Anxiety, depression, and asthma: New perspectives and approaches for psychoneuroimmunology research

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ABSTRACT

The field of psychoneuroimmunology has advanced the understanding of the relationship between immunology and mental health. More work can be done to advance the field by investigating the connection between internalizing disorders and persistent airway inflammation from asthma and air pollution exposure. Asthma is a prominent airway condition that affects about 10% of developing youth and 7.7% of adults in the United States. People who develop with asthma are at three times increased risk to develop internalizing disorders, namely anxiety and depression, compared to people who do not have asthma while developing. Interestingly, sex differences also exist in asthma prevalence and internalizing disorder development that differ based on age. Exposure to air pollution also is associated with increased asthma and internalizing disorder diagnoses. New perspectives of how chronic inflammation affects the brain could provide more understanding into internalizing disorder development. This review on how asthma and air pollution cause chronic airway inflammation details recent preclinical and clinical research that begins to highlight potential mechanisms that drive comorbidity with internalizing disorder symptoms. These findings provide a foundation for future studies to identify therapies that can simultaneously treat asthma and internalizing disorders, thus potentially decreasing mental health diagnoses in asthma patients.

1. Introduction

Internalizing conditions are characterized by inward-focused symptoms, including sadness, fear, and social withdrawal, and understanding of mechanisms underlying internalizing disorders, namely anxiety and mood disorders, has increased dramatically in recent years (Wilner et al., 2016). Overall in the United States, mental health conditions affect 20.6% of the adult population, and anxiety disorders and major depression affect 19.1% and 7.1% of adults, respectively (NIH Mental Health Information: Statistics, 2021). Lifetime risk was reported as 31% for developing any anxiety disorder and 21.4% for any mood disorder by age 75 years, and this was greater in females compared to males (Altemus, 2006; Costello et al., 2003; Jalnapurkar et al., 2018; Katon et al., 2007; Kessler et al., 2007; Strine et al., 2008). Brain regions (e.g. amygdala, hippocampus, prefrontal cortex) and neurotransmitters/proteins (e.g. serotonin, brain derived neurotrophic factor (BDNF), gamma-aminobutyric acid, glutamate) implicated in these types of disorders are becoming better understood, and their activation pathways are harnessed for treatment of mental health conditions (McEwen et al., 2012; Rieder et al., 2017; Spear, 2000). An important predictor of depression, anxiety, and other mental health conditions is respiratory function/problems (i.e. asthma, exposure to air pollution), and mental health research may well be served by understanding mechanisms specific to these precursors. (see Fig. 1)

Psychoneuroimmunology research broadly focuses on understanding the interaction of mental health and immunology. Specifically related to mental health, elevated cytokine levels have been associated with anxiety and depression disorders. For example, elevated interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and C reactive protein are more frequently observed in patients with anxiety compared to controls (Costello et al., 2019). Elevated circulating IFN-γ and interleukin (IL)-6 were observed in major depression disorder (MDD) compared to control subjects (Gabbay et al., 2009; Mitchell and Goldstein, 2014). Increased peripheral cytokine levels activate brain cells, including microglia and astrocytes, to promote cytokine production in the brain, leading to manifestation of mood disorder symptoms (Brites and Fernandes, 2015; Capuron and Miller, 2011). Gene and protein IL-1β, TNF-α, and IL-6 levels were elevated in prefrontal cortex samples from people with DSM-IV-diagnosed depression-related conditions who committed suicide compared to non-depressed patient samples (Pandey et al., 2012). Enlarged, hyperactive microglia in this and other emotion-related brain regions are associated with increased depression- and anxiety-like behavior in rodents, and sex differences exist in glial and mental...
measures that are highly specific to mental health symptoms. The purpose of this review is to highlight how chronic challenges to the immune system, specifically those associated with asthma and air pollution, cause lasting inflammation that can have specific mental health implications. Preclinical models and clinical research are only beginning to identify important connections between immune system and brain areas/pathsways associated with mental health conditions. This work serves as the foundation to improve treatment for patients affected by chronic immune and comorbid mental health conditions.

2. Asthma and air pollution: lung immunology and mental health relationship

Asthma affects ~10% of youth in the United States and ~36% of youth worldwide, making it the most common chronic health challenge that children and adolescents experience (Cinibami et al., 2012, 2015; Mattiuzzi and Lippi, 2020). Asthma can persist throughout life, and overall asthma prevalence as of 2018 in the United States was 8.9% (Zhou and Liu, 2020). Sex differences exist in asthma that differ by age, where asthma is more prevalent and experienced as worse disease in boys under 10 years of age but in girls at/after puberty and in adulthood (Flores et al., 2019; McCallister and Mastronarde, 2008; Skotheim et al., 1992). Lung inflammation is a hallmark characteristic of asthma. Dendritic cells in the airway stimulated by antigens promote a Th2 immune response featuring critical cytokines, including IL-4, IL-5, and IL-13, that promote recruitment of eosinophils, proliferation of mast cells, mucus buildup, and B cell class switching to immunoglobulin E (Burrows et al., 1989; Busse and Lemanske, 2001; Fujita et al., 2012; Gour and Wills-Karp, 2015; Holgate, 2008; Kips, 2001). Asthma has a distinct immunology that can lead to many outward symptoms, including bronchoconstriction, wheezing, and mucus production (Gordon, 2008). Such chronic immune activation and inflammatory symptoms experienced early in development can lead to perpetuating later-life health consequences.

Air pollution serves as a significant stressor for healthy living, can affect respiratory health, and is associated with elevations in cytokines and immune molecules. Individuals with greater exposure to air pollution demonstrated higher breath levels of TNF-α, leukotriene B₄, and nitrous oxide derivatives compared to those with lower exposure (Dauchet et al., 2018; Vossoughi et al., 2014). Air pollution exposure during early life was also associated with higher circulating IL-6 and IL-10 (Dauchet et al., 2018). Urban environments are detrimental for human health due to high exposure to air pollution among other health stressors, and as such, urbanization is a significant risk factor for asthma onset (e.g. odds ratio: 1.2, 95% CI: 1.04 to 1.5, p = 0.01) and worse asthma disease (Aligne et al., 2000; Beasley et al., 2015; Kurt et al., 2016; Theoharides et al., 2012; To et al., 2012). Interestingly, people living in urban environments are at greater odds to develop anxiety (21%) and mood disorders (39%) compared to people in rural environments (Poon et al., 2010). Thus, it is important to consider how external environmental factors like air pollution affect a person’s asthma, immunology, and mental health.

One important downstream co-morbidity observed after having childhood asthma is later-life anxiety and/or depression, with onset as early as adolescence. A recent meta-analysis indicated anxiety disorders were prevalent in almost 23% of adolescents with asthma, as compared to 7–8% prevalence in the general youth population (Dudeny et al., 2017; Gandour et al., 2019). Adolescents with asthma also had higher incidence and likelihood to develop major depression compared to controls (Chen et al., 2014). Other survey studies have indicated between 16.3 and 35% of participants met criteria for anxiety or depressive disorder diagnoses, and these conditions were more common in people with worse asthma symptoms (Katon et al., 2007; Richardson et al., 2006; Vila et al., 2000). Similar findings are indicated in rodent models of asthma, where mice or rats exposed to allergens later exhibited increased anxiety-like and depression-like behaviors (Caulfield et al., 2017, 2018;
Lewkowich et al., 2020; Tonelli et al., 2009). While research clearly shows a link between having asthma in early life and subsequent development of internalizing disorder symptoms, work has just begun to uncover potential driving mechanisms. A focus on this connection between asthma-related immunology and mental health would help fill this gap in the literature and help broaden the scope and depth of psycho-neuroimmunology research.

3. Preclinical models of asthma

Recent preclinical studies have begun to investigate broad mechanisms underlying the connection between asthma and anxiety. In one model, inflammation and bronchoconstriction were independently induced with chronic house dust mite (HDM) and methacholine (MCH) exposure, respectively, during development (Caulfield et al., 2017, 2018, 2021b). HDM exposure stimulated increased expression of genes associated with an acute inflammatory response (e.g. increases in IL-5, IL-1β mRNA). Increased airway inflammation, mucus, and T1J2 cytokine gene expression were also observed in adulthood three months after the end of HDM exposure, indicating a long-term inflammatory effect. Mice exposed to HDM demonstrated depressive-like behaviors three months after exposure, demonstrating a lasting effect on mental health paired with the persistent airway inflammation (Caulfield et al., 2017, 2018, 2021b).

After chronic exposure to MCH throughout development, mice demonstrated increased anxiety-like behaviors and increased corticosteroid production in adulthood, along with decreased brainstem serotonin transporter expression, increased hippocampal corticotropin releasing hormone (CRH) receptor 1 (Crhr1), and elevated hippocampal serotonin receptor 1α expression (Caulfield et al., 2017). Further, marginal increases in hippocampal microglial activation were observed in early adulthood following chronic MCH exposure (Caulfield et al., 2021b). Together, these results reveal that central nervous system changes, specifically related to serotonin- and CRH-signaling pathways, are implicated in the relationship between different asthma and internalizing disorder symptoms.

In another rodent study on broad immune effects related to post-traumatic stress disorder and panic disorder, adult male mice exposed to HDM did not show anxiety-like or depression-like behavior (elevated zero maze and forced swim test, respectively). However, exposure to HDM did produce increased freezing behavior in a contextual fear paradigm, global brain increases in IL-17 A-secreting cells, and elevated neuronal activation in emotion-associated brain regions (prefrontal cortex and basolateral amygdala) (Lewkowich et al., 2020). Another rodent study indicated that re-exposure to ovalbumin (OVA) caused increased anxiety-like behaviors in mice as well as increased activity in and greater activation of microglia and astrocytes in the amygdala and medial prefrontal cortex (Dehdar et al., 2019). Together, these findings indicate that peripheral immune challenges to stimulate allergic asthma symptoms also alter prefrontal cortex, hippocampus, and amygdala activity and immune cell activity in the brain. These are all potential pathways that may influence symptoms associated with anxiety and depression and set the stage for further investigation into underlying mechanisms.

Other preclinical research has been conducted to identify behavioral and brain changes associated with asthma therapy. Inhaled corticosteroids, a common class of medications for asthma, are used to control lung inflammation by reducing immune cells in the airway and preventing cytokine production and other factors that enhance inflammation (Barnes, 2010, 2017; Grim et al., 2001; Hossny et al., 2016). The two most common corticosteroids used are fluticasone propionate (FLU) and budesonide. In one study, mice were chronically exposed to HDM and FLU during development – a period that is analogous to when asthma is most prevalent in humans. FLU exposure led to reduced weight gain during development, elevated basal glucocorticoid concentrations in circulation, and reduced anxiety-like behavior in adulthood. Additionally, HPA function-associated gene expression in the hippocampus (CRH, Crhr1, and CRH receptor 2), circulating corticosterone, and anxiety-like behavior were associated with one another (Caulfield et al., 2021a).

Another study, which utilized OVA and budesonide in adolescent female mice, demonstrated that OVA exposure increased anxiety-like behavior, decreased dendritic length and number of spines on hippocampal pyramidal cells, and increased hippocampal BDNF expression. Budesonide reversed some anxiety-like behaviors and the number of dendritic spines, but it did not affect dendrite length in hippocampal neurons or BDNF expression (Zhuang et al., 2018). Overall, animal studies suggest that corticosteroid treatment during development may alleviate anxiety-related behavioral symptoms associated with allergic asthma but not associated hippocampal function. In humans, worse anxiety and depression symptoms have been reported in clinical asthma patients who are corticosteroid dependent, and asthma patients with depression suffer from worse asthma symptoms and increased emergency room visits (Almedani et al., 2013; Amelink et al., 2014). A better understanding of how inhaled corticosteroids affect mental health pathways in asthma could inform novel clinical therapies for patients that exhibit asthma and develop comorbid internalizing disorders.

4. Preclinical models of air pollution

Some rodent studies have investigated airway inflammation in the context of air pollution and its relation to anxiety and depression-like behaviors, and the results are informative and represent real-world human experiences. One study investigated the effects of exposure to traffic-related particulate matter in utero and during early development in male rat pups. Rats exposed to pollution particulates had decreased circulating IL-18 and vascular endothelial growth factor, increased anxiety-like behavior, and less developed neurons in the anterior cingulate and hippocampus (Nephew et al., 2020). Another study chronically exposed male mice to particulate matter for nine months beginning in adolescence, which resulted in increased depressive-like behaviors in the forced swim test and increased anxiety-like behavior on the open field test. Mice exposed to this particulate matter also demonstrated increased pro-inflammatory cytokine expression (TNF-α, IL-1β) and decreased neuronal spine density in the hippocampus (Fonken et al., 2011). Thus, these results provide further evidence toward the importance of understanding long-term effects of chronic immune activation on mental health measures. Research on young male and female mice aimed to determine how maternal stress and prenatal exposure to diesel exhaust pollution would affect mental health-related outcomes in the offspring. Male and female offspring differentially regulated IL-10 expression in the brain in utero (embryonic day 18), and only males exposed to pollution exhibited increased IL-10 in the brain in adulthood. Stress and pollution exposure together resulted in a synergistic increase in Tlr4 gene expression in the brain at postnatal day 30 and increased anxiety-like behavior in adulthood (Bolton et al., 2013). Thus, exposure to air pollution as an immune stressor can affect the brain and mental health-related outcomes, suggesting possible mechanisms to further explore to better understand how such immune challenges are driving behavior.

5. Clinical asthma and mental health connections

Clinical research on asthma patients has established a significant comorbidity with mental health conditions, especially in younger populations (Dudeney et al., 2017; Peters and Fritz, 2011). In recent years, studies have investigated brain areas that may play a mechanistic role in asthma and internalizing disorder comorbidity in humans using magnetic resonance imaging (MRI). For example, patients with asthma demonstrated abnormal structural connectivity in the bilateral frontal gyr, right-side temporal and parietal cortices, and limbic regions compared to healthy controls, suggesting altered emotion-related brain area function in patients with asthma (Gao et al., 2019). Activity in emotion-processing brain circuits (e.g. anterior insula) has also been associated with increased inflammation in asthma (Rosenkrantz et al., 2012). In one
study, patients with asthma were assessed to have high or low chronic life stress. Following the Trier Social Stress Test, those with low stress had increased glucose metabolism in the anterior insula and decreased glucose metabolism in the mid-cingulate cortex and higher levels of airway inflammation as measured by fraction of exhaled nitric oxide (FeNO) compared to high-stress patients. Additionally, worse asthma control was associated with worse internalizing disorder symptoms (anxiety and depression). Expression of IL-17 pathway cytokines in sputum may serve as markers for the relationship between psychological stress and asthma-related inflammation (Rosenkranz et al., 2016). In patients with asthma, smaller volume of pallidum was associated with increased anxiety in response to a stressor, whereas in controls the anxiety responses were associated with hippocampus and amygdala volume, suggesting that different regions are involved in anxiety pathology in asthma (Ritz et al., 2020). Further, among participants with asthma, those with depression demonstrated decreased homogeneity in the pallidum compared to that of participants without depression, and this was associated with worse and unusual asthma symptoms (Xiong et al., 2016). Together, these findings implicate critical limbic and emotion-related brain areas in the pathology of asthma that may serve as links to internalizing disorders. These studies suggest that these brain regions should be an area of focus for further research on asthma and mental health comorbidity. In addition, these areas could be targeted for improved treatment to prevent internalizing disorder development in people with asthma.

6. Conclusions and future directions

To better understand how different aspects of immunology are associated with mental health outcomes, utilizing preclinical models is vital and can allow for a more controlled setting to understand disease processes and highlight translational relevance to real-world conditions. These studies can inform clinical research by pointing to specific brain regions and pathways that may be the most important biological mechanisms underlying asthma-mental health comorbidity. Knowledge of underlying mechanisms will help optimize development of targeted therapies. Preclinical and clinical evidence suggests that asthma is associated with development of internalizing disorder symptoms, and broad pathways have been described that should be further investigated to elucidate specific mechanisms driving these connections. The future of psychoneuroimmunology can benefit from embracing these lines of study, highlighting relationships and uncovering mechanisms connecting mental health and chronic immune activation. Preclinical models are translationally relevant to the clinical world. Treatments can be designed that target specific immunological challenges and dysregulation. Further, once neural pathways are identified, specific treatments can be developed that may alleviate both asthma and internalizing disorder symptoms, potentially allowing for decreased rates of internalizing disorders and symptom development in these asthma patients. Finally, we must recognize that many health conditions do not present the same way in both males and females, and with this understanding, we can approach future research where both sexes are accounted for and that studies are designed with the power to examine sex differences in all analyses for the best clinical success.

Conflict of interest statement

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