ORIGINAL ARTICLE

Psychological Factors in Asthma

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Asthma has long been considered a condition in which psychological factors have a role. As in many illnesses, psychological variables may affect outcome in asthma via their effects on treatment adherence and symptom reporting. Emerging evidence suggests that the relation between asthma and psychological factors may be more complex than that, however. Central cognitive processes may influence not only the interpretation of asthma symptoms but also the manifestation of measurable changes in immune and physiologic markers of asthma. Furthermore, asthma and major depressive disorder share several risk factors and have similar patterns of dysregulation in key biologic systems, including the neuroendocrine stress response, cytokines, and neuropeptides. Despite the evidence that depression is common in people with asthma and exerts a negative impact on outcome, few treatment studies have examined whether improving symptoms of depression do, in fact, result in better control of asthma symptoms or improved quality of life in patients with asthma.

Key words: *asthma, depression, pathophysiology, treatment*

Psychological factors may influence the symptoms and management of asthma, and numerous pathways may contribute to the links between asthma and psychiatric disease states such as depression. The notion that emotional stress can precipitate or exacerbate acute and chronic asthma[1] has been recognized anecdotally for many years. Psychological barriers, such as faulty symptom attribution, adoption or rejection of the sick role, and low self-esteem, may negatively impact treatment adherence. Conversely, the presence of a chronic and potentially life-threatening illness may exert enough stress that an anxiety or depressive disorder emerges in vulnerable patients. As a consequence, epidemiologic associations between major depressive disorder (MDD) and asthma might be apparent but not reflect a shared pathophysiologic vulnerability. Alternatively, there may be aspects of dysregulation in key biologic systems, such as the neuroendocrine stress response or cytokine system, that predispose people to both asthma and psychiatric illness independent of the psychological impact of one chronic illness on the other. More provocatively, perhaps, there may be components of central or peripheral nervous system dysfunction that predispose people to asthma or worsen the course of asthma independent of behavioural response style or the experience of illness-related stress or depression.

The purpose of this review is to summarize the disparate reports in the literature that point toward an association between asthma and psychological factors. The review has four primary components. The first briefly examines the evidence that psychological interventions can be beneficial in the treatment of asthma, ignoring whether the patients involved in the intervention have any a priori evidence of psychological distress or impaired psychosocial function. The second part of the review addresses the limited literature on whether the presence of psychiatric illness, primarily major depression or an anxiety disorder (AD), has a negative impact on asthma outcome and whether treatment of the psychiatric condition improves these outcomes and also considers the epidemiologic evidence of an association between asthma and depression. The third section considers the multiple biologic factors that could contribute to a shared vulnerability for depression and asthma as several key systems share patterns of dysregulation across these illnesses. Finally, we discuss a nascent literature examining the central nervous system (CNS) correlates of an asthmatic response.

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Psychological Interventions Aimed at Improving Adherence and Asthma Control

A number of studies have examined the efficacy of psychological therapies at improving various aspects of asthma control or quality of life. These studies have been reviewed for both adults[2] and children[3,4] and are not discussed in detail here. Because psychotherapy models can be grouped according to their theoretical frameworks or methods of operation, the various approaches are briefly discussed below:

1. Behavioural therapies focus on identifying the processes by which behaviour has been learned via association, reward, or observation and modifying behaviour using methods such as systematic desensitization, selective reinforcement, and positive modeling. The behaviour itself, rather than the underlying motivations, is the focus of behavioural interventions. Dahl found positive results following behavioural therapy when school absenteeism and use of as-needed medications were the outcome measures.[5]
2. Cognitive therapies focus on identification and constructive management of incorrect and damaging thoughts, such as perceptions of helplessness or inappropriate fear of asthma attack, that can trigger episodes. Information (eg, about the relationships between anxiety and bronchoconstriction) also targets cognitions.
3. Cognitive behaviour therapy (CBT) incorporates the key elements of both behavioural and cognitive models and is currently used more frequently than either cognitive or behavioural therapies alone. Two studies measuring asthma knowledge as an outcome reported benefits of CBT,[6,7] and CBT has been reported to have a positive effect on self-efficacy measures.
4. Relaxation techniques are generally conducted with or without biofeedback and were the focus of several earlier studies of psychological interventions in asthma. Relaxation techniques control stress and anxiety, which, in asthma, may improve breathing and respiratory function. Such programs generally include progressive relaxation, autogenic training, which focuses on attending to bodily feelings and mentally controlling them, and hypnosis or deep relaxation, which may be induced using mental imagery. This is often accompanied by autosuggestion to create positive thoughts and feedback of biologic indicators, which the subject must control via relaxation. Alexander and Weingarten measured the effect of relaxation therapy on peak expiratory flow and found effects favouring the treatment group compared with the control group.[8,9] In addition, self-hypnosis-assisted relaxation reduced emergency room visits, again in a single study that also found that self-reports of asthma improved in the self-hypnosis group.[10] In contrast, hospital admission rates were not decreased following biofeedback,[11,12] nor were self-hypnosis rates or use of as-needed medications,[13] but emergency room visits were in a single study.[11] The results from these studies highlight the variability in outcome measures employed and the difficulty of understanding these studies in a systematic manner given this variability.
5. Psychodynamic psychotherapies attempt to uncover the emotional issues and response styles that drive patients to behave in maladaptive ways. Controlled trials of dynamic therapy are infrequent, and there is little evidence that they are likely to be of utility in a significant number of patients with asthma.
6. Counseling involves talking over problems with a health professional. In supportive counseling, the counselor acts primarily as a good listener who provides emotional support. Supportive therapy sometimes has a problem-solving focus and may be helpful for patients experiencing an acute crisis.
7. Family therapy attempts to understand family dynamics. Gustafsson and colleagues concluded that dysfunctional family interaction seems to be the result rather than the cause of wheezing in children.[14] There is evidence that family therapy may improve symptoms in children with asthma.
8. Educational approaches do not attempt to alter core psychological processes and therefore are not psychological therapies as such. They are already the subject of systematic reviews[15] and are routinely included as necessary components of optimal asthma care.
9. Breathing retraining exercises include a range of techniques for improving breathing control in asthma (eg, Buteyko technique, yoga, and transcendental meditation). These are not regarded as standard psychotherapies, although aspects of breathing retraining may be included in behavioural therapy or CBT. A Cochrane review[16] has previously examined the effectiveness of breathing retraining exercises, suggesting that conclusions must be viewed with caution.

Despite the trials of various psychological approaches in asthma, there are no sufficiently powered studies of any single therapy to draw conclusions regarding the utility of these approaches for improving asthma-related outcome. The systematic review that examined the efficacy of psychological treatments in children with asthma included

12 studies that met inclusion criteria, but the studies were small and the quality was poor. The authors stated that they could draw no conclusions regarding the effectiveness of psychological interventions for children with asthma because of the limited literature and variability among extant studies. Thus, in the aggregate, the benefit of psychological interventions for children and adults with asthma is difficult to assess because of the diversity of techniques used, the variety of outcomes measured, and the absence of appropriately powered trials.

A key issue apparent from these studies is how to select patients with asthma for psychological intervention. It may be that a randomized controlled trial that includes any patient with asthma who is willing to participate is not the most appropriate design as it is roughly analogous to including normal-weight people in a weight loss trial for obesity. Trials in which the population is enriched to have psychosocial distress or stress may more precisely reflect patients who are able to benefit, by virtue of having significant room for improvement, in the way in which they understand the illness and themselves in relation to the illness. Similarly, patients with very mild and well-controlled asthma are unlikely to have much room for improvement following a psychological intervention. It is probable that there is nonrandom overlap between these two groups, so the patients with the worst asthma control will, with some frequency, be those with the worst psychological adjustment to the illness. Examining the benefit of psychological therapies in this group might yield a stronger signal than in many previous trials. Furthermore, access to good psychological therapy is generally limited by therapist availability; therefore, such treatment arguably will be reserved in the clinical setting for patients with the most distress and the most to benefit from intervention. In summary, it is unfortunately possible that there is a reasonably sized subset of patients with poor asthma control related to poor psychological coping but that effective interventions for these people are not being routinely received or even offered because the trials to date do not allow conclusions to be made with any confidence.

Relationships between Asthma and Psychiatric Illness

Epidemiologic Associations between Asthma and Depression

The prevalence of MDD is higher in people with asthma relative to the general population. Individuals with allergic disease also have higher rates of MDD than nonatopic individuals.[17,18] The presence of atopic disease increases the risk of depression in both men and women, although a more substantial body of evidence exists for the latter,[19] in whom the prevalence of MDD is generally higher. Patients with MDD or the other common mood disorder, bipolar affective disorder, also have an increased risk of developing immunoglobulin (Ig)E-mediated allergic conditions, including asthma, than the general population.[20–22] Asthma and hay fever also occur more frequently in patients with mood disorders and their family members than in those with schizophrenia.[23]

Unfortunately, the literature on the prevalence of psychiatric disorders in patients with asthma is complicated by a number of issues, not the least of which is the problem of accurately defining and detecting cases of both disorders. There is significant variation in the rates of MDD in patients with asthma that appears in part secondary to ascertainment issues. Population-based studies have not reported rates of comorbidity as high as studies that evaluated depression in a clinical cohort of patients with asthma, for whom lifetime rates of asthma have been recorded to be as high as 47%.[24,25] This may represent an accurate reflection of the asthma population as it is possible that the overall rates of psychiatric illness in those with mild and well-controlled asthma are low, with elevated rates observed in patients surveyed in tertiary care clinical settings who are likely to have more severe and chronic asthma. Regardless, the fact that individuals with asthma manifest higher rates of MDD and vice versa suggests that the two conditions may have shared pathogenic elements.

Familial Associations between Asthma and Depression

Further support for a link between asthma and MDD comes from family studies that suggest that the prevalence of one disorder is increased in the family members of index cases with the other. The initial evidence for this link came from mothers whose children had asthma but did not have MDD.[26,27] In some studies, rates of depression in family members were related to the severity of the child's asthma symptoms, raising the possibility that these were related to the stress of having an ill child.[28,29] Wamboldt and colleagues reported that mood but not ADs were increased in the relatives of adolescents with severe asthma and that the onset of these problems was equally likely to have occurred before as after the proband's asthma diagnosis.[30] More recent studies provide further proof that the prevalence of mood disorders is increased in the parents of children with asthma[31] even when childhood mental illness is considered.[32]

Evidence supporting a genetic link between asthma and depression comes from Wamboldt and colleagues' study of Finnish twin pairs in which they assessed the prevalence of atopic disease and depressive symptomatology.[33] They found a within-person correlation between atopic and depressive symptoms of 0.103 and, using a best-fit model, estimated that 64% of this association was due to shared familial vulnerability, mainly additive genetic factors.

Common Environmental Risk Factors for Asthma and Depression

Obesity

Obesity generates a systemic inflammatory milieu[34] that increases the risk of numerous somatic conditions, including both asthma[35] and MDD. Epidemiologic studies suggest that there is an increased prevalence of asthma in obese adults, that this relationship is dose dependent, and that the link is stronger in women.[36] This association may reflect the direct mechanical effects of obesity,[37] immune system alterations,[38] or the effect of hormones such as leptin[39] imposed by excess weight.

Obese individuals also appear to be at increased risk of developing MDD.[40] The etiology of this seemingly bidirectional relationship is unknown but likely involves genetic and environmental influences, including the psychological experience of being overweight, as well as alterations in various hormones and cytokines. Although iatrogenic and clinical disease factors are most often implicated, it is possible that MDD and obesity share common pathogenic factors,[41] including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis,[42] neurotransmitter systems,[43,44] and/or immune function.[45,46]

Smoking during Pregnancy

Maternal smoking during pregnancy has been proposed to increase the risk of both MDD[47] and asthma.[48] Adolescents exposed to cigarette smoking in utero have an increased risk of MDD prior to correcting for confounding and selection factors but not after this correction.[47,49] Smoking in pregnancy is also associated in epidemiologic studies with an increased risk of asthma in children, adolescents, and adults, even when confounding variables are controlled for.[48] Numerous mechanisms have been proposed to account for this relationship, including the effects of smoking on fetal respiratory system development,[50] lung cyclic adenosine monophosphate (cAMP) levels, and phosphodiesterase 4 (PDE_4) activity, which together may increase airway hyperresponsiveness.[51]

Interestingly, asthmatics who are currently smoking or who have smoked in the past are relatively resistant to the anti-inflammatory effects of glucocorticoids (GCs).[52,53] Smoking and the oxidative stress it produces can affect GC receptor nuclear translocation and nuclear cofactors.[54,55] Cases of severe GC-resistant asthma also manifest an increase in oxidative stress.[56] It is possible therefore that exposure to cigarette smoke in utero has similar effects on these pathways, increasing the risk of GC resistance and diseases associated with GC dysregulation later in life, including asthma and depression.

Asthma and Anxiety

Katon and colleagues conducted a review of the literature on the relationships between asthma and anxiety in children, adolescents, and adults.[57] They concluded that up to one-third of children and adolescents may meet the criteria for a comorbid AD. The rates of AD in adults with asthma ranged from 6 to 24%, although the studies had many of the same limitations as the studies of depression and asthma, including issues with small samples, ascertainment biases, and questionable methods of confirming the diagnosis of asthma or AD.

A study examined not only the rates of depression and anxiety in adolescents but also the likelihood that the comorbid psychiatric condition was recognized and treated.[58] Only about one-third of youth with anxiety had the condition recognized within the last year, and only about one in five youth with MDD had adequate treatment. A commentary accompanying this article concluded that the methods used by Katon and colleagues were probably conservative in the estimates of rates receiving treatment, so the actual rates of treatment of MDD or anxiety in youth with asthma may be even lower than 20%.[59] Thus, there appears to be a significant dissociation between studies that, despite limitations, suggest that anxiety and MDD occur frequently in asthma and studies that suggest that in routine clinical practice comorbid psychiatric conditions are infrequently recognized in patients with asthma and even less frequently treated.

Treatment of Psychiatric Symptoms to Improve Asthma and Health-Related Quality of Life

Pharmacologic Treatment

There is a notable paucity of data examining whether treating MDD in people with asthma will improve asthma

outcome. Brown and colleagues randomized 90 patients with asthma and an episode of depression to citalopram, a commonly used antidepressant, or placebo.[60] The impact of this intervention on asthma symptoms was difficult to evaluate between antidepressant- and placebo-treated patients because at end point there was no difference in depression scores between antidepressant- and placebo-treated patients. Nonetheless, antidepressant-treated patients required fewer oral corticosteroids and there was a correlation between asthma symptom severity and depression symptoms. Perhaps the most interesting result in the study was the fact that patients who had substantial improvement in depressive symptoms (regardless of whether they were medication or placebo treated) had greater improvement in a variety of asthma-related scales than patients whose depressive symptoms did not improve significantly. These results do, therefore, support the notion that treating depressive symptoms may improve outcome in patients with asthma.

To our knowledge, only one other trial, conducted several decades ago, has evaluated the impact of antidepressant treatment on asthma outcome. In 1969, Sanger examined whether the antidepressants amitriptyline and doxepin improved depressive and anxiety symptoms in patients with allergic diseases, including some patients with asthma.[61] Doxepin appeared to have a more potent effect than amitriptyline because the particularly potent antihistaminergic properties of doxepin are not known.

Behavioural Treatment

We were unable to find any studies that had focused specifically on using psychological treatment for MDD in patients with asthma. Given that there are time-limited psychotherapies that are acceptable to patients, safe and effective treatments for MDD, it is unfortunate that no information exists on whether use of such therapies would improve asthma as well as depressive symptoms. A recent trial examined the benefit of CBT for patients with somatization disorder, in which patients have a preoccupation with physical symptoms that are disproportionate to any identifiable pathophysiologic process.[62] CBT was effective in this study, and the gains were maintained so that at follow-up months after treatment finished, there was evidence that patients were accessing medical resources less often than those who had not received CBT. These results provide indirect evidence to suggest that patients whose limitations associated with asthma appear greater than that predicted by the physical severity of the illness might benefit from CBT.

Pathophysiologic Links between Asthma and Depression

Stress and GC Resistance

The experience of significant stress early in life is a risk factor for the development of both MDD and asthma and, via GC resistance, may represent the most important link between the two conditions. A subset of patients who are exposed to psychological/emotional stress early in life have subtle dysregulation of the sympathetic and parasympathetic nervous systems and the HPA axis, including GC resistance, which bias the immune system toward a T helper (Th)2 response,[63,64] immune system hyperactivity, and inflammation. It is possible that increased inflammation brings out a latent genetic risk for both asthma and depression, with the former having either a lower threshold for expression or with developmental factors interacting with inflammation to produce asthma. Depression, which, compared with asthma, is uncommon in prepubertal children, may have a higher threshold for symptom expression, requiring an increased duration of exposure or higher levels of GC resistance.

Immune development may also be influenced by prenatal imprinting or programming.[65,66] Stress in utero not only results in the overexpression of cortisol in the mother but also stimulates secretion of corticotropin-releasing hormone (CRH) by the placenta. Such exposure appears to alter humoral immune responses and individuals' sensitivity to stress in postnatal life.[67] Postnatal stress has also been implicated in the development and exacerbation of asthma.[68] Parenting difficulties when a child is 3 weeks old were a predictor of early-onset childhood asthma in those predisposed to the disorder.[69] Other studies suggested that parenting difficulties,[70] but not family stress,[71] are associated with asthma.

GCs effectively suppress asthma symptoms in most people; however, a small number of patients fail to respond to exogenous steroids, even when they are given high doses.[72] Although GC-resistant patients exist on a spectrum, they have significant illness burden and present significant management challenges. They have usually had asthma longer than the average patient and manifest irreversible airflow obstruction and a greater inflammatory burden.[73] GC signaling defects are also present in depressed patients.[74] Nearly 50% of persons with depression have elevated cortisol levels,[75] with higher rates of

dexamethasone nonsuppression in those with psychotic depression[76] and a higher number of lifetime depressive episodes.[77] Cortisol and CRH levels in cerebrospinal fluid (CSF) are increased in depressed patients,[78,79] especially dexamethasone nonsuppressors.[80] Somatic treatments such as electroconvulsive therapy and medications normalize elevated CRH levels.[81,82]

Resistance to GCs may occur as a result of a number of factors, with long-term exposure to inflammatory cytokines often proposed as a key factor. The mechanisms through which this occurs may involve mitogen-activated protein kinase (MAPK), nuclear factor κB (NF-κB), and cyclooxygenase (COX) pathways (see Pace and colleagues for a review[83]). Stressful experiences may cause the developing autonomic nervous system (ANS) to be more labile, which can evolve into emotionally triggered asthma symptoms.[30]

Cytokines

Cytokines affect inflammatory responses, and the processes they govern are implicated in the pathophysiology of many diseases, including those with CNS manifestations. Peripheral cytokines increase glial cell release of cytokines in the brain via the vagus and glossopharyngeal nerves rather than acting directly on the brain themselves.[84] The intersection of the cytokine and HPA systems is mechanistically relevant to the development of both asthma and MDD.

Depression is characterized by immune activation, particularly the innate immune system.[85] Sickness behaviour, the emotional and behavioural symptoms that develop as a consequence of acute infection or cytokine therapy, appears to be the result of increased levels of the proinflammatory cytokines interleukin (IL)-1 and tumour necrosis factor (TNF) and is the most frequently cited evidence linking cytokine activation with depression. Vital to the development of sickness behaviour is the enzyme indoleamine-2,3-dioxygenase (IDO), which is increased in interferon (IFN)-treated patients who become depressed and degrades tryptophan into the neurotoxic metabolites quinolinic acid and 3-hydroxykyurenine, which cross the blood-brain barrier and bind glutamate receptors. IDO appears to affect brain monoamine neurotransmission, and this may be the mechanism by which it affects mood.[86] Proinflammatory cytokines may also induce tissue resistance to GCs by inhibitory effects on the expression or function of GC receptors, which might contribute to CRH release secondary to reduced feedback inhibition as well as an increase in cytokine release.[87]

A number of cytokines are dysregulated in patients with MDD, including IL-6,[88] which participates in the transition from innate to acquired immunity and in the polarization of immune responses from a Th1 to a Th2 type,[89] which is also of relevance to asthma development. IL-1β appears to be increased in those with asthma[90,91] and depression[88] and in those with depression and asthma.[92] Through IL-5, it results in increased production of intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule 1 (VCAM-1) by endothelial cells (see below).[93] IL-1β alters behaviour in rodents, inducing anorexia, sleep disturbances, and memory impairment; it also alters monoamine and neuropeptide neurotransmitter metabolism.[94]

High levels of TNF can exacerbate inflammatory and pro-oxidative functions.[95] TNF levels are increased in those with MDD[88,96] and are associated with asthmatic complications. TNF acts preferentially on smooth muscle cells in airways, resulting in damage to bronchial epithelial cells as well as leakage of these and endothelial cells.[97] TNF protein and gene expression levels appear to be increased in the bronchoalveolar lavage fluid of asthmatics,[98] and the TNF receptor–IgG1Fc fusion protein appears to improve lung function in these patients.[99]

Thus, despite the complexity of elucidating the role of the cytokine system in either depression or asthma, there is substantive evidence that the diseases share dysregulation of some key cytokines. Whether this overlap reflects a specific relationship or simply common states of inflammatory processes remains to be clarified. Unfortunately, the same dilemma is relevant to most of the systems discussed below.

Immune System Imbalance: Type 1 Th1 versus Th2 Phenotypes

Some propose that a reduction in exposure to microbes is responsible for the increasing prevalence of asthma as a lack of exposure may lead to a polarization of the allergen specific T-cell response toward Th2 instead of Th1 immunity.[100] IL-4 is particularly important in that it regulates IgE isotype switching, VCAM-1 production and Th cell commitment, and allergen-induced eosinophilia in asthmatics.[101,102] IL-5 plays an important role in eosinophil differentiation and survival. IL-13 is involved in airway hyperresponsiveness in these individuals.[100]

The role of Th1-Th2 cytokine balance has, not surprisingly, been much less extensively investigated in those with MDD. Although numerous studies have examined plasma cytokine and immune cell levels in those

with depression, few have examined the balance between Th1 and Th2 cytokines in this population. Pavon and colleagues examined the serum levels of cortisol as well as Th1 (IL-2 and IFN-γ) and Th2 (IL-4 and IL-13) cytokines in 33 unmedicated outpatients with MDD and compared them with 33 nondepressed controls.[103] In this study, the depressed patients appeared to have a preference for Th2 immune responses. Given that cortisol was also elevated in this sample, and given the propensity for cortisol to increase Th2 activity,[104] it may be that the immune shift to a Th2 response was driven by altered activity in the HPA axis. Mendlovic and colleagues also demonstrated a predilection for a Th2-like profile of cytokine secretion from the T cells of a small sample of depressed patients compared with controls.[105]

Nuclear Factor κB

NF-κB is a major transcription factor that is induced by a large number of factors, including proinflammatory cytokines and other mediators of stress, and plays a role in the development of immunity. Dysregulation, including aberrant activation of the NF-κB pathway, is seen in numerous diseases, including asthma and MDD.[106]

NF-κB exists in the cytoplasm of cells in an inactive form bound to its inhibitor IκB. When proinflammatory cytokines such as TNF bind their receptors, it results in NF-κB translocation to the nucleus, which promotes gene expression. It has been hypothesized that activation of this pathway is relevant to the pathophysiology of MDD since certain cytokines appear to contribute to the development of depression in some individuals (see above) and since serotonin-containing neurons, long implicated in the development of depression, also contain NF-κB. One group has hypothesized that cytokines' activation of NF-κB leads to depression via increases in *5HT1A* gene expression, which result in decreased firing of serotonin neurons and serotoninergic neurotransmission.[107]

Asthma is also characterized by abnormal activation of cytokines and adhesion molecules and is triggered by a number of environmental agents, many of which result in NF-κB activation. NF-κB appears to have an important role in allergic inflammation,[108] and inhaled GCs have demonstrated inhibitory effects on NF-κB.[109] It is possible, then, that a number of factors common to the pathophysiology of asthma and MDD, including alterations in the HPA axis and cytokine dysregulation, converge on NF-κB signaling, which may serve as a final common pathway contributing to the development of these disorders.

Oxidative Stress

Oxidative stress may be relevant to the pathogenesis of asthma.[110] The capacity of the body's natural antioxidant system appears reduced in those with asthma in times of disease stability,[111] as well as exacerbation.[112] Levels of oxidative stress are elevated not only locally in airways but also systemically,[113] and levels of oxidative stress markers appear to correlate with disease severity.[114] Increases in oxidative stress have also been implicated in shifting immune responses to a Th2 phenotype.[115]

Psychological stress may affect the body's capability to deal effectively with reactive oxygen species and increase oxidative stress.[116,117] MDD is associated with increased levels of reactive oxygen species,[118] and depressed people have evidence of excess oxidative damage,[119,120] independent of other causes of oxidative injury.[121] Those with multiple depressive episodes appear to incur more damage than those with fewer.[122]

Increased innate immune responses[123] and inflammation[124] are also associated with MDD and can increase oxidative stress and may contribute to or account for the above findings. Indeed, overstimulation of the enzyme IDO raises levels of metabolites of kynurenine and 3-hydroxykynurenine, which increase oxidative stress.[86] It is currently unknown whether oxidative stress contributes to or is an epiphenomenon of the pathogenesis of depression.[125]

Intracellular Adhesion Molecule 1

Intracellular adhesion molecule 1 (ICAM-1) is involved in the leukocyte adhesion, persistent inflammation, and cellular recruitment critical to the pathogenesis of asthma. ICAM-1 initiates intracellular signaling events and modulates the activation and proliferation of inflammatory cells as well as cytokine production,[126] leading to bronchial hyperresponsiveness and airway inflammation.[127] Increases in soluble ICAM-1 are apparent in asthma exacerbations[128] after allergen provocation[129] and correlate with asthma severity.[130]

ICAM-1 appears to be expressed in increased amounts in the brains and serum of depressed patients[131–134] and remains elevated even after adjustment for potential confounders.[135] It also appears that soluble ICAM-1 levels play a role in the development of depression in IFN-treated patients. Patients with malignant melanoma who developed depression on this treatment had higher soluble ICAM-1 levels than those who did not, and the levels correlated with depression severity. These results have been

interpreted as suggesting that increases in soluble ICAM-1 reflect the breakdown of the blood-brain barrier, which might then allow cytokines to enter and affect mood changes by modulating neurotransmission.[136]

Whether increased levels of soluble adhesion molecules are involved in the pathogenesis of MDD or merely reflect a state of persistent, low-grade inflammation is not known, but this may represent another link between depression and asthma. Alternatively, this finding may be related to a primary immune dysfunction with increased cytokines and HPA axis abnormalities, which increased levels of soluble ICAM may reflect.

Prostaglandins and COX-2

COX-2 and its metabolites exert complex effects in the lung as some act as pro- and others as anti-inflammatory mediators.[137] COX-2 gene expression is increased in asthmatic patients' airways; however, increased COX-2 activity suppresses the asthmatic response. That prostaglandin (PG) levels appear to be increased in those with depression suggests that COX-2 activity is increased in these individuals as well. Unlike most tissues, COX-2 is constitutively expressed in the brain[138] and interacts with immune and neurotransmitter systems there. COX-2 may exert its effects by increasing PGE_2 levels to stimulate IL-6 production. These findings may account for why treatment with COX-2 inhibitors has been associated in a few studies with reduced depressive symptomatology.[139,140] Activation of COX-2 increases PGE_2 concentrations, which can stimulate the HPA axis. The COX pathway also appears to interact with GC signaling and may modulate GC receptor responses. Thus, it is possible that COX-2 exerts its influence on affect via this mechanism.[83]

PGs may also be involved in the pathogenesis of asthma[141] and MDD. They are produced by almost all cell types and participate in the inflammatory cascade that occurs in airways.[142] PGs D_2, E_2, and F_2 have a variety of effects on airway physiology, including polarizing immune cells to a Th2 phenotype, attracting immune cells, stimulating proinflammatory cytokines, increasing mucus production and vascular leakage, and causing constriction of bronchial smooth muscle.[142]

PGE_2 is increased in the CSF,[143] serum,[144] and saliva[145] of patients with MDD and correlates with the severity of depression.[146] Mastocytosis, a disorder in which there is overproduction of PGD_2, often manifests depressive symptomatology,[147] and PGs influence behaviour,[148] sleep,[149] and appetite.[150] PGE_2 also appears to have a direct effect on the promotion of sickness behaviour.[151]

Phosphodiesterase 4

PDE_4 is found in a number of cell types, including neurons and immune and airway cells. Both asthma and MDD may involve overactivity of PDE_4.[152] For example, the main gene involved in mucin secretion, *MUC5AC*, is overexpressed in those with asthma,[153] and PDE_4 inhibition may ameliorate this. Rolipram, a PDE_4 inhibitor, inhibits neutrophilic and eosinophilic inflammation and the release of cytokines from Th1 and Th2 cells, as well as airway epithelium, basophils, monocytes, and macrophages.[154] Also of relevance to asthma is the fact that PDE_4 inhibitors reduce fibrosis and remodeling in the airway via inhibition of certain matrix metalloproteinases (MMPs). Clinically, PDE_4 inhibitors reduce early and late inflammatory response to allergens in mild to moderate asthmatics and may produce small improvements in forced expiratory volume in 1 second in asthmatics.[155]

Second-messenger impairments affecting cell survival and neuroplasticity are also believed to underlie MDD,[156] and cAMP-mediated signaling is implicated in the pathophysiology of MDD.[7] PDE_4 is expressed in neurons in the hippocampus, striatum, substantia nigra, and cerebral cortex, as well as in astrocytes and, of relevance to depression, in the areas of the brain that are involved in reward and affect.[157] PDE_4 also participates in cAMP pathways affected by known antidepressants.[158] Rolipram, a PDE_4 inhibitor, has antidepressant-like effects in preclinical animal models and plays a role in induction of hippocampal neurogenesis,[159] which may be necessary for antidepressants to effect behavioural change.[160] Moreover, reduced expression of PDE_4 appears to protect mice against depressive symptomatology.[161]

Matrix Metalloproteinases

MMPs are proteolytic enzymes that degrade extracellular matrix components.[162] The production and function of MMPs are regulated by molecules such as the tissue inhibitors of matrix metalloproteinases (TIMPs), cytokines (eg, TNF, IL-1β), and growth factors. It is speculated that cytokines and MMPs interact in complex ways as a means of producing some of the symptoms of asthma.[163]

MMPs may participate in airway remodeling, and increased levels of MMP-9 have been detected in asthma, related to elevated numbers of neutrophils and eosinophils in the airways[162] and correlated with asthma severity. In mouse models of asthma, MMP-9 absence is associated with a decrease in airway infiltration by inflammatory cells,[164] perhaps by decreasing dendritic cell migration.[165]

A number of MMPs are not detectable in nonpathologic CNS states but are found in diseases of the CNS.[166] Certain MMPs can convert TNF and IL-6 to their active forms, a mechanism by which MMPs might promote an inflammatory milieu in the CNS.[167] Psychological stress, mediated by activation of the HPA and sympathetic-adrenal medullary axes, as well as cytokine alterations, affect MMP and TIMP levels.[168]

Histaminergic System

Histamine is made and released by inflammatory cells and neurons and participates in the regulation of inflammatory responses in several conditions, including asthma. Histamine enhances secretion of proinflammatory cytokines, including IL-1α and -1β, IL-6, and a number of chemokines.[169] Histamine acts as a chemoattractant for eosinophils and mast cells and is released from mast cells during allergic reactions. Moreover, it appears to shift the immune response to Th2 dominance.[170] Histamine exposure causes bronchoconstriction in all humans, although asthmatics are more sensitive to this effect than nonasthmatics, and treatment with H_1 receptor antagonists has been shown to improve symptoms and pulmonary function and may delay asthma onset in high-risk individuals.[171–173]

Histamine also acts as a neurotransmitter in the brain and has been proposed to be involved in the pathogenesis of depression[174] as histamine type 3 receptor blockers may have antidepressant effects.[175] Alterations in histaminergic activity may also contribute to the experience of mental and physical fatigue experienced by depressed patients.[25,176]

Adenosine

Adenosine is an endogenous nucleoside present at low levels under normal conditions; however, its concentrations increase in the setting of stress and inflammation.[177] Adenosine has proinflammatory and immunomodulatory effects and may be involved in the pathogenesis of asthma.[178–180]

Increased adenosine levels may result in depressive symptoms. The involvement of adenosine in the pathophysiology of mood disorders was first proposed when increases in endogenous adenosine levels led to behaviour consistent with learned helplessness and behavioural despair in laboratory animals.[181,182] Antagonists to adenosine receptors, particularly A_{2A} antagonists, appear to have antidepressant properties,[183] which may be mediated by increases in dopaminergic transmission in the frontal cortex.[184]

Nitric Oxide

Nitric oxide (NO) is the only molecule in the body that acts as a hormone, reactive oxygen species, and neurotransmitter. The neurotransmitter and vasodilatory actions of NO are mediated mainly by guanylate cyclase activation in cells, which leads to an increase in the production of cyclic guanosine monophosphate and its dependent kinases.[185] Some evidence suggests that NO may be involved in the pathogenesis of asthma.[186] Evidence supports the role of NO in the pathogenesis of depression and in a number of the symptoms of this syndrome, including cognitive difficulties, sleep, and alterations in appetite.[185,187] In the brain, neuronal nitric oxide synthase (NOS) produces NO after activation of the *N*-methyl-D-aspartate receptor by glutamate[185] and acts as a modulator of the HPA axis.[188] Neuronal NOS production is also regulated by GCs in the hippocampus, suggesting that it has a role in the body's response to stress.[187] It appears to be colocalized with a number of neuropeptides in the hypothalamus, including arginine vasopressin, CRH, and oxytocin. Neurons in the prefrontal cortex, amygdala,[189] and the serotoninergic cells of the dorsal raphe nucleus also contain NOS.[190]

Neuropeptides

Many neuropeptides exist and have been implicated in the pathophysiology of inflammatory diseases, although we limit our discussion to those mediators that appear to be of relevance to both asthma and MDD. The airway is innervated not only by sympathetic and parasympathetic nerves but also by sensory nerves referred to as the noncholinergic-nonadrenergic that originate mainly from the vagal ganglia. Not surprisingly, a bidirectional relationship exists between the airway surface and the nerves that innervate it, and neuropeptides appear to mediate this relationship.[191]

Tachykinins are proinflammatory neuropeptides of which substance P (SP) and neurokinin A (NKA) are members. They regulate neurogenic inflammation in the airway.[192] SP binds NK1 receptors located mainly in the airway epithelium, submucosal glands, and vessels, whereas NKA binds NK2 receptors found predominantly on smooth muscle cells.[193] NKA constricts airway smooth muscle cells with particularly potent effects in smaller airways, producing bronchoconstriction in asthmatics,[194]

and SP causes mucus secretion. When aerosolized, SP induces inflammation and hyperresponsiveness of airways.[195] Despite the theoretical appeal of blocking tachykinin receptors, human testing with antagonists has been met with mixed results.[191] However, this may be in part due to difficulties with drug delivery.

Neuropeptides function as neurotransmitters and neuromodulators and are involved in the regulation of emotion and responses to stress.[196] Thus, they have become attractive targets for manipulation with regard to mood disorders. Indeed, SP receptor antagonists have been demonstrated to possess antidepressant effects in double-blind randomized controlled trials. Antagonists to NK1, the main tachykinin receptor in the human brain, appear to have some antidepressant efficacy in treating humans with depression and anxiety.[197]

ANS (Parasympathetic Division)

Efferent parasympathetic fibres of the vagus regulate numerous functions, whereas afferent fibres (comprising 80% of the nerve) carry sensory information from the head, neck, abdomen, and chest. Messages are carried to the dorsal medullary complex, particularly the nucleus tractus solitarius, which relays information to other brain regions, including the locus ceruleus and raphe nucleus, as well as limbic, paralimbic, and cortical regions. The parabrachial nucleus also relays information to the hypothalamus, amygdala, and thalamus.[198]

Some have suggested that depression produces a state that favours airway constriction in those with asthma. Depression appears to be a state of cholinergic dominance and asthma a condition marked by cholinergic dysregulation.[199] This hypothesis is supported by evidence that shows that some antidepressants result in bronchodilation in laboratory animals.[200] In animals in which hopelessness is induced, cholinergic tone in the ANS increases.[201] Another study reported that children who died of asthma had states of hopelessness in the days preceding their deaths, postulated to have contributed to mortality via ANS dysregulation manifested as increased cholinergic/vagal activation in sad and hopeless individuals.[202] In 1997, Miller and Wood reported that higher levels of induced sadness were associated with greater vagal and presumably cholinergic activation, reflected by increased heart rate variability (HRV) and oxygen saturation variability than happiness in 24 children aged 7 to 18 years.[203] They suggested that this supported the theory that sadness could evoke autonomic patterns that could mediate airway constriction. This work supported previous findings of increased cholinergic/parasympathetic tone in those experiencing hopelessness/depression[201] and Miller and Wood's previously hypothesized model implicating mood-associated vagal mediation of pulmonary function.[203]

The increased reactivity of asthmatic patients' airways may be secondary to abnormal ANS control.[204] The parasympathetic/vagal component in particular appears to be relevant to asthma pathogenesis as it is involved in bronchoconstriction secondary to exercise and alterations in airway surface temperature. Asthma is related to abnormal ANS function, including both bronchial hyperreactivity to cholinergic drugs and reduced sensitivity to adrenergic dilators. Alterations in autonomic function have also been noted in asthmatics following exercise relative to nonasthmatic individuals. Enhanced cholinergic airway responsivity has also been postulated to contribute to the development of asthma.[205]

The literature examining HRV in patients with depression has been mixed, with some[206,207] but not all[208,209] studies suggesting that HRV is lower in depressed patients, in keeping with excessive sympathetic modulation of the heart rate or inadequate parasympathetic tone. Moreover, vagal nerve stimulation (VNS), an experimental treatment for depression in which the vagus is stimulated, sheds some doubt on whether excess parasympathetic stimulation contributes to depressive symptoms. There is some evidence, however, that VNS therapy may have effects on the airways of certain individuals.[210]

Thus, it is possible that frequent experience of the emotional states of sadness and hopelessness, common in those with MDD, may mediate, via increased cholinergic activity, an increased risk of asthma in some individuals, although it has been proposed that the enhanced cholinergic responses may be secondary to asthma rather than a pathogenetic contributor.

Risk of Treatment?

Little attention has been paid to the effects that treatments for either asthma or MDD have on the risk of development of the other. Serotonin has been controversially implicated in the pathophysiology of asthma, and patients with symptomatic asthma display increased plasma serotonin levels relative to asymptomatic individuals.[211] Serotoninergic receptors present in human airways, when activated, appear to stimulate IL-6 release in these cells.[212] Moreover, serotonin may have immunomodulatory effects.[213] Reports requiring replication suggested that

tianeptine, a selective serotonin reuptake enhancer, reduces respiratory symptoms in asthmatics.[214] Although it is therefore conceivable that selective serotonin reuptake inhibitors could trigger or worsen asthmatic symptoms via release of IL-6, there are no clinical data to support this. However, tianeptine also appears to have antidepressant effects and may modulate asthma symptoms via this mechanism.

The long-term treatment of asthma and not the experience of asthma itself may also contribute to the risk of developing depression in asthmatics. It has been suggested that corticosteroid treatment taken for a number of indications is associated with depressive symptoms,[215,216] although these results are limited by the fact that the indications and route of steroid treatment were not known. Thus, it is also possible that in a subset of patients with asthma, perhaps those treated recurrently with oral corticosteroids, that treatment contributes to or accounts for an increase in the rates of MDD seen in this population.

CNS Correlates of Asthma

It is increasingly accepted that psychological stress can modulate asthma symptoms.[217,218] There is anecdotal and empirical evidence that the stable variable of nonhypnotic suggestibility can determine the susceptibility of asthmatic patients to suggestion of bronchoconstriction, providing a construct for understanding how some, but not all, patients with asthma might be particularly influenced by asthma-related cues.[219] Until recently, however, there were no studies that directly imaged the brain during exposure to asthma-related stimuli.

In a seminal study, Rosenkranz and colleagues used functional magnetic resonance imaging (fMRI) to examine activity in the anterior cingulate cortex (ACC) and insula during exposure to asthma-related words when patients with asthma were exposed to allergen.[220] Although there was a small sample of patients, the results provide provocative evidence that these brain regions were hyperresponsive to asthma-related emotional cues and afferent physiologic signals. The ACC receives input regarding key physical symptoms (eg, shortness of breath) of relevance to asthma (for an extensive review of the ACC, see Devinsky and colleagues[221]). Along with the insula, the ACC is also crucial for the processing of emotional stimuli and is implicated in the pathophysiology of MDD. Rosenkranz and colleagues contextualized their study by stating that ''despite the compelling support for a model integrating psychological and physiological factors in asthma, the brain has been largely absent from any discussion of its mechanistic underpinnings.''[220]

Capuron and colleagues also used fMRI in patients receiving IFN therapy and found that IFN-treated patients had activation of the dorsal ACC during a visuospatial task that was not present in control subjects.[222] Interestingly, IFN-treated patients performed well on the task but appeared to require more extensive involvement of the ACC than was necessary from control subjects. Although indirect, this study supports the hypothesis that the ACC may be important for understanding the interface of cognition, emotion, and peripheral inflammation. Furthermore, a study of patients with damage to the ACC found that they had impaired autonomic cardiovascular responses in response to mental stress.[223] Studies such as these, which integrate brain imaging with physiologic symptoms or inflammatory markers, are complex to undertake but represent extraordinary opportunities to reveal the role of the brain in modulating various components of the asthmatic response.

Conclusions

Studies of psychological intervention in patients with asthma are limited in their interpretation by the heterogeneity of patient samples, intervention technique, and outcome measures. It is possible that more focused trials of patients with measurable degrees of stress, depression, or psychosocial dysfunction would yield a more definitive answer regarding whether targeting psychological factors in at-risk patients can improve asthma outcome.

Asthma and stress-related psychiatric disorders share a number of environmental risk factors and pathophysiologic mechanisms. Perhaps the most persuasive of these is the early experience of stress and its effects on GC resistance as a vulnerability and prognostic factor for both depression and asthma. There are many physiologic points of intersection between asthma and MDD, however, and the specificity of these associations remains to be determined. Preliminary but promising studies are using functional imaging modalities to examine the CNS response to bronchoconstriction and allergen challenge. Further studies that also examine respiratory, immune, and neuronal responses to challenge may uncover relations between central and peripheral effects that clarify the relationships between cognitive and emotional events and asthma and point toward pharmacologic and nonpharmacologic strategies for improving the outcome of asthma.

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