Brain, Behavior, and Immunity xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Stress, asthma, and respiratory infections: Pathways involving airway immunology and microbial endocrinology

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ARTICLE INFO

Article history:
Received 4 July 2012
Received in revised form 18 September 2012
Accepted 26 September 2012
Available online xxxx

Keywords:
Stress
Asthma
Infection
T helper cells
Mucosal immunity
Mucosa
Bacteria

ABSTRACT

Stress and infections have long been independently associated with asthma pathogenesis and exacerbation. Prior research has focused on the effect of psychological stress on Th cells with particular relevance to atopic asthma. In this review, we propose new perspectives that integrate the role of infection in the relationship between psychological stress and asthma. We highlight the essential role of the mucosal epithelia of the airways in understanding the interaction between infections and the stress-asthma relationship. In addition, we review findings suggesting that psychological stress not only modulates immune processes, but also the pathogenic qualities of bacteria, with implications for the pathogenesis and exacerbation asthma.

1. Introduction

Scientists have long been interested in the adverse impact of psychological stress on health. Stress has been consistently associated with the development and deterioration of many medical conditions such as cardiovascular disease, HIV, and cancer (e.g., Cohen et al., 2007). There is also compelling evidence that life-events, emotions, stress, and psychopathology can affect asthma (for earlier reviews, see Lehrer et al., 2002; Weiner, 1977) and respiratory infections (e.g., Cobb and Steptoe, 1998; Cohen, 2005; Drummond and Hewson-Bower, 1997; Marsland et al., 2002; Pedersen et al., 2010). Similarly, respiratory infections are strongly linked to exacerbations of asthma (Nicholson et al., 1993; Jackson and Johnston, 2010), and there are suggestions that a tight relationship exists between psychological stress, respiratory infections, and asthma (Sakellariou and Papadopoulos, 2008; Wright et al., 2005). However, the exact interactions between these factors are not fully understood.

Although little is known about the mechanism behind the mutual associations between stress, infection, and asthma, research has explored a number of potential autonomic and molecular pathways involved in this relationship, including various components and processes of the immune system. Research has focused on the impact of stress on T helper (Th) cell immune processes (Elenkov and Chrousos, 2006), whereas other aspects of this interaction, such as mucosal immunity, are largely unexplored. The role of bacterial colonization and infection in the development of the immune system and asthma has recently gained attention among researchers. More recent *in vitro* microbiology research on virulence of pathogens in reaction to stress hormones provides new perspectives on the effects of stress and the risk for infection and asthma exacerbation (Sperandio et al., 2003; Everest, 2007).

This review focuses on significant insights into interdisciplinary research from psychology, neurology, epidemiology, immunology, endocrinology, and microbiology, which could provide potential mechanisms that link stress, asthma, and respiratory infections. The initial introductory sections provide an overview of relevant aspects of asthma and respiratory infections. We then proceed to illustrate the most thoroughly explored aspects of the interaction between stress and Th cell function, including the effect of stress on asthma exacerbation and increased susceptibility to infection. New perspectives on the asthma-stress relationship involving the role of the mucosal epithelia are then introduced as important under-researched areas. This novel focus may provide a more parsimonious and integrative conceptualization of the interaction between psychological stress, infections, and asthma exacerbation. Finally, new hypotheses will be discussed that consider the direct interaction of stress hormones with infectious microorganisms, which will give rise to a novel perspective on infection and disease exacerbation as a process intimately linked to communication between bacteria and their human hosts. Although these perspectives

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http://dx.doi.org/10.1016/j.bbi.2012.09.012

are developed using the example of respiratory infection and asthma, they may ultimately be relevant for a much broader range of interactions between psychological and organic disease processes.

2. Asthma: global burden, disease manifestation, and immune pathophysiology

Asthma is a condition characterized by chronic airway inflammation that is related to airway hyperresponsiveness, variable airway obstruction, and mucus overproduction that results in episodic and recurrent symptoms, such as wheezing, coughing, and breathlessness (National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program [NHLBI/NAEPP], 2007; Bateman et al., 2008). Airway obstruction and symptoms may be reversible depending on the severity of the disease. Later consequences are airway remodeling with changes in structure and function of the epithelium, basement membrane, mucus cells, smooth muscle layer, and vessels of the airways, which lead to partial irreversibility of obstruction (Al-Muhsen et al., 2011; Bousquet et al., 2000). Asthma is among the most prevalent chronic diseases; in children, it now leads the chronic disease statistics. There are an estimated 300 million asthmatics worldwide (Masoli et al., 2004). This condition represents a significant financial burden, as it is estimated that asthma causes a loss in disability-adjusted life years (DALYs) that amounts to 15 million per year worldwide.

Recent research suggests that asthma is a complex disease that may be manifested in several subtypes, each with potentially different underlying immune processes (Holgate, 2002; Wenzel, 2006). In fact, it is estimated that atopic asthma in adults only accounts for 37% of asthma cases across countries on average (Pearce et al., 1999), with 56.3% among individuals 6–59 years old in the US located (Arbes et al., 2007). Atopy prevalence varies by age, gender and race, among other factors. Among asthmatics, atopic prevalence is higher for young men (up to 74.1% [95% C.I.55.8-86.7]), with higher education level, and with residence in metropolitan areas. The field has yet to more concretely define asthma subtypes, but there is evidence for subpopulations of asthmatics with a distinct immunological basis for the pathogenesis and exacerbation of their diseases (*endotypes*, Lötvall et al., 2011). For example, components of the innate immune system, such as bronchial epithelial cells, alveolar macrophages, dendritic cells, and natural killer (NK) cells, may play a central role in asthma pathophysiology of certain subtypes of asthma. The NK cells, in particular, can cause airway hyperreactivity and are involved in allergic and non-allergic asthma pathogenesis. They can secrete Th2 cytokines fomenting allergic asthma. NK cells are also involved in asthma inflammation that is derived from neutrophils, by expressing IL-17, which recruits neutrophils. NK cells can also destroy regulatory T (T reg) cells that usually reduce asthmatie inflammation (Matangkasombut et al., 2009). While the late phase eosinophil infiltration is characteristic of inflammatory processes in allergic asthma, other subtypes of asthma may be defined more by the presence of neutrophils in the airways (Douwes et al., 2002).

Immunological processes underlying asthma are typically conceptualized in terms of atopy. This is a condition in which individuals have an excess of a humoral immune response to allergens involving the antibody immunoglobulin (IgE). Furthermore, atopy is considered to be a genetic predisposition to respond with elevated IgE to allergens, in contrast non-atopic individuals who tend to express IgG in response to allergens (Akdis, 2006). The

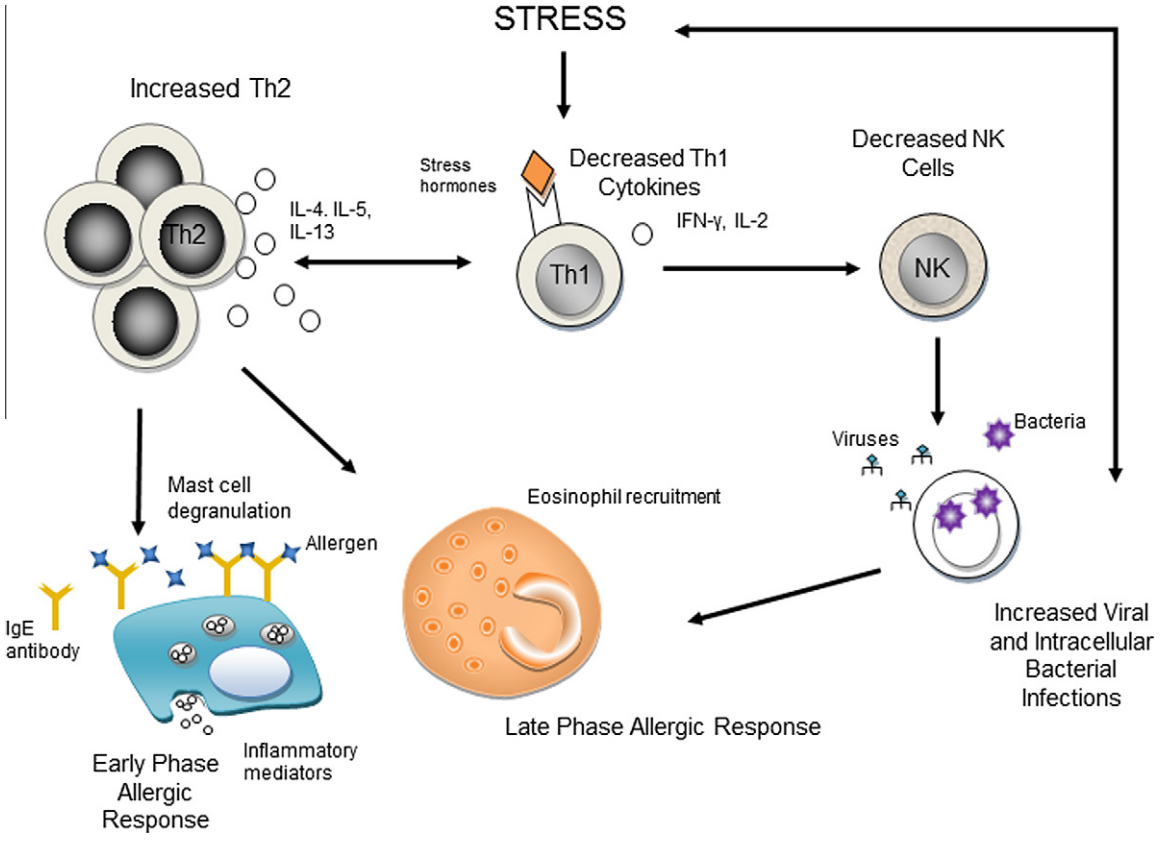

Fig. 1. Stress increases Th2 immune responses by suppressing Th1 cytokine (through adrenergic receptors) that usually inhibit Th2 cells. The release of Th2 cytokines such as IL-4, IL-5 and IL-13 that exacerbate allergic inflammation in asthma by increasing IgE production and mast cell degranulation with the release of inflammatory mediators such as histamine or leukotrienes (early-phase response) and eosinophilic infiltration (late-phase response). The decrease in Th1 cytokines decreases cellular immune processes, such as those initiated by NK cells, and increases the likelihood of infection.

Please cite this article in press as: Trueba, A.F., Ritz, T. Stress, asthma, and respiratory infections: Pathways involving airway immunology and microbial endocrinology. Brain Behav. Immun. (2012), http://dx.doi.org/10.1016/j.bbi.2012.09.012