# Stress, cortisol and depression

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## Abstract

Evidence suggests that chronic stress affects the hypothalamic-pituitary-adrenal (HPA) axis and plays an important role in the pathogenesis of depression. In this short article we describe the link between chronic stress, HPA axis abnormalities, sleep disturbance, metabolic abnormalities and depression. We also discuss how hair cortisol measurements can be used as a biomarker of chronic stress. We suggest that hair cortisol measurements can also be used to monitor improvement as a result of treatments such as antidepressants and mindfulness.

## Introduction

The HPA axis is affected by both internal physiological stressors (e.g. cytokines, hypoxia, macromolecules) and by external stressors (e.g. source of anxiety, fear), which threaten homeostasis. Cortisol binds to cortisol receptors throughout the body. This hormone receptor complex is to be found in the nucleus of cells, where it binds to DNA (docking). The consequences of this bond vary considerably; depending on the type of cell, cortisol can induce some genes whilst suppressing others. In cases where the HPA axis is overactive, the amount of cortisol in the nucleus of the cells may increase by approximately tenfold. Mounting evidence suggests dysfunction of the HPA axis in major depression. It has been suggested that the assessment of the HPA axis activity may be a useful tool in clinical practice (1-4). Indeed, Nemeroff (1) has emphasised the opportunity for "early intervention in at-risk individuals" and suggests that those who have been exposed to untoward early life stress can be considered an "at-risk population".
Emerging evidence points to the usefulness of hair cortisol analysis as an indicator of sub-acute and chronic stress (5). This raises the question of whether it is worth exploring the potential use of hair cortisol levels prophylactically in primary care to assess HPA axis activity in individuals at risk. Could hair cortisol also be used to monitor the response to treatment of depression in clinical practice in an effort to provide more effective personalised care?

## Chronic stress and the HPA axis

Cortisol has an important role as a regulator and modulator of intermediate metabolism and the immune system. It influences the secretion of adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) via the hypothalamic-pituitary feedback system. The hormones CRH, ACTH and cortisol form a regulatory system with feedback inhibition in order to adjust the plasma cortisol level to the respective requirements. The activation of the HPA axis during stress affects all the systems in the body. Overall, the HPA axis presents a "common pathway".

The temporal lag between activation of the HPA axis in chronic stress and the onset of psychopathology is demonstrated by the time gap between the individual experiencing trauma or other severe stressors (e.g. significant losses, abuse, bullying, neglect) and the emergence of clinical symptoms. This, therefore, provides "a window of opportunity" for early detection of dysregulation, assessment and early intervention.

## Hair cortisol: a biomarker of chronic stress

Van Uum et al. (5) reported increasing use of hair cortisol levels in a variety of pathological situations, given that it can provide a long-term measure of systemic cortisol exposure. Dettenborn et al. (6) used hair cortisol analysis to rate levels of psychological stress. Individuals who had been unemployed for at least a year were compared with currently employed control subjects. Cortisol concentrations were significantly higher in the unemployed group.

## Chronic stress, HPA axis, depression and suicidality

A case control study by Agid et al. (7) showed that the rate of parental loss in the depressed patient group was 29.1%, in the bipolar group 17.7% and in the schizophrenia group 22.4%, compared to rates of 7.6 - 7.9% in the control subjects. The biological vulnerability seems to be mediated, at least in part, by persistent activation and hyper-responsiveness of the hypothalamic and extra-hypothalamic corticotrophin-releasing factor (CRF) circuits (8). Nemeroff et al. (1), in their pilot clinical study, also demonstrated that women with a history of child abuse, with or without major depression, presented with hyperactivity of the HPA axis in response to a social stressor (Trier Social Stress Test). Furthermore, an excess of cortisol, and dexamethasone suppression, have been reported for a long time in patients with mood disorder. Major depression is associated with dysfunction of the HPA axis, showing hyper-activation, and blunting of the normal diurnal cortisol profiles.

Aihara (9) found that in patients with major depressive disorder enhanced cortisol normalised after successful pharmacotherapy. The results indicated that depressed patients remitted with antidepressant medication, presenting resolution of HPA dysregulation and alteration of regional glucose metabolism in the prefrontal cortical, limbic and paralimbic areas. Jokinen et al. (2) explored the predictive value of the dexamethasone suppression test (DST) for suicide in a group of depressed patients with and without an index suicide attempt. They found that the non-suppressor status was significantly associated with suicide, indicating that HPA axis hyperactivity is a risk factor for suicide in this group.

## Early life stress

Evidence points to early life stresses inducing metabolic derangements. Indeed, early life stress can alter the expression of the genes in peripheral tissues, such as glucocorticoid receptor and 11-beta hydroxysteroid dehydrogenase. Morris et al. (10) proposed that interactions between altered HPA axis activity and liver 11-beta hydrogenase modulates both tissue and circulating glucocorticoid availability, with adverse metabolic consequences.

## Chronic stress, HPA axis and metabolic abnormalities

The metabolic syndrome encompasses a cluster of cardiometabolic abnormalities, including hypertension, abdominal obesity, hyperglycemia and dyslipidemia. It has been suggested that increased activity of the HPA axis, with increased levels of glucocorticoid hormones may contribute to the development of metabolic syndrome (11). Furthermore, normal physiological differences in long-term cortisol secretion, assessed through hair cortisol levels, show a relevant relationship with the metabolic syndrome (12).

New evidence has emerged on early life stress induced metabolic derangements (e.g. hyper-insulinemia and altered insulin sensitivity on exposure to a high energy diet later in life). Vogelzangs et al. (13) suggested that there is a synergistic relationship between depression, cortisol and the metabolic syndrome.

Research indicates that modulation of the HPA axis is possible by treating the underlying condition, achieving a healthier weight, and improving length and quality of sleep, such as by increasing the slow wave phase.

## Sleep and the HPA axis

At times of stress, amygdala glucocorticoid receptors (GRs) may be preferentially activated, increasing CRH. Elevated CRH increases electroencephalogram (EEG) frequency, decreasing slow-wave sleep (SWS) and increasing light sleep and wakefulness. On the other hand, sleep disturbance (insomnia, sleep ap-

noea) can aggravate HPA axis dysfunction. In the case of obstructive sleep apnoea, every time the patient gasps for breath at night, there is pulsatile cortisol release and autonomic activation. However, when an individual is able to achieve better quality sleep, the slow wave sleep (SWS) can suppress the HPA axis. Helping patients to improve their quality of sleep can help to modulate the HPA axis. This would have beneficial metabolic effects. It would also help them to be able to respond to treatment better.

## HPA axis and mindfulness

A case-control study by Brunner et al. (14) provided evidence that chronic stress may be a cause of metabolic syndrome. Using data from the Whitehall II Cohort, the authors showed that metabolic syndrome was associated with levels of the 24-hour cortisol metabolite, normetanephrine output and cardiac autonomic activity. Differences in cortisol output and cardiac autonomic activity associated with metabolic syndrome were reduced in cases that had subsequently resolved, indicating that the changes are potentially reversible. Psychosocial factors explained, in part, the increased normetanephrine output associated with the metabolic syndrome. Adverse cardiac autonomic functions related to the syndrome were attributable both to psychosocial factors and the degree of obesity. The metabolic syndrome may be an intermediary between long-term psychosocial stress and coronary disease. Markers of inflammation predict weight gain, diabetes and chronic heart disease. The longitudinal component of the study provided evidence for the reversibility of the neuroendocrine and inflammatory alterations linked with the metabolic syndrome. Cresswell and Lindsay (15) have proposed an evidence-based biological model of mindfulness, stress buffering and health. They propose a conceptual model of the biological pathways linking mindfulness and stress-buffering. This account suggests that mindfulness training might alter neural stress-processing dynamics in high-stress participants and reduce sympathetic-adrenal-medullary (SAM) axis or HPA axis reactivity. They also propose that mindfulness can have a stress-buffering effect. Well-controlled studies have suggested that mindfulness training interventions can improve a broad range of mental and physical health outcomes (e.g. HIV pathogenesis, depression relapse, inflammation). This biological model suggests that mindfulness may alter neural stress-processing dynamics. In high stress participants, mindfulness can reduce SAM or HPA axis reactivity and help normalise dysregulated stress signaling in these systems. Social support and mindfulness can also help to modulate the HPA axis. Stalder et al. have shown the beneficial effects on metabolism of small changes in long-term secretion of cortisol (12).

## Conclusion

A large body of evidence suggests that there are long-term neurobiological consequences of chronic stress. There also seems to be a temporal gap between the over-activation of the HPA axis and the emergence of symptoms in different syndromes. Evidence has shown that persistently raised levels of cortisol can lead to metabolic abnormalities and are linked with conditions such as depression. The HPA axis is fundamentally a dynamic system that changes over time (16).

Could we use hair cortisol to carry out longitudinal studies? Indeed, could we also identify the "at risk population", monitor them, and intervene early by helping individuals to develop protective factors, modulate the HPA axis, and reduce the risk of metabolic abnormalities and development of psychopathology? Clinical practice seems to support the value of protective factors such as social support, mindfulness training, counselling, and developing skills in resilience. Furthermore, could we intervene early in primary care to protect the "patients at risk" and also patients who are developing early symptoms of mental health problems? Would it be useful to look at the prevalence of child abuse, neglect, significant losses, trauma and their possible link with the prevalence of psychiatric disorders? Would it also be helpful to have national programmes to improve awareness on how to manage chronic stress in schools, making this part of the curriculum? Indeed, should we encourage more awareness of the implications of chronic stress (e.g. bullying, abuse, neglect), and have more resources for pastoral care and counselling available in schools and universities? This could be further supported by counselling facilities, training in mindfulness, and workshops available to the public, and to primary, secondary and even tertiary care. In view of the current evidence, a prophylactic and proactive approach would seem reasonable to improve the overall health of the nation, reducing morbidity and complications. Indeed, this could constitute a cost-effective long-term strategy. Further understanding might be gained by carrying out longitudinal

studies in order to better understand the dynamics of the HPA axis and SAM axis over time, and to explore the time between activation of the HPA axis and the emergence of the first signs and symptoms of pathology in conditions such as depression. In addition, the HPA axis can be further explored by using hair cortisol levels in vulnerable individuals before and after mindfulness training, along with measurements of cardiometabolic parameters, to shed further light on how mindfulness training helps.


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