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Increased parasympathetic tone as the underlying cause of asthma: A hypothesis

Manish Goyal [a,*], Harinder Jaseja [b], Narsingh Verma [c]

[a] Department of Physiology, All India Institute of Medical Sciences, New Delhi 110 029, India
[b] Department of Physiology, G.R. Medical College, Gwalior 474 001, MP, India
[c] Department of Physiology, C.S.M. Medical University, Lucknow 226 003, UP, India

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SUMMARY

Asthma is a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheo-bronchial tree to multiple number of stimuli. Immunological theory does not explain all features in asthma, for example hyper-reactivity of the airways. Neurogenic theory also fails to explain the pathogenesis of asthma comprehensively. Higher parasympathetic tone has been reported in asthmatics but has never been suggested as a major underlying cause of asthma. This article attempts to explain the occurrence of hyper-responsiveness, inflammatory/allergic reactions and broncho-constriction in asthma on a common basis of inherent higher parasympathetic tone in asthmatics. The higher background parasympathetic firing leads to increased nitric oxide (NO) production owing to its co-localization with acetylcholine (ACh) in inhibitory non-adrenergic and non-cholinergic (i-NANC) nerves. NO is a neurotransmitter of i-NANC system and it mediates bronchodilation. Increased NO release has been found to be responsible for hyper-responsiveness and increased inflammation in the airways. The authors suggest that an inherently higher background parasympathetic tone in concert with inflammation or a specific genetic background could modify the effects of NO on lung homeostasis in humans leading to increased susceptibility to an asthmatic state.

Introduction

Asthma is defined as "A chronic inflammatory disorder of the airways in which many cells play a role: particularly mast cells, eosinophils, and T lymphocytes. In susceptible persons, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible, either spontaneously or with treatment" [1].

An important feature of asthma is an exaggerated broncho-constrictor response to a wide variety of stimuli. This airway hyper-responsiveness can be attributed in part to airway inflammatory response as airway markers of inflammation correlate with bronchial hyper-responsiveness but at the same time anti-inflammatory therapy, which reduced airway hyper-responsiveness, did not abolish it [2]. Thus, other factors in addition to inflammation may contribute to airway hyper-responsiveness.

Pathogenesis of asthma

Asthma is a complex disorder as various factors interact and influence its expression in patients. Factors that influence the risk of asthma could be host factors (which are primarily genetic) and environmental factors (like allergens, infections, occupational sensitizers, smoking, air Pollution, diet, etc.) that trigger asthma symptoms [1]. However, the mechanisms whereby they influence the development and expression of asthma are complex and interactive.

Airway narrowing is the final common pathway leading to symptoms and physiological changes in asthma. Primarily the pathogenesis of asthma has been attributed to excessive irritability of the airways. Two opposing thoughts have prevailed: physiologists emphasizing the hyper-reactivity of asthmatic airways to diverse stimuli due to an abnormality in nervous control mechanisms [3] whereas, immunological theories attributing the antigen-induced release of mast cell mediators as the primary abnormality in the pathogenesis of asthma.

It is known that T lymphocytes (particularly Th2 subtype of T helper cells) promote allergic phenomenon while the other subtype, the Th1 cells are involved in virus defence and antagonize the allergic response. The immunologic theory assumes that there is a shift of balance from Th1 cells to Th2 cells in asthmatics. Atopic patients show increased levels of interleukin 4 (IL-4), which is responsible for the induction of the Th2 cell response that in turn provides the signals for Immunoglobulin E (IgE) production. IgE production is associated with allergic hypersensitivity responses to inhaled allergens. Cross-linking to the IgE on mast cells β subunit of the high affinity IgE receptor (FcεRI) triggers the release

* Corresponding author. Tel.: +91 11 29522126.
E-mail address: drmanishgoyal@rediffmail.com (M. Goyal).

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of preformed vasoactive mediators, synthesis of prostaglandins and leukotrienes, and transcription of cytokines [4], resulting in inflammatory manifestations seen in asthmatic airways [5]. Apart from T helper cells, mast cells, basophils, eosinophils, CD8+ T cells and bronchial fibroblast and smooth muscle cells can all produce inflammatory mediators that recruit eosinophils and neutrophils. The simple concept that asthma results from the interaction of antigen with antibody failed to explain the observations that mediators such as histamine had only trivial effects in normal subjects, that many asthmatics had no evidence of allergy, that many atopic subjects were not asthmatic, and that many non-immunological stimuli caused broncho-constriction.

The neurogenic theory which physiologists endorse is based on the observation that the exaggerated broncho-constriction to non-immunological stimuli could be inhibited by atropine, which blocks post-ganglionic vagal pathways, suggesting the involvement of a parasympathetic neural reflex in the constrictor response [6].

Electrical field stimulation can lead to a propranolol resistant (non-adrenergic), neurally-mediated relaxation of bronchial smooth muscle [7,8]. In humans, this neural mechanism is of particular importance, as in the absence of adrenergic innervation, it is the sole bronchodilator pathway.

The parasympathetic innervation mediates both cholinergic contractions and non-adrenergic, non-cholinergic (NANC) relaxations of the trachealis [9,10]. NO and VIP have been identified as major neurotransmitters of i-NANC mediated relaxation and are co-localized in cholinergic nerve endings [11]. Belvisi et al. showed NO to be a more important mediator, as i-NANC responses were found to be totally blocked by L-NAME (N (G)-nitro-L-arginine methyl ester), which is a nitric oxide synthase (NOS) inhibitor [12]. With the identification of NANC system and neuropeptides, the focus has shifted from asthma as a pure immunological disease to a complex interaction and/or disbalance in immunological and neurogenic mechanisms.

Evidences of increased parasympathetic tone in asthmatics

The parasympathetic nerves, innervating airways, are tonically active producing a stable, readily reversible baseline tone of the airway smooth muscles [13] which can be abolished by atropine or ipratropium bromide infusion [14,15], which forms the basis of clinically observed improvement in asthmatic symptoms. Electrophysiological recordings from both preganglionic and post-ganglionic parasympathetic nerve fibres also confirm the existence of a persistent outflow of parasympathetic activity to the airways [16].

Increased high frequency variability on spectral analysis of heart rate supports the view that, in humans, airway tone is mainly vagally controlled. Hashimoto et al. reported a higher vagal tone and correspondingly low sympathetic tone measured as high frequency and low frequency variance in asthmatics [17] and this increased vagal tone was found to be present even in stable asthmatics [18]. Ostrowska-Nawarycz et al. in addition, showed that the parasympathetic tone as reflected by variance in high frequency is dependent also on the severity of asthma [19].

In asthmatics, increase in trans-pulmonary pressure during broncho-constriction, directly affecting intra-thoracic baroreceptors and hypoxia induced chemo-reflex may produce alteration in autonomic tone. However, increase in airway parasympathetic tone and cardiac parasympathetic tone after MBC were demonstrated to be correlated significantly in asthmatics [20]. In addition Knöpfli et al. and Fujii et al. also demonstrated the relationship between airways and cardiac autonomic tone with exercise induced broncho-constriction [21,22].

The asthmatics not only have an increased basal parasympathetic tone resulting in baseline-constricted airways but also exhibit enhanced broncho-constriction to various agents, which are known to stimulate sensory nerves. Majority of sensory nerve fibres are non-myelinated C-fibres, which act as afferent pathways as well as contain neurotransmitters of NANC system (including proinflammatory neuropeptides) that can be released after activation and exhibit efferent functions. An up-regulation in the function of sensory nerves may lead to augmented afferent and efferent function which, in asthma, could contribute to bronchial hyper-responsiveness, inflammation and re-modeling of the airway wall [23]. Activation of C-fibres by stimuli such as capsaicin and bradykinin causes rapid shallow breathing, preceded by apnea, with hypotension, bradycardia, airway mucous secretion and vasodilation, suggesting that all these responses are part of a vagal reflex [24,25]. Autacoids released as a result of airway inflammation can lead to substantial increase in afferent nerve activity, consequently altering pulmonary reflex physiology. In a manner analogous to hyperalgesia associated with inflammation in the somato-sensory system, increases in vagal afferent nerve activity in inflamed airways may lead to increased parasympathetic activity in the airways [6].

Higher parasympathetic tone releases increased amounts of nitric oxide

The dysfunction in α, β and M2 receptors, although held responsible for increased background parasympathetic tone in several studies [26,27], appears to be acquired secondarily rather than a primary defect [28–30].

Different frequencies of stimulation may have different profiles of secretion from parasympathetic nerves [31]. In general the "conventional" neurotransmitters, ACh and norepinephrine (NE), have greater quantities released at lower firing frequencies and the neuropeptides at higher frequencies [32]. Moffat et al. used preganglionic stimulation (resembling in vivo) of the vagus nerve, which only at frequencies above 4 Hz elicited NANC relaxation of the trachealis muscle [33]. Higher NO output in asthmatics can be ascribed in part to higher parasympathetic nerve firing which occurs along with Ach release.

Role of nitric oxide in airways

Nitric oxide (NO) is a ubiquitous intercellular messenger being synthesized from L-arginine by NO synthases (NOS) [34]. There are three isoforms of NOS; type I (neuronal), type II (inducible), and type III (endothelial). Among the three distinct NOS isoforms, NOS1 and NOS3 are constitutively active, exhibiting rapid responses to a small amount of NO, while NOS2 is constitutively expressed in the human airway epithelium and inflammatory cells (including macrophages) and is further up-regulated many times by inflammatory agents [35–37]. Also there is a complex interplay between different NOS isoforms in controlling the production of NO, for example, NOS1 has been shown to regulate NOS2 expression [38]. One of the potentially beneficial effects of NO is derived from its broncho-dilating actions that are mediated via the interaction of NO with guanylate cyclase in smooth muscle cells [39]. Weschler et al. reported an increase in concentration of NO in exhaled breath in asthmatics [40]. It may seem paradoxical, that asthmatics have elevated levels of exhaled NO, in the context of a disease characterized by bronchial hyper-reactivity [41].

Studies from knockout mice models suggest that exhaled NO is primarily synthesized by NOS2 (inducible NOS) [42], which appears to be up-regulated in mice lacking NOS1 or NOS3. It is intriguing that mice lacking NOS2 have significantly reduced