Experimental Neurology 248 (2013) 338–342

Contents lists available at ScienceDirect

Experimental Neurology

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

Commentary

Asthma: a clinical condition for brain health

Lavinia Albéri*

Institute of Anatomy, Department of Medicine, University of Fribourg, Fribourg, Switzerland

ARTICLE INFO

Article history:
Received 26 June 2013
Accepted 2 July 2013
Available online 12 July 2013

Referred to:
"Chronic asthma results in cognitive dysfunction in immature mice" Experimental Neurology 247 (2013) 209–217

According to the World Health Organization, bronchial asthma is a chronic inflammatory respiratory condition, which affects at present more than 150 million people worldwide, mostly children. Asthma defined as bronchial hyper-responsiveness to allergens results from the expansion of Th2 lymphocytes secreting an array of inflammatory cytokines (IL-4, IL-5, IL-9, IL-13 and granulocyte macrophage colony stimulating factor, GM-CSF)(Holgate, 2012). In the past 25 years the cases of asthma have more than doubled in western society with the highest morbidity around urbanized areas (D'Amato et al., 2013). It has been shown that allergic asthma correlates strongly with environmental factors such as tobacco exposure (Chilmonczyk et al., 1993), air pollution (Kim et al., 2013), pollination (D'Amato et al., 2005) and diet (Ali and Ulrik, in press). Nevertheless, recent genome wide association studies (GWAS) have indicated susceptibility loci that contribute to the aberrant immune response to allergens and can determine the onset and the severity of the disease (Tamari et al., 2013). In addition, other recent works suggest that parental or prenatal exposure to environmental pollutants as tobacco can induce epigenetic modification in immune cells and may be responsible for the endemic of asthma in young children (Salam et al., 2012; Wang et al., 2013). Asthma appears, therefore, a complex chronic disease of environmental and genetic etiology (Fig. 1). The high incidence in the young population and the prolonged treatment with anti-inflammatory drugs to contain the symptoms and avoid deadly apnea episodes make asthma a serious clinical condition for the patients and a significant economic burden for the health care providers. Furthermore, secondary effects of breathless on blood oxygenation can have long-term consequences on brain function. Indeed, asthmatic children are at risk of developing intermittent hypoxia and sleep apnea which have been seen to correlate with lower IQ scores and are at risk of developing attention deficit disorder (Bass et al., 2004). Nevertheless, a direct link between asthma and cognitive deficit has been so far elusive. The article from Guo et al. in this issue of Experimental Neurology uses an ovalbumin animal model of asthma and indicates, for the first time, that chronic asthma can affect cognitive performance and have irreversible effect on synaptic function and neurogenesis (Guo et al., 2013). In this commentary we will touch upon the implication of their findings for brain health.

Animal models of asthma: from sensitization to inflammatory reaction

Based on the endemic of asthma observed in the last two decades, several clinically relevant animal models have been established to develop treatments for asthma. This research has been essential in understanding the underlying mechanisms of airways inflammation, hypersensitivity and susceptibility to organic and inorganic allergens. The common feature of the asthma animal models is represented by a sensitization phase to an exogenous antigen followed by long-term exposure with the same or another protein at lower concentrations. At the cellular level, airborne allergens which, in early life, come in contact with the airway epithelium can break down the epithelial cell barrier causing the release of soluble chemoattractant (CCL17, CCL22 among others) and cytokines (IL-33, IL-25, TNFα and GM-CSF among others)(Holgate, 2012). The released ligands and cytokines, then, recruit dendritic cells from the bone marrow to the underlying mucosa and promote their specification. Mature dendritic cells, with antigen presenting capacity, can take up the exogenous allergens captured by Immunoglobulin E (IgE) and migrate to the local lymph nodes where they interact with naïve T cells. As a result of this interaction T cells are specified into Th2 cells which produce a wide array of cytokines. The characteristic differentiation of T cells into Th2 memory cells at the expenses of Th1 cells, is regulated by IL-4 produced by dendritic cells or resident basophils (Holgate, 2012). Th2 cells, which are a more immature T-cell type, release high amount of cytokines that contribute to Th2 cell expansion (IL-4), IgE synthesis from B cells (IL-4 and IL-13), mast cell differentiation and maturation (IL-3, IL-9 and IL-13), eosinophil maturation (IL-3, IL-5 and GM-CSF) and basophil recruitment (IL-3 and GM-CSF)(Holgate, 2012). This allergic cascade exacerbates the inflammatory reaction and leads to epithelial hypertrophy and airway remodeling resulting in wheezing and breathlessness. The ovalbumin model of asthma recapitulates several of the features of the human respiratory condition including airways hyper-responsiveness, epithelium thickening and respiratory weakness. Nevertheless, ovalbumin, which is contained in the egg white, is not considered to be an allergen to human and recently exposure to particulates, tobacco, mites, bacteria or viruses have been integrated in the ovalbumin protocol to resemble more closely the human condition (McAnulty, 2011). One of the mechanisms for exacerbation of the airways inflammatory reaction in

* Corresponding author. Fax: +41 26 3009733.
E-mail address: lavinia.alberi@unifr.ch.

0014-4886/$ – see front matter
http://dx.doi.org/10.1016/j.expneurol.2013.07.002

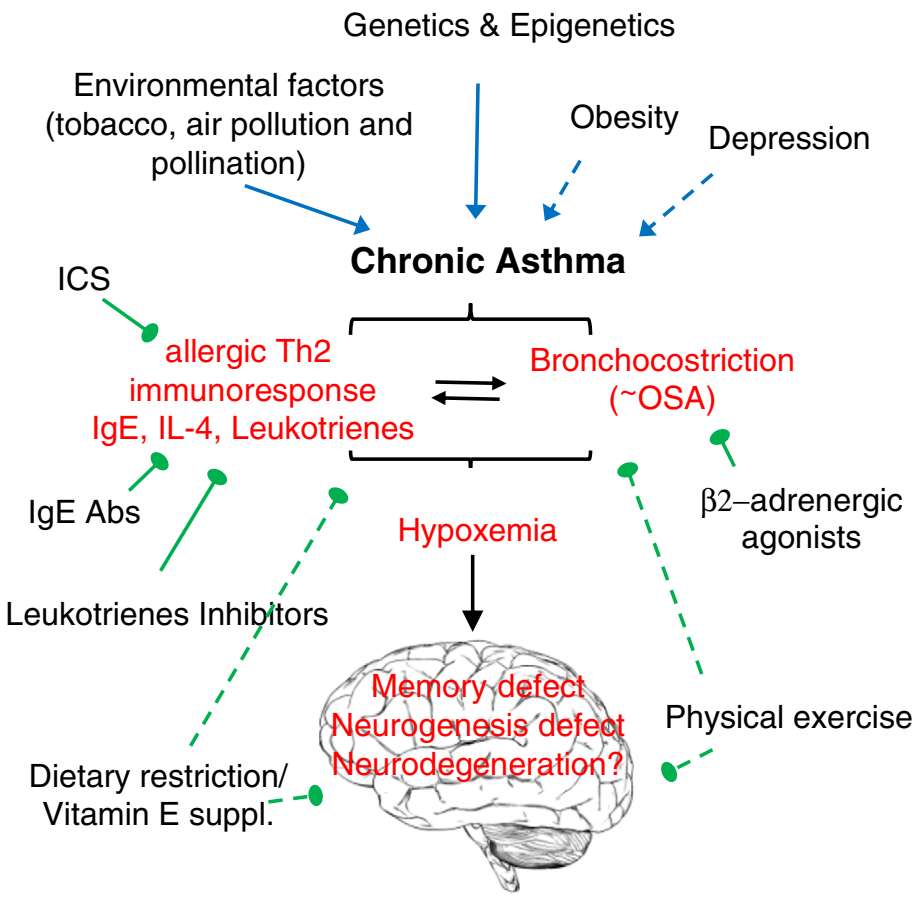

Fig. 1. Illustration of the asthma cascade on airways inflammation and on brain function. Allergic asthma is triggered by environmental, genetic and epigenetic factors (blue filled arrows). Asthma is aggravated by conditions as obesity and depression (blue dashed arrows). Allergic asthma causes airways inflammation and bronchoconstriction (wavy dash indicates OSA as an associated symptom). Airways hyper-responsiveness as a result leads to Hypoxemia with detrimental effect on brain functions. Therapeutical approaches used in the practice are indicated by green filled oval arrows. Adjuvant therapeutical strategies are indicated by green dashed oval arrows. ICS = Inhalant Corticosteroid, IgE Abs = Immunoglobulin E antibodies and OSA = Obstructive sleep apnea.

chronic asthma has been attributed to epigenetic mechanisms involving dysregulation of miRNAs. In particular, miRNA-21, which inhibits IL-12 expression, aTh1 differentiation factor, leads to the increased Th2 differentiation amplifying the allergic reaction (Lu et al., 2011). This indicates that early inflammatory signals may actively contribute to propagate the allergic reaction. On the other hand, neonatal exposure to virus or bacteria has so far failed to aggravate the symptoms of asthma, indicating that neonatal contact with allergen species may protect from developing an allergic reaction (Olszak et al., 2012; Siegle et al., 2010). This would be in line with the evidence that children raised in rural areas are at lower risk of developing asthma based on early immunization to variety of bacterial and natural allergens (Ege et al., 2011). Furthermore, it has been demonstrated that obese mice have a higher risk of developing asthma due to the sustained release of chemokine from adipose tissue (Leptin, TNF, IL-6, VEGF and others). These cytokines are pro-inflammatory and have been shown to favor Th2 cells differentiation actively contributing to airways hyper-responsiveness (Shore, 2007). These studies corroborate the epidemiological research indicating obesity as a risk factor for developing asthma (Kheirandish-Gozal and Gozal, 2012). Despite the evidence that asthma susceptibility has an inheritable component, very few models have been established to address the trans-generational transmission of allergic reactions. Nevertheless, one study has indicated that the dietary intake of the methyl donor, folate, from the pregnant mother can silence RUNX3 expression through methylation of CpG islands on the RUNX3 promoter region. RUNX3, which regulates T cell development, if suppressed, leads to differentiation of T cells into Th2 lineage increasing the severity of the allergic reaction in the offspring (Hollingsworth et al., 2008). Prenatal and early life epigenetic modifications appear, therefore, critical for developing allergic asthma. On the whole, asthma research has unraveled important mechanisms underlying the airways immune response to allergens and the long-term respiratory symptomatic, but very little attention has been given to the resulting effects of oxygen deprivation on the central nervous system. Nevertheless, cross-correlative studies have indicated that obstructive sleep apnea (OSA), which is clinically associated to bronchial asthma (Alkhalil et al., 2009), can affect cognitive performance and attention in children (Bass et al., 2004), adults (Kheirandish-Gozal and Gozal, 2012) and animal models (Gozal et al., 2001; Row et al., 2003, 2002). Interestingly, Guo and colleagues in this issue of Experimental Neurology have shown that ovalbumin induced bronchial asthma has a direct effect on synaptic plasticity, neurogenesis, memory and brain inflammation in mice (Guo et al., 2013). The common features of intermittent hypoxia and asthma (bronchoconstriction, dyspnea and inflammation) and the frequent comorbidity (Alkhalil et al., 2009) suggest that reduced blood oxygenation (Hypoxemia) in asthma may be a critical factor for developing long-term neurological deficits.

Effect of chronic asthma on neuronal function

It is established that blood oxygenation is critical for brain function. Hypoxia is considered one of the main causes of brain damage