Psychological Stress and Asthma: A Mini-review of Neuroendocrine-Immune Responses and the Mediation of Neuropeptide Y

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The prevalence of asthma morbidity and mortality has increased significantly in recent decades, concurrently with increasing mental health problems worldwide. Asthma has long been considered as an archetypal psychosomatic disease. However, evidence supporting the link between psychosocial stress and asthma is just emerging. The stress-asthma link is supported by evidence that chronic stress suppresses hypothalamo-pituitary-adrenocortical (HPA) axis activity and its anti-inflammatory effect, resulting in blunted HPA axis responsiveness seen in asthma patients. However, marked inter-individual variability in responses to stress exists. Some are more vulnerable than others to the effects of stress in terms of asthma risks and morbidity. Recent studies suggest the main contribution of neuropeptide Y (NPY) in modulating HPA-axis responsiveness and explaining inter-individual variation in resilience to stress and asthma in animal models and clinical samples. The temporal and spatial expression pattern of NPY and its receptors (Y1 and Y5) is determined in the airways of asthmatic mice. Peripheral NPY concentration and the genetic variation in the NPY gene has been investigated in asthma in multiple studies. Studies have attempted to explain the underlying mechanisms of the "neuroimmune" crosstalk as a contributor to the development of the airway inflammation and asthma. Such a psychoneuro-immunological perspective in asthma research represents a new psychosomatic approach in pharmacological therapy of asthma, and may open the door for future potential use of NPY agonists in treating asthma. Future brain imaging research using specific NPY-receptor ligands is required to better understand the relationship between central release of NPY and asthma.

Asthma has shown increasing prevalence among children in various populations. According to the International Study of Asthma and Allergies in Childhood (ISAAC) surveys, there is an increase in cumulative asthma prevalence from 5.5% in 1967 to 13.7% in 1987 and 20.0% in 1994 in children. Among 12 to 15 year olds, 20.7% were ever diagnosed with asthma in 1994, but this has increased to 27.4% in 2001. The increased prevalence and severity of asthma amidst the background of increasing mental health problems in adolescent children call for research into the relationship between stress and asthma [1-9].

1 ACUTE AND CHRONIC PSYCHOLOGICAL STRESS IN ASTHMA AND THE HYPOTHALAMO-PITUITARY-ADRENOCORTICAL (HPA) AXIS RESPONSE

1.1 Psychological stress in asthma

Asthma has long been thought to be an archetypal psychosomatic disease. However, empirical evidence in support of the link between psychosocial stress and asthma has been elusive. With increased understanding of both the neurobiology of stress and asthma pathophysiology, elucidating the role of psychological stress in early life on asthma development and control is now distinctly possible. This has taken place in the broad context of studies in animals and humans on (prenatal and) early life programming by maternal stress and early caregiving experiences with lasting effects in disrupting the regulation of stress response pathways in the sympathetic and adeno medullary (SAM) system and the hypothalamo-pituitary-adrenocortical (HPA) axis [10-13].

1.2 HPA axis response in acute and chronic psychological stress

Although hypothesized to be a complex neuroendocrine-immune system interaction [14] in which the HPA axis plays a major role, the underlying biological mechanism of the association between stress and asthma has
only just begun to be elucidated. Only recently has data emerging from murine models shown that stress produce a marked increase in allergen-induced airway inflammation [15-18]. Different mechanisms may be involved in acute versus chronic stress. In acute stress, activation of the HPA axis and consequent cortisol release lead to reduction of airway inflammation. However, continuous prolonged or intermittent stimulation, as in chronic stress, suppresses HPA axis activity and its anti-inflammatory effect [17,19]. This is corroborated by clinical studies in which asthma patients who are not treated with inhaled corticosteroids (ICS) are likely to have an attenuated activity and/or responsiveness of their HPA axis. In line with this concept, most asthmatic children demonstrate improved HPA axis responsiveness on conventional doses of ICS, as their airway inflammation subsides [20-21].

1.3 Early life stress exposure on asthma in adulthood

For a disease known to have its origin in childhood, there are few clinical and epidemiological studies of the effect of early life stress exposure on asthma in adulthood [22]. Only two animal studies have reported that psychological stress in mice in childhood produced long lasting effect in aggravating adult asthma [23-24]. Studies which show that early life stress may increase the risk of childhood asthma are only just beginning to emerge [12-13].

2 INTERPLAY BETWEEN THE NEUROPEPTIDE Y SYSTEM AND THE CLASSICAL HPA STRESS RESPONSE

A few recent studies indicated that stressful life events increase the risk of asthma exacerbations [25]. It is well known that the HPA axis functioning of responses to stress show marked inter-individual variability which is likely to be determined by genetic, environmental factors, and the timing of stress exposure. Among these, a strong determinant of such inter-individual differences in stress response may be found in neuropeptides released by neurons that act as neuronal signalling molecules and modulate the release of neurotransmitters and hormones [26].

2.1 Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter discovered in the arcuate nucleus of the hypothalamus. NPY co-exists with adrenalin (A) and noradrenaline (NA) in neurons of the nucleus of the solitary tract and the autonomic nervous system, and augments the vasoconstrictor effects of noradrenergic neurons, and regulates the release of many neurotransmitters including adrenalin and noradrenaline.

2.2 Interplay between the Neuropeptide Y system and the classical HPA axis

There is an interplay between the NPY system and the classical HPA acute stress response system and SAM axis. NPY-ergic activity directly stimulates the synthesis and release of CRF and a series of stress-related responses including the sustained release of cortisol, adrenalin and noradrenaline. Repeated stress (when combined with a high-fat, high-sugar diet - often associated with stress behaviour) stimulates the release of neuropeptide Y, increasing food intake and fat storage [27]. This may explain the typical stress response behaviour of calorie consumption (and incidentally may also be linked to obesity-associated asthma).

2.3 NPY: an endogenous anxiolytic agent and immunomodulator

Evidence suggests that, under physiological conditions, NPY functions as an endogenous anxiolytic agent that buffers against the effects of stress on the mammalian brain. NPY-ergic activity which negatively feedbacks in anxiolytic fashion on CRH (which is anxiogenic and increases food intake) may be regarded as “anti-stress” [28]. High neuropeptide Y levels are associated with better performance in studies of special operations soldiers under acute and extreme training stress, but chronic stress seen in long-term patients with PTSD have been shown to have reduced plasma neuropeptide Y levels [29-30]. Low levels of neuropeptide Y are also found in depressed patients, and a variety of antidepressant drugs increase neuropeptide Y levels. The balance between neuropeptide Y and CRH neurotransmission is therefore important to the long term emotional responses to stress, and relieves allostatic load. The peripheral level of NPY is possibly a marker of sympathetic nervous activity and a marker of stress-resilience. NPY also exerts a major influence on humoral and cellular immune functions, which intimately involve asthma pathophysiology. NPY modulates potent immunological effects such as immune cell distribution, T helper cell differentiation, mediator release, or natural killer cell activation [31].

3 RESEARCH ON THE ROLE OF NEUROPEPTIDE Y IN ASTHMA

The widespread distribution and physiological effects of NPY suggest that it may play an important role in asthma [32]. NPY exists not only in neurons, but as well in neuroendocrine and inflammatory cells in the lung. Exposure to stressful events may result in the release of NPY in the airways and peripheral circulation during asthma exacerbations [33]. There are few studies on NPY in asthma exacerbations in prior research. Only 25 papers were found while searching in PubMed Datebase with keywords of “neuropeptide Y” and “asthma”, among which four reviews and 7 irrelevant papers were excluded. A Google scholar search using keywords “neuropeptide Y” and “asthma” uncovered one other 1 original study which addressed the relationship between NPY and asthma which was not covered in the 25 papers found in Pubmed. Original papers from 1995 onwards (13 in total) are included in the literature review of the role of NPY in asthma shown in Table 1 [32-44].

3.1 Findings from animal studies

Makinde et al. investigated the temporal and spatial expression pattern of NPY and its receptors (Y1 and Y5) in asthmatic airways in a mouse ovalbumin (OVA) model [32]. They reported that elevated NPY levels in the bronchoalveolar fluid (BALF), which was secreted by activated macrophage-like cells, were negatively correlated with IL-4, TGF-β1 and TGF-β2 levels. NPY-Y1 and -Y5 receptor
Table 1. Characteristics of Original Studies on the Relationship between NPY and Asthma from 1995 onwards.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participant/Animal</th>
<th>Key Outcomes</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu Y</td>
<td>2016</td>
<td>Young adult asthma patients</td>
<td>NPY polymorphisms, asthma, obesity</td>
<td>rs5574 CT and rs17149106 GT are associated with asthma independent of obesity</td>
<td>NPY is associated with asthma in young adults</td>
</tr>
<tr>
<td>Li S</td>
<td>2016</td>
<td>Mice and human</td>
<td>Foxp1, Foxp4, AHR, Npy</td>
<td>Loss of Foxp1 and Foxp4 in airway epithelial cells promotes AHR and induces ectopic Npy expression in mice. In human airways, NPY amplifies metha choline-induced bronchoconstriction. Loss of Npy expression rescues AHR in Foxp1/4 knockout mutants</td>
<td>NPY plays and role in epithelial induction and noneosinophilic asthma</td>
</tr>
<tr>
<td>Lu Y</td>
<td>2016</td>
<td>Mice</td>
<td>Serum NPY level, leukocyte subsets</td>
<td>Serum NPY level positively correlated with total leukocyte count and eosinophil number in stress-exacerbated asthmatic mice</td>
<td>Association of peripheral NPY levels with leukocyte subsets in asthma</td>
</tr>
<tr>
<td>Lu Y</td>
<td>2015</td>
<td>Young adult acute and stable asthma patients and healthy controls</td>
<td>Psychological stress, NPY, asthma, IL-4</td>
<td>NPY mediates the association of psychological stress and IL-4 levels at baseline and 1-year follow-up of asthma patients</td>
<td>NPY plays a pivotal role in the association between psychological stress and asthma</td>
</tr>
<tr>
<td>Lu Y</td>
<td>2015</td>
<td>Young adult human subjects</td>
<td>BMI, inflammation (CRP, IL-6, TNF-α), adiponectin, NPY, asthma prevalence, IL-4</td>
<td>Inflammation, NPY, and adiponectin were associated with asthma prevalence independent of each other.</td>
<td>Plasma NPY concentration was independently associated with asthma prevalence and IL-4 level</td>
</tr>
<tr>
<td>Buttari B</td>
<td>2014</td>
<td>Healthy human blood donors</td>
<td>NPY-NPY-Y1 receptor-DC axis, IL-6, IL-10</td>
<td>NPY induces DCs migration via NPY Y1 receptor and ERK and p38 mitogen-activated protein kinases. NPY corrected Th2 polarizing profile to DCs through up-regulating IL-6 and IL-10 production.</td>
<td>NPY induces potent immature DCs migration and promotes Th2 polarization</td>
</tr>
<tr>
<td>Makinde TO</td>
<td>2013</td>
<td>Mice</td>
<td>Expression pattern of NPY and its receptors in asthmatic airways</td>
<td>NPY is elevated in asthma and negatively correlated with Th2 cytokine levels. NPY is localized to macrophage-like cells.</td>
<td>NPY may regulate immune activities in asthma</td>
</tr>
<tr>
<td>Jaakkola U</td>
<td>2012</td>
<td>Young adults</td>
<td>NPY polymorphism</td>
<td>Over-weight and NPY-399T allele (without NPY-Pro7 allele) increase 2.5 times risk of asthma. Atherosclerosis risk is reduced in asthmatics.</td>
<td>NPY polymorphism increases asthma risk in overweight young adults. Asthma is associated with reduced atherosclerosis risk.</td>
</tr>
<tr>
<td>Macia L</td>
<td>2011</td>
<td>Mice</td>
<td>NPY expression in lung AA1 in NPY- and Y1-deficient</td>
<td></td>
<td>NPY exacerbates AA1 via its Y1 receptor</td>
</tr>
<tr>
<td>Aldrich MC</td>
<td>2009</td>
<td>Parent–child asthma trios</td>
<td>Single SNP and haplotype associations</td>
<td>rs5574, rs16143, &amp;rs5574</td>
<td>Variant occurring in the NPY region may be associated with asthma among Puerto Ricans</td>
</tr>
<tr>
<td>Doniec Z</td>
<td>2004</td>
<td>Children with mild asthma and matched controls</td>
<td>Serum leptin and NPY levels</td>
<td>No difference between patients and controls</td>
<td>Mild asthma in children seems not to affect neurohormonal regulation of energy balance.</td>
</tr>
<tr>
<td>Chanez P</td>
<td>1998</td>
<td>Patients with asthma and controls</td>
<td>Number of NPY-immunoreactive nerves</td>
<td>NPY-immunoreactive nerves were significantly decreased in the smooth muscle of patients. There was no correlation between disease severity and the number of nerves found in the biopsies.</td>
<td>This study does not confirm previous findings in autopsy material of some defects in sensory and VIP-containing nerves in severe asthma.</td>
</tr>
<tr>
<td>Larsson K</td>
<td>1995</td>
<td>Asthmatic patients</td>
<td>Neuropeptide Y-like immunoreactivity in arterial plasma</td>
<td>No elevations</td>
<td>Bronchoconstriction does not seem to be a stimulus for neuropeptide Y-like immunoreactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuropeptide Y-like immunoreactivity overflow</td>
<td>No activation</td>
<td></td>
</tr>
</tbody>
</table>

NPY = Neuropeptide Y, AAI = allergic airway inflammation, SNP = single nucleotide polymorphism.
expressions were localized to structural and inflammatory cells in the lung tissue. The study by Macia L et al. showed that NPY, the release of which is strongly upregulated during stress, exacerbates allergic airway inflammation (AAI) in mice, via its Y1 receptor. The development of AAI was associated with elevated NPY expression in the lung and that lack of NPY-mediated signalling in NPYKO mice or its Y1 receptor in Y1KO mice significantly improved AAI. In vivo, eosinophilia in the BALF as well as circulating immunoglobulin E (IgE) in response to AAI, were significantly reduced in NPY- and Y1-deficient compared with wild-type mice. These changes correlated with the blunting of the Th2 immune profile which is characteristic for AAI, as shown by the decreased release of interleukin-5 during ex vivo re-stimulation of T cells isolated from the thoracic draining lymph nodes of NPY- or Y1-deficient mice. The authors concluded that their study demonstrated that signalling through Y1-receptors emerges as a critical pathway for the development of airway inflammation and as such potentially opens novel avenues for therapeutic intervention in asthma [34].

3.2 Peripheral and airway NPY research in humans

Doniec et al. examined serum level of NPY and leptin in children with mild asthma and observed no correlation of NPY levels in the asthmatic and the healthy [35]. Chanez P et al. found significantly decreased NPY-immunoreactive nerves in the smooth muscle of asthmatic patients. But no correlation between disease severity and the number of nerves was found in the biopsies [36]. Larsson K reported that there were no elevations of neuropeptide Y-like immunoreactivity in arterial plasma. And no neuropeptide Y-like immunoreactivity overflow activation could be demonstrated of the Th2 immune profile which is characteristic for AAI, as shown by the decreased release of interleukin-5 during ex vivo re-stimulation of T cells isolated from the thoracic draining lymph nodes of NPY- or Y1-deficient mice. The authors concluded that their study demonstrated that signalling through Y1-receptors emerges as a critical pathway for the development of airway inflammation and as such potentially opens novel avenues for therapeutic intervention in asthma [34].

3.3 Genetic variation in the NPY gene and stress and asthma

Research suggests genetic variation in the NPY gene may influence stress responses. In 2009, Aldrich MC et al. conducted a candidate gene association study to examine the role of NPY in asthma. Six haplotype tagging single nucleotide polymorphisms (SNPs) and two candidate SNPs were genotyped in 298 Mexican parent-child asthma trios and 394 Puerto Rican asthma trios. Trios were analyzed for single SNP and haplotype associations using the transmission disequilibrium test (TDT). Results showed that Puerto Ricans exhibited a significant association between rs5574 and asthma prevalence. Two SNPs, rs16143 and rs5574, were related to severe asthma. A haplotype in the single haplotype block identified among Puerto Ricans was associated with both asthma prevalence and severity. But associations with asthma and NPY variants were not statistically significant among Mexicans. The authors concluded that a variant occurring in the NPY region may be associated with asthma among Puerto Ricans, suggesting a genetic susceptibility to stress that may differ by race/ethnicity [33]. NPY polymorphism (NPY-399T allele without NPY-Pro7 allele) is also associated with 2.5 times increased risk of asthma in overweight young adults, but independent of the reduced atherosclerosis risk in asthma [38].

3.4 Exploration of mechanisms of neuroimmune crosstalk

The exact mechanisms involved in the immune response initiation of asthma remain unclear. Recent studies have highlighted the “neuroimmune” crosstalk as a contributor to the development of the airway inflammation [45,46]. Indeed, dysfunction of airway innervation can lead to asthma symptoms like breathlessness and cough. Neutrophin and tachikin like bradykinin A and substance P, secreted by sensory nerves innervating the lung, may directly contribute to the immune cell activation, bronchoconstriction and vasodilatation eventually leading to asthma development. On the other hand, neural mediators can also play a protective role as levels of a-melanocyte-stimulating hormone, which is known to have anti-inflammatory effects and protect mice from AAI, is decreased in the lung of asthmatic patients. NPY induces potent immature DCs migration via the NPY-NPY-Y1 receptor-DC axis and promotes Th2 polarization through the upregulation of cytokine production such as IL-6 and IL-10 [39]. However, the most convincing circumstantial evidence that the nervous system has a key role on asthma development is that psychological stress worsens asthmatic syndrome. Stress causes a highly complex response and thus what causes its worsened effects on asthma remains elusive. Stress is also known to stimulate the release of certain neuropeptides by sympathetic nerves, with NPY being the most prominent one [34]. Importantly, the above studies provided some evidence of the relationship between NPY and asthma. NPY may play a critical role in modulating the relationship between stress (and anxiety and depression) and asthma exacerbations. However, given that the contradictory results of previous studies and the limited number of studies, and that stress was not included as a variable in these studies, further and more in-depth studies are still required. A psychoneuroimmunological perspective in asthma research will help to advance understanding of asthma pathophysiology and its treatment outcomes. Our previous studies suggested a positive association of serum NPY concentration and total leukocyte count and eosinophil number in stress-exacerbated asthmatic mice [42]. In young adult asthma patients with acute exacerbation or in quiescent stable status, we showed that perceived stress and NPY were significantly and positively associated with the levels of Th2 cytokine IL-4 at baseline and 1-year follow-up. NPY mediated the association of psychological stress with IL-4. The HPA index measure of transient biological stress, independently of NPY was a significant predictor of IL-4 at baseline but not at one year follow up. NPY may be a plausible neuroendocrine mediator for the persistent effect of perceived stress on heightening Th2 immune and inflammatory responses in asthma [41]. The obesity-asthma association is also partly explained by NPY [40]. However, NPY polymorphisms are associated with prevalent asthma independent of obesity [44]. The findings may provide some evidence for the potential use of
NPY agonists representing a new psychosomatic approach in pharmacological treatment of asthma and other psychosomatic disorders.

4 SUMMARY AND OUTLOOK

Widespread evidence shows that the prevalence and incidence of asthma worldwide is growing alarmingly, especially in children and adolescents. The increasing asthma prevalence is occurring concurrently with increasing mental health problems, and despite the effectiveness of inhaled corticosteroids used in treating asthma disease. The connection between stress and asthma has huge aetiological significance, and may represent the next leap in advancing knowledge about asthma aetiology, prevention and treatment. Research into the role of neuropeptides in asthma will greatly enhance the understanding of asthma pathophysiology from a psychoneuroimmunological perspective. Future brain imaging research using specific NPY-receptor ligands is a direction of research which would be helpful to better understand the relationship between central release of NPY and asthma and the underlying mechanisms.

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Notes

The authors declare no competing financial interest.

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