muscle to bradykinin in asthmatic subjects. Because bradykinin causes only weak contraction of proximal human airways in vitro, bradykinin is likely to cause airway obstruction in asthma largely through indirect mechanisms such as neural mechanisms and mediator release (Barnes et al. 1998). However, bradykinin constricts peripheral human airways partly via direct stimulation of B_2 receptors on airway smooth muscle cells and partly via the release of thromboxane (Hulsmann et al. 1994; Molimard et al. 1994).

In guinea pigs, the bronchoconstrictor response induced by direct administration of bradykinin into the airways is largely inhibited by atropine and by the depletion of sensory

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neuropeptides (Ichinose et al. 1990), suggesting that both a cholinergic reflex and the release of sensory neuropeptides are involved. Tachykinin receptor antagonist also inhibits the bronchoconstriction (Sakamoto et al. 1993), indicating the importance of sensory neuropeptide release. Activation of sensory C-fibers by bradykinin has been demonstrated by a single fiber recording method (Fox et al. 1993). In asthmatic subjects, both anticholinergic agents (Fuller et al. 1987) and nonselective tachykinin receptor antagonists (Ichinose et al. 1992) significantly reduce bradykinin-mediated bronchoconstriction, supporting the involvement of cholinergic and antidromic release of tachykinins from sensory nerves in the response. Bradykinin causes a feeling of tightness in the chest and coughing, presumably via sensory C-fiber activation. Actually, tachykinin receptor antagonist inhibits the coughing as well as bronchoconstrictor response (Ichinose et al. 1992).

The bronchoconstrictor effect of bradykinin is also modulated by endogenous nitric oxide (NO). In asthmatic patients, inhalation of an NO synthase (NOS) inhibitor potentiates the bronchoconstriction of bradykinin, suggesting that bradykinin release NO in the airways to counteract the action of bradykinin (Ricciadolo et al. 1996). This potentiation effect is not observed in more severe asthma, presumably because of the loss of the epithelial source of NO (Ricciadolo et al. 1997).

Bradykinin also has an action on bronchial vessels via B2 receptors. Bradykinin causes airway microvascular leakage through sensory neuropeptides and platelet activating factor (PAF), because both tachykinin (Nakajima et al. 1994) and PAF antagonists (Rogers et al. 1990) reduce the response. Bradykinin also shows a vasodilator action on bronchial vessels and causes an increase in airway blood flow (Corfield et al. 1991; Parsons et al. 1992). This is consistent with the high density of bradykinin receptors on bronchial vessels (Mak and Barnes 1991). These vascular effects may cause bronchial wall edema/hyperemia of the airways, which seem to be important in airway obstruction and hyperresponsiveness (Kimura et al. 1992).

Other airway effects of bradykinin are mucus secretion from submucosal glands and stimulation of epithelial ion transport (Leikauf et al. 1985) via B2 receptors (Proud et al. 1993).

Enzymes such as angiotensin converting enzyme (ACE), neutral endopeptidase (NEP), and carboxypeptidase-N degrade bradykinin. Regarding the airway responses by bradykinin, the former two enzymes are important (Ichinose and Barnes 1990b; Lotvall et al. 1991).

Airway autonomic nervous system dysfunction and asthma

Airways are richly innervated by four nervous systems, namely adrenergic, cholinergic, inhibitory nonadrenergic noncholinergic (i-NANC), and excitatory NANC (e-NANC) nervous systems. Dysfunction or hyper-function of these systems may be involved in the inflammation or airway hyperresponsiveness observed in asthmatic patients. The cholinergic nervous system is the predominant neural bronchoconstrictor pathway in humans. Airway inflammation shows exaggerated acetylcholine release from cholinergic nerves via dysfunction of the autoreceptor, muscarinic M2, which is possibly caused by major basic protein or IgE. Vasoactive intestinal peptide (VIP) and NO released from i-NANC nerves act as an airway smooth muscle dilator. The effects of VIP and NO are diminished after allergic reaction by inflammatory cell-mediated tryptase and reactive oxygen species. Thus, in asthmatic airways, the inflammatory change-mediated neural imbalance may result in airway hyperresponsiveness. Tachykinins derived from e-NANC nerves have a variety of actions including airway smooth muscle contraction, mucus secretion, vascular leakage, and neutrophil attachment, and may be involved in the path-

ogenesis of asthma. Since tachykinin receptor antagonists are effective for bradykinin- and exercise-induced bronchoconstriction in asthmatic patients, these drugs may be useful for asthma therapy.

Reactive nitrogen/oxygen species in bronchial asthma

Asthma is a chronic inflammatory disease of the airways in which various resident and migrated cell-derived molecules play a role (McFadden and Gilbert 1992). Because reactive oxygen and related species including NO have a potent proinflammatory action (Barnes 1990; Nathan 1992), these molecules may be involved in the airway inflammatory process (Ichinose et al. 2000a). In animal models, allergen- (Ikuta et al. 1992; Miura et al. 1996) and ozone-induced (Takahashi et al. 1993) airway inflammation and airway hyperresponsiveness are largely modified by inhibitors of synthesis of reactive oxygen and related species or by scavengers of radical species, supporting this hypothesis. Further, in asthmatic airways, NO production is increased, possibly via inducible NO synthase (iNOS) (Hamid et al. 1993), and steroid treatment reduces the NO generation (Kharitonov et al. 1994), suggesting that NO may be partly responsible for the asthmatic airway inflammation.

Other types of reactive oxygen, such as superoxide anion (O_2^-) may also be exaggerated in asthmatic airways via upregulation of xanthine oxidase (XO) in microvascular endothelial cells and NADPH oxidase in the infiltrated eosinophils (Sedgwick 1995). NO rapidly reacts with O_2^- which is released from inflammatory cells including eosinophils, and results in the formation of the highly proinflammatory molecule peroxynitrite (Beckman et al. 1990). However, the role of peroxynitrite in the inflammatory process of the late allergic response (LAR) after allergen challenge, which most resembles asthmatic airway inflammation, has not yet been elucidated. The aim of this study is to examine the role of peroxynitrite in the microvascular hyperpermeability during the LAR in sensitized guinea pigs. We assessed the NO, O_2^- and peroxynitrite production by measuring the NO concentration in the expired air, O_2^- generating enzyme activity, and peroxynitrite-induced nitration product immunostaining, respectively. We quantified the airway microvascular permeability by means of Monastral blue dye trapping between the postcapillary endothelium. The functional role of the NO, O_2^- and peroxynitrite on the microvascular permeability was assessed using each molecule's synthase inhibitor or scavenger. Further, we also quantified the eosinophil accumulation into the airways during the LAR and examined the role of NO, O_2^- and peroxynitrite in the eosinophil response. We have reported that peroxynitrite formed by NO and O_2^- is an important molecule for the microvascular hyperpermeability but not the eosinophil accumulation during the late allergic airway responses (Sugiura et al. 1999).

Reactive nitrogen species in COPD

Chronic obstructive pulmonary disease (COPD) is a major medical problem and there is evidence that it is increasing throughout the world (Murray and Lopez 1996). Inflammation of the airways seems to play an important role in the pathogenesis of the disease. However, in comparison to bronchial asthma, the inflammatory mechanisms of COPD are less understood (Barnes 1998).

Oxidative stress and defense unbalance may be one of the causes of COPD (Pinamonti et al. 1996; Rahman et al. 1996; Repine et al. 1997). The large production of NO during inflammatory-immune processes of the respiratory tract is thought to constitute a host defense mechanism, although this comes at a price because a high level of NO can also cause respiratory tract injury and thus contribute to the pathophysiology of inflammatory airway diseases such as COPD and asthma (Kharitonov

et al. 1994). Recently, excessive NO production, presumably via inducible NO synthase (iNOS), has been reported in asthmatic airways (van der Vliet et al. 1999), although its presence is controversial in COPD airways.

The adverse effects of NO are thought to be engendered, in part, by its reaction with superoxide anion, which is released from inflammatory cells, yielding the potent oxidant peroxynitrite (Beckman et al. 1990; Beckman 1996). Peroxynitrite adds a nitro group to the 3-position adjacent to the hydroxyl group of tyrosine to produce the stable product nitrotyrosine (Beckman et al. 1992; Ischiropoulos et al. 1992). Alternatively, NO reacts with O_2 to form nitrite. The oxidation of nitrite by neutrophil-derived myeloperoxidase (MPO) or by other related peroxidases (Eiserich et al. 1998) results in the formation of nitryl chloride and nitrogen dioxide (NO_2). This mechanism has also been found in inflammatory conditions. Although tyrosine nitration is generally attributed to peroxynitrite, the peroxidase-dependent nitrite oxidation pathway is also involved. Therefore, nitrotyrosine is a collective indicator for the involvement of reactive nitrogen species.

Recently, we have reported that abundant nitrotyrosine positive staining cells as well as iNOS positive cells were observed in the induced sputum both in COPD and asthmatic patients compared with healthy subjects (Ichinose et al. 2000b). The nitrotyrosine positive cells were significantly more obvious in COPD than in asthma, suggesting that the oxidative stress by reactive nitrogen species may be exaggerated in the airways of these diseases, especially in COPD. Further, because the nitrotyrosine positive cell counts were significantly correlated with the airway obstructive changes in COPD, the hyperproduction of reactive nitrogen species may be an important factor in the pathogenesis of COPD.

In COPD patients, steroid-induced improvement in the airway caliber and hyperresponsiveness is significantly correlated with the reduction of the reactive nitrogen species production (Sugiura et al. 1999), indicating that the modulation of the reactive nitrogen species may be useful for future COPD therapy (Ichinose et al. 2001).

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