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Cortisol response to acute stress in asthma: Moderation by depressive mood

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HIGHLIGHTS

- Cortisol responses to acute stress depended on depressive mood and asthma.
- Cortisol responses to acute stress were moderated by depressive mood in asthma.
- Cortisol response to acute stress was greater in asthmatics with depressive mood.

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ABSTRACT

Both individuals with asthma and depression show signs of a dysregulated hypothalamus-pituitary-adrenal axis. However, little is known about the cortisol response to stress in the context of co-occurring asthma and depressive mood. Thirty-nine individuals with asthma and 41 healthy controls underwent a combined speech and mental arithmetic stressor. During the course of the laboratory session, salivary cortisol was collected 5 times, with 1 sample at 0 min before the stressor and 4 samples at 0, 15, 30 and 45 min after the stressor. Depressive mood in the past week was assessed with the Hospital Anxiety and Depression Scale at the beginning of the session. Depressive symptoms moderated cortisol response to the acute stressor, but only among asthmatic patients. Higher depressive mood was associated with a significant increase in cortisol, whereas low depressive mood was associated with no cortisol response. In healthy participants, depressive mood had no substantial effect on cortisol response to the stressor. These findings suggest that depressive mood and chronic inflammatory diseases such as asthma can interact to augment cortisol response to stress.

1. Introduction

Research suggests that the hypothalamus-pituitary-adrenal (HPA) axis can be dysregulated in mental disorders and medical conditions. Adverse effects of elevated cortisol levels in depression have been linked to a range of conditions, including abdominal obesity, loss of bone density, hypertension, peptic ulcers, and diabetes [6]. Depression can also be associated with asthma, as studies have shown an elevated comorbidity of both conditions (e.g., [31,36,57]). However, the potential contribution of the HPA axis to this comorbidity has not been explored well. Given that airway inflammation is the hallmark of asthma and that corticosteroids are still the first line of treatment [22,41], knowledge about HPA axis activity in stress and depression could serve asthma management efforts well.

Hypoactivity of the HPA axis has been identified in several allergic disorders including asthma. Asthmatic children have been shown to have lower basal endogenous cortisol levels compared to healthy controls [4,35]. One study found that children with allergic asthma display a blunted cortisol response to an acute laboratory stressor (Trier Social Stress Test, a combination of free speech and mental arithmetics under evaluative pressure) compared to healthy controls [15]. Children and adults with allergic conditions other than asthma have also shown blunted cortisol responses exposed to this laboratory stressor [9,11–14,63]. It can be speculated that the use of corticosteriod medication in this population could explain the hypoactivity of the HPA axis, however, there is evidence that indicates that alterations in HPA axis are independent of medication use [15]. However, most of the studies involving asthma samples have focused on children and adolescents,

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and there is evidence that hypoactivity is more pronounced in allergic patients with more severe symptoms of allergy and acute exacerbations [9].

In contrast, evidence suggests that hyperactivity of the HPA axis is a central feature of depression [68]. This may be manifested in overall elevations of cortisol levels and flatter diurnal slopes [43]. For cortisol responses, studies have found a stronger cortisol response to acute stressors among women with chronic depression compared to healthy controls [28,69]. Similarly, women with remitted depression had heightened cortisol response to a laboratory stress challenge [30]. A number of reports with child and adolescent samples have also provided evidence for stronger cortisol elevations following psychological stress [19,26,39,40,49]. In addition, a stronger cortisol response to stress was also found in women with an elevated risk of developing depression (indicated by a short allele of the 5-HTTLPR gene; [23]). Other aspects of HPA-axis reactivity also indicate a tendency towards hyperactivity in depression. Men with current depression and a history of early life abuse showed stronger cortisol responses to dexamethasone [70]. A meta-analysis of 17 studies with children and adolescents with depression also found robust evidence for elevated cortisol responses to dexamethasone [38]. Interestingly, there is some evidence that elevated cortisol responses to dexamethasone can also predict the development of depression [67]. Another study found that participants with subclinical depressive personality traits had a greater cortisol response when exposed to reboxetine (a selective norepinephrine reuptake inhibitor; [29]).

However, findings on stress-responsiveness of the HPA axis are not fully consistent, with some studies showing similar unresponsiveness in depressed and non-depressed individuals [50], similar responses [65], or even hyporesponsiveness in depressed samples [17,40]. A meta-analysis including these earlier studies found some evidence for hyperresponsiveness, with studies that take place in the morning, involve older participants, and include more severe cases of depression being more likely to show hyporesponsiveness [7]. The severity-dependence was confirmed in a study with adolescents ([26], in interaction with childhood maltreatment) but age-dependence was reversed in a study with dysphoric children and adolescents (hyperresponsiveness in the latter group; [24]) It is important to note that the type of depression can also alter results, for example melancholic depression is related to hyperactive HPA axis and atypical depression is related to hypoactive HPA functioning [21]. Individuals with atypical depression unlike melancholic depression can experience positive affect when they experience a positive event [46].

The mechanism and consequences of a potential dysregulation of the HPA axis in depression or asthma have been subject to speculation. Exaggerated and prolonged secretion of cortisol to stress in depression may be due to a defective negative feedback to the HPA axis that normally guides recovery to normal cortisol levels after a stressor [68]. Dexamethasone usually leads to a decrease in cortisol release by activating the negative feedback to the anterior pituitary gland that results in reduced secretion of ACTH and ultimately diminished cortisol secretion [71]. Individuals with depression have also shown HPA axis hyperactivity in the form of elevations in corticotropin releasing hormone (CRH) levels in the cerebrospinal fluid and also display heightened CRH levels in the limbic region of the brain [20]. The same study also provided evidence that the administration of dexamethasone in patients did not result in the usual reduction in cortisol. It is possible that the chronic elevation in cortisol leads to a resistance to the anti-inflammatory effects of glucocorticoids and as such it has been associated with more pronounced immune activation or inflammation, specifically of cytokines IL-1 β and IL-6, which in turn are related to neurodegeneration [68]) Another cytokine involved in inflammatory responses, interferon alpha (IFN-α), can contribute to glucocorticoid resistance by impairing glucocorticoid receptor function [42] and is related to symptoms of sickness such as fatigue [16] in individuals with depression. Additionally, in-vitro studies have linked higher glucocorticoid levels to elevations in asthma-related cytokines [2,55]. Thus, higher stress-induced levels of cortisol could pose a risk factor for exacerbation in systemic and/or airway inflammation in asthma.

Although a relationship has been observed between allergy, asthma, and depression in the literature, links between these conditions have not been well elucidated [62]. To the best of our knowledge cortisol responses to acute stressors in individuals with comorbid asthma and depressive mood have not been previously examined. In addition, we sought to focus on cortisol responses to acute stressors in individuals with subclinical depressive mood. Understanding how smaller fluctuations in depressive mood are related to HPA functioning is important because such fluctuations may occur more frequently during the course of a life with asthma and are more common in the population in general. The literature cited above points to an importance of subclinical variations in depressive symptoms for HPA-axis reactivity to stress (e.g., [17,24,29]). We have also found that smaller variations in depressive mood are associated with stress-related changes in fraction of exhaled nitric oxide (FeNO) in asthma, a measure of airway inflammation [52,60].

The specific aim of the current study was to examine the moderating effect of depressive mood on cortisol responses to an acute laboratory stressor, the Trier Social Stress Test, in asthma. Based on the available literature the prediction of cortisol responses to stress for those who suffer from asthma and depression is not necessarily straightforward. We expected, on balance, that individuals with subclinical depressive mood would have greater elevations in cortisol following the stressor than those low in depressive mood. This may counteract possible hypoactivation of the HPA axis in asthma and make those patients appear more normal in responding. However, in mixed samples of allergic and nonallergic asthma patients that are well controlled, allergy-induced hypoactivation may be missing, which, in combination with depression, would then translate into the exaggerated cortisol secretion typically observed in nonasthmatic individuals.

2. Method

The data were collected as part of a larger study on stress reactivity in asthma. Here we analyze salivary cortisol in response to the laboratory stress protocol and examine the moderating effects of depressive mood. Approximately one half of the cortisol data analyzed here had been included in a previous publication that focused on the changes of exhaled nitric oxide to acute stress [51]. Analysis of moderation by depressive mood was not attempted in this earlier paper because of the difference in focus and the smaller sample size. Nitric oxide and depressive mood data from the expanded sample were subsequently analyzed and published [53], but cortisol data were dropped in response to suggestions of the reviewers that they would distract from the main theme of the paper.

2.1. Participants

Eighty participants, healthy controls ($n = 41$) and asthmatics ($n = 39$) were recruited from a private university in the Southwest of the US and its surrounding community through advertising by posters, flyers and internet sites. Participants in the asthma and healthy control groups were matched for gender and age. Asthmatic participants had a diagnosis of asthma from a physician, while healthy individuals had no asthma diagnosis. Exclusion criteria included current smoking (smoking in the past 6 months), severe psychopathology (including substance dependence, depression, and schizophrenia) assessed using screening questions from the Structured Clinical Interview for DSM-IV, health problems (cardiovascular conditions, lung disease, or chronic inflammatory conditions other than asthma), and corticosteriods in oral or injected form in the past 3 months. Oral or injected corticosteroids have systemic effects whereas inhaled corticosteroids have more of a