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Asthma: a clinical condition for brain health

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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.

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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

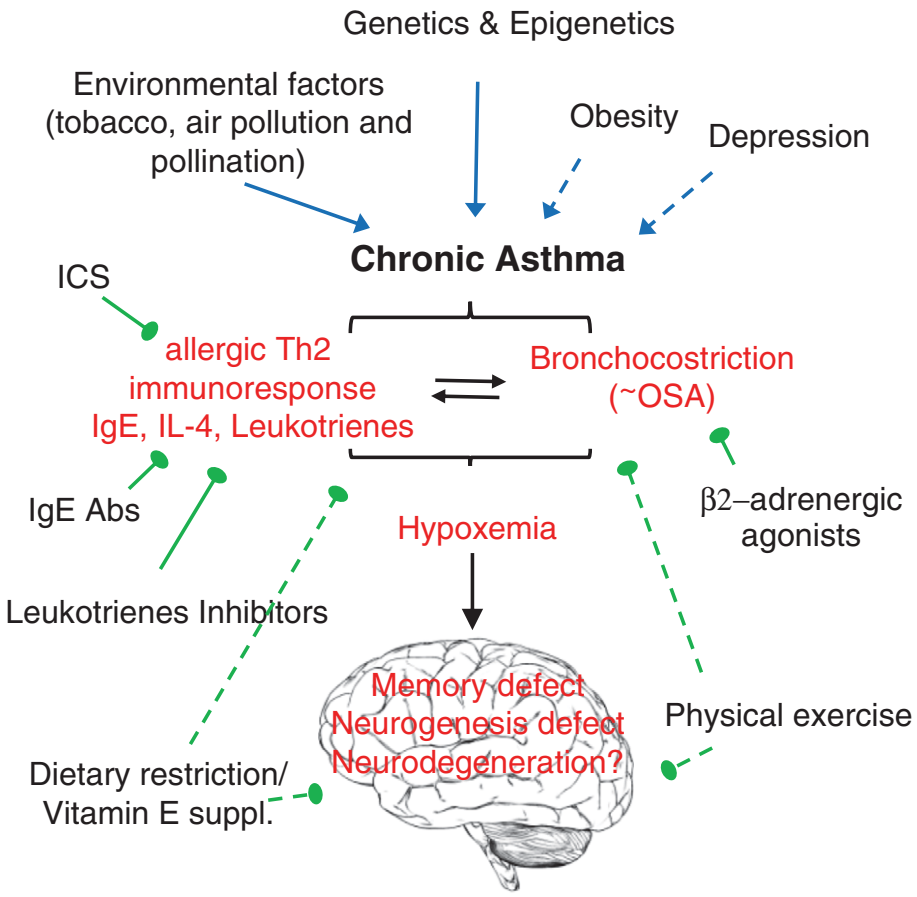

Fig. 1. Illustration of the asthma cascade on airways inflammation and on brain function. Allergic asthma is triggered by environmental, genetic and epigenetic factors (blue filled arrows). Asthma is aggravated by conditions as obesity and depression (blue dashed arrows). Allergic asthma causes airways 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

and cognitive impairment. In addition, dyspnea episodes during life are considered a major risk factor for developing neurodegenerative disease (Daulatzai, 2012). Asthma due to the airways thickening may lead early on to dyspnea and obstructive sleep apnea independently of age or gender (Alkhalil et al., 2009). Early studies from the group of Gozal have shown that obstructive sleep apnea, without interfering with the sleep pattern, leads to spatial memory impairment, neuronal cell death and gliosis in adult (Gozal et al., 2001) and immature rats (Row et al., 2002). In later studies, the same group has resolved that the spatial memory impairment may result from reduced c-AMP responsive element binding protein (CREB) activity (Goldbart et al., 2003) and reduced synaptic plasticity (Payne et al., 2004). Most recent evidence indicate that brain derived neurotrophic factor (BDNF) which is critical for synaptic plasticity and memory formation (Mattson, 2008), is reduced in intermittent hypoxia and BDNF infusion can rescue the synaptic plasticity deficit (Xie et al., 2010). These studies have demonstrated for the first time how chronic dyspnea can have detrimental effects on brain function. The recent paper from Guo et al. using an experimental model of asthma recapitulates some of the former findings in intermittent hypoxia. Guo and colleagues have found that mice treated with the allergen ovalbumin from the first weeks of life (sensitization phase) and challenged until mid-early adulthood (2 months of age) display a spatial learning and memory deficit (Guo et al., 2013). Treatment with the inhalant corticosteroid (ICS), Budenoside, despite reducing the inflammatory reaction in the lungs, failed to rescue the cognitive impairment. This might be explained by the subtle reduction in smooth muscle thickness by Budenoside treatment which may not prevent bronchoconstriction and can result in central hypoxia. Further studies using a therapeutical combination of ICS and a β_2 adrenergic agonist, as used in the clinical practice (Ankerst, 2005), may improve blood oxygenation through bronchodilatation in the ovalbumin model of asthma. Moreover, the authors confirmed that the neurocognitive deficit results from impairment in long-term potentiation (LTP) of CA1 synapses (Guo et al., 2013). LTP is a physiological correlate of memory and its induction depends on NMDA receptors signaling. Whereas, the maintenance of LTP is attributed to the increase of AMPA receptor at the post-synapse or due to the insertion of AMPA receptors on constitutive silent synapses, which become activated (for original references Sweatt, 2009). Surface AMPA receptors insertion leads to actin anchoring through CamKII resulting in the enlargement of the spine heads and augmenting the strength of the synaptic connection (Sweatt, 2009). Interestingly, in the asthma model presented, LTP induction is unaltered whereas maintenance is affected. This suggests that AMPA receptors trafficking may be compromised without affecting the NMDA component. In addition to the LTP deficit, the authors observed that basal transmission was reduced in the ovalbumin treated group suggesting a reduced strength between CA3 and CA1 synapses (Sweatt, 2009). Indeed, Guo and co-authors reported profound changes in spine density in CA3 region as well as an increase in mitochondrial size. Both LTP maintenance and basal transmission could be partially reversed by Budenoside treatment. This might be explained by the effect of Budenoside on mitochondrial function in CA3 neurons as indicated by the reduction in mitochondrial size and the decrease in the ROS target, Hypoxia inducible factor 1 α (Hif1α). Indeed presynaptic mitochondria have been shown to release Ca^{2+} through Na^{+}/Ca^{2+} exchanger in an activity dependent fashion, strengthening synaptic transmission (Yang et al., 2003). In asthma, enlarged mitochondria might be unresponsive to activity dependent changes but rather engaged in processing reactive oxygen species (ROS) as a result of hypoxia, as indicated by the increase in Hif1α expression. Indeed, it has been shown that, in intermittent hypoxia, ROS are strongly induced (Row et al., 2003). CA1 dendritic mitochondria have been, also, shown to contribute to synaptic function (Li et al., 2004). It is likely that the rescue in mitochondrial function through Budenoside treatment occurs also at CA1 dendrites partially rescuing the synaptic potentiation. Nevertheless, the moderate improvement in early LTP maintenance by ICS treatment does not translate in better spatial learning and memory performance suggesting that memory processing requires a threshold potentiation level to trigger and maintain de novo synthesis of proteins constituting the molecular pool of memories (Sweatt, 2009). Indeed, in the asthma condition, levels of the early immediate genes c-fos and Arc are reduced in hippocampal tissue and cannot be rescued by Budesonide. C-fos and Arc transcription are downstream of CREB regulation (Benito et al., 2011; Ying et al., 2002), it is plausible to think that, similar to the intermittent hypoxia model (Goldbart et al., 2003), CREB activation may be reduced. The defect in CamKII/CREB activation might, therefore, explain also the LTP deficit as a result of decreased AMPA receptor tagging through CamKII (Kessels and Malinow, 2009). The other possibility is that, as it has been shown in several models of intermittent hypoxia (Gozal et al., 2001, 2003) and altitude hypoxia (Maiti et al., 2007, 2008), sporadic cell death may be ongoing in chronic asthma, thus, interfering with neural activity and network plasticity. The presence of VEGF, a marker of brain inflammation and angiogenesis, may suggest so, although further studies addressing this question will help understand whether asthma can also have effects on neuronal survival.

Neurogenesis in asthma

The adult mammalian brain presents at least two neurogenic niches, the subventricular zone (SVZ) of the forebrain and the subgranular zone (SGZ) of the dentate gyrus. Those unique brain regions have regenerative capacity and can respond to physiological stimuli as exercise (van Praag et al., 1999) and learning (Sisti et al., 2007) as well as injuries such as stroke (Arvidsson et al., 2002) and seizures (Madsen et al., 2000). Neurogenesis in the hippocampus has been shown to be directly implicated in associative memory (Shors et al., 2001), pattern separation (Vivar and van Praag, 2013) and reduced neurogenesis has been associated to poorer learning and memory performance (Jessberger et al., 2009). The molecular mechanisms beyond the neurogenic drive in physiological conditions have been attributed to neurotrophins as BDNF (Lee et al., 2002), and the increase in network activity (Deisseroth et al., 2004). Interestingly BDNF expression is induced by synaptic potentiation (Patterson et al., 1992), indicating that neuronal activity has self-propagating effects through neurotrophin-induced neurogenesis and plasticity. On the other hand, in condition of hypoxic injury, VEGF appears to play a more prominent role (Jin et al., 2002; Shimotake et al., 2010) indicating that the neurovascular unit is instrumental in modeling plasticity following injury. In several brain injury models, the hypoxic microenvironment stimulates neurogenesis as a result of increased Hif1α signaling (Cunningham et al., 2012). Nevertheless, based on the limited regenerative capacity of the brain, it is still debated whether new born neurons can survive and integrate in the circuit. Indeed, several reports have raised the possibility that long-term inflammation can prevent neurogenesis and neuronal integration limiting brain regeneration (Ekdahl et al., 2009). In the asthma ovalbumin model Guo et al. show a similar discrepancy: despite an increase in VEGF levels as a result of increased hypoxia (Hif1α)(Manalo et al., 2005) and ongoing angiogenesis, as indicated by the angiogenic factor GCPR 124 (Kuhnert et al., 2010), there is a substantial decrease in neurogenesis (Guo et al., 2013). Treatment with Budenoside improves only slightly neurogenesis and reduces circulating VEGF levels as a result of reduced Hif1α, whereas levels of the angiogenic marker GPCR 124 remain unaltered. This result is difficult to reconcile with the existing literature on the proliferative activity of VEGF (Jin et al., 2002; Shimotake et al., 2010; Sun et al., 2003), however it remains possible that the simultaneous action of neuronal network activity (Bruel-Jungerman et al., 2006), growth factors and endothelial factors contribute to neural stem cells proliferations. Indeed, in the asthma model studied, synaptic potentiation and neuronal activity, indicated by c-fos and Arc, are reduced. On the other hand, it is possible that chronic asthma induces chronic inflammation not only peripherally but also centrally interfering with neurogenesis and other neuronal processes. In fact, it has been

reported that T-cells shape microglia responses in physiological and pathological conditions contributing to learning and memory processing, neurogenesis and neuroprotection (Ziv et al., 2006, 2007). It remains possible that aberrant T cell differentiation, as observed in allergic asthma (Holgate, 2012), may interfere with the central immuno-neuronal homeostasis impairing neuronal functions. In line with this hypothesis, treatment with Budenoside, which dampens the immunological response, can improve by 40% neurogenesis as compared to the asthma condition, but cannot rescue completely the phenotype. The incomplete rescue by Budenoside might also be explained by the intrinsic inhibitory activity that glucocorticoids have on proliferation (Ekstrand et al., 2008). Further studies investigating the brain microenvironment in asthma animal models will help unravel the mechanism beyond the hippocampal neurogenesis defect and its consequences on memory processing.

Treating asthma beyond chronic inflammation

Based on the recent findings indicating that allergic asthma has detrimental effects on cognitive functions and neuronal integrity, therapeutical approaches should be considered to limit these secondary yet crucial effects. The elective therapy for allergic asthma is based on anti-inflammatory ICS. Nevertheless, it has been shown that long-term monotreatment with corticosteroid can induce tolerance and have adverse effect on hypothalamic–pituitary–adrenal axis and on bone growth in children (Ankerst, 2005). In recent years, co-treatment of ICS with long-acting β_2-agonists, reducing muscle contraction, is pre ferred as the drugs combination is synergistic and prevents overdosage and secondary effects (Tamm et al., 2012). Other therapeutical substances as leukotriene antagonists (Price et al., 2011) and immunotherapy with anti-IgE antibodies (Milgrom et al., 1999) have been put forward as alternative to ICS or implementation to asthma therapy. Nevertheless, asthma is a chronic and complex disease with growing proportions and considering lifestyle corrections as reducing dietary intake and physical exercise can have additional advantage to the classical therapy both on lungs' and brain's function. Indeed it has been reported that both physical activity and dietary restriction or the combination of the two can improve significantly airways responsiveness (Johnson et al., 2007; Lucas and Platts-Mills, 2005; Scott et al., 2013; Walders-Abramson et al., 2009) as well as memory performance (Mattson, 2000). It is thought that reducing the calorie intake has a direct effect on mitochondrial metabolism reducing ROS production which is cytotoxic and could contribute to neurodegeneration in the long-term (Mattson et al., 2008). On the other hand, physical activity in asthmatic patients could boost BDNF levels improving synaptic plasticity, neurogenesis and ultimately reverting the memory defect (Mattson, 2008). In addition, it has been indicated that difficult to cure asthma subjects are often diagnosed with depression (Lieshout and MacQueen, 2008). It is unclear at present whether there is a mechanistic link between asthma and depression. Nevertheless, there is increasing evidence suggesting that depression increases pro-inflammatory cytokine and ROS production (Jones and Thomsen, 2013). Antidepressant therapy may be sought in those patients to improve not only the central symptoms but also the immunological response. In addition, dietary implementation with antioxidants, as Vitamin E, may further prevent mitochondrial dysfunction in the airways (Mabalirajan et al., 2009) as well as display neuroprotective effects on the long-term (Mattson et al., 2008). Based on the fact that many cellular processes are conserved between cells in the human body, asthma therapy in the practice should consider novel treatment directed at improving the immunological response as well as brain health (Fig. 1).

Conclusions

On the whole, it appears that chronic asthma, besides the airway inflammation symptoms, has significant effects on cognitive processing through impairment of synaptic plasticity and neurogenesis. In addition, poorly treated asthma may have, on the long-term, detrimental effect on neuronal survival both through hypoxia and mitochondrial dysfunction. In light of these important findings, asthma should therefore be considered as a secondary neurological condition.

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