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Invited Review

Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression

Thaddeus W.W. Pace, Fang Hu, Andrew H. Miller *

Department of Psychiatry and Behavioral Sciences, Winship Cancer Institute, Emory University School of Medicine, 101 Woodruff Cricle, Suite 4000, Atlanta, GA 30322, USA

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Abstract

Glucocorticoids play an essential role in the response to environmental stressors, serving initially to mobilize bodily responses to challenge and ultimately serving to restrain neuroendocrine and immune reactions. A number of diseases including autoimmune, infectious and inflammatory disorders as well as certain neuropsychiatric disorders such as major depression have been associated with decreased responsiveness to glucocorticoids (glucocorticoid resistance), which is believed to be related in part to impaired functioning of the glucocorticoid receptor (GR). Glucocorticoid resistance, in turn, may contribute to excessive inflammation as well as hyperactivity of corticotropin releasing hormone and sympathetic nervous system pathways, which are known to contribute to a variety of diseases as well as behavioral alterations. Recent data indicate that glucocorticoid resistance may be a result of impaired GR function secondary to chronic exposure to inflammatory cytokines as may occur during chronic medical illness or chronic stress. Indeed, inflammatory cytokines and their signaling pathways including mitogen-activated protein kinases, nuclear factor-κB, signal transducers and activators of transcription, and cyclooxygenase have been found to inhibit GR function. Mechanisms include disruption of GR translocation and/or GR-DNA binding through protein–protein interactions of inflammatory mediators with the GR itself or relevant steroid receptor cofactors as well as alterations in GR phosphorylation status. Interestingly, cAMP signal transduction pathways can enhance GR function and inhibit cytokine signaling. Certain antidepressants have similar effects. Thus, further understanding the effects of cytokines on GR signaling and the mechanisms involved may reveal novel therapeutic targets for reversal of glucocorticoid resistance and restoration of glucocorticoid-mediated inhibition of relevant bodily/immune responses during stress and immune challenge.

Keywords: HPA axis; Glucocorticoid receptor; Cytokine; Signal transduction; Depression; Mitogen activated protein kinase; Nuclear factor-κB; Signal transducers and activators of transcription; Cyclooxygenase; cAMP; Protein kinase A

1. Introduction

Glucocorticoids play a fundamental role in restraining inflammatory and neuroendocrine responses to a variety of challenges including pathogen exposure and stress (Raison and Miller, 2003). Indeed, glucocorticoids suppress critical inflammatory signaling pathways including nuclear factor-κB (NF-κB) and inhibit stress-related outflow pathways including corticotropin releasing hormone (CRH), the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Glucocorticoids therefore play a critical role in balancing bodily responses to challenge, serving to both restore and maintain homeostasis.

Failure of glucocorticoids to inhibit inflammatory and neuroendocrine responses to challenge may contribute to

* Corresponding author. Tel.: +1 404 727 8260; fax: +1 404 727 3233.
E-mail address: amill02@emory.edu (A.H. Miller).

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disease development (Raison and Miller, 2003). For example, recent data indicate that excessive inflammation may play a significant role in a number of medical illnesses including cardiovascular disease, diabetes, and cancer (Raison et al., 2006). Moreover, excessive HPA axis responses, including increased production and release of CRH, and SNS hyperactivity are hallmarks of depression. Given the central role of glucocorticoids and their signaling pathways in the maintenance of health and the prevention of disease, it is not surprising that a number of disorders characterized by excessive inflammatory responses including rheumatoid arthritis, asthma, and inflammatory bowel disease as well as depression have been associated with resistance to the inhibitory effects of glucocorticoids (Pariante and Miller, 2001; Raison and Miller, 2003). In the case of major depression, a clinical disorder characterized by significant alterations in mood, neurovegetative function and cognition, glucocorticoid resistance has been one of the most reproducible biological findings in the disease, occurring in up to 80% of patients (see below) (Holsboer, 2000; Pariante and Miller, 2001; Heuser et al., 1994).

The etiology of glucocorticoid resistance in both inflammatory and neuropsychiatric disorders is unknown and likely involves multiple factors including genetic influences. Nevertheless, mounting data suggest that inflammation itself may contribute to reduced glucocorticoid sensitivity. For example, data have established that cytokine signaling pathways can interact with glucocorticoid receptor (GR) signaling pathways and thereby disrupt glucocorticoid action (Miller et al., 1999). Such effects of cytokines and their signaling pathways on hormone receptors have been demonstrated in a number of other conditions with pathophysiologic relevance including the effects of tumor necrosis factor (TNF)-α and NF-κB on Vitamin D receptor signaling and its relevance to osteoporosis (Nanes, 2003), the effects of TNF-α on insulin receptor signaling and its relevance to diabetes (Hotamisligil, 1999), and the effects of IL-1 and TNF-α on insulin-like growth factor receptor signaling and its relevance to muscle wasting in disorders such as Acquired Immune Deficiency Syndrome (Broussard et al., 2004; Kelley, 2004). Thus, the effects of cytokines and their signaling pathways on hormone signaling in general, and GR signaling in particular, is an important area of investigation regarding both the pathophysiology and treatment of inflammatory and neuropsychiatric diseases. In this review, we will focus on the potential contribution of inflammation and activation of cytokine signaling pathways to glucocorticoid resistance and its relevance to major depression.

2. Glucocorticoid resistance and the pathophysiology of depression

One of the most reliably reported neurobiological alterations in major depression is both HPA axis hyperactivity and impaired HPA axis glucocorticoid feedback sensitivity. Depressed patients have been shown to exhibit increased concentrations of the HPA axis hormone, cortisol, in plasma, urine, and cerebrospinal fluid (CSF) (Pariante and Miller, 2001). In addition, depressed patients have been found to exhibit an exaggerated cortisol response to adrenocorticotropin hormone (ACTH) (Holsboer, 2000; Nemeroff, 1996; Pariante and Miller, 2001). Of note, increases in HPA axis activity are especially apparent in individuals who are older and/or who are more severely depressed (Pariante, 2004).

HPA axis hyperactivity observed in patients with major depression is largely thought to result from hypersecretion of corticotropin-releasing hormone (CRH). Indeed, depressed patients exhibit increased concentrations of CRH in CSF, increased CRH mRNA and protein in the paraventricular nucleus of the hypothalamus (postmortem samples), and a blunted ACTH response to CRH challenge (likely reflecting downregulation of pituitary CRH receptors) (Nemeroff, 1996; Pariante and Miller, 2001). Moreover, downregulation of CRH receptors in frontal cortex of victims of suicide (many of whom were presumably depressed) has been described (Nemeroff, 1996). Hypersecretion of CRH may contribute to the behavioral features of major depression, in that administration of CRH to laboratory animals has been shown to lead to a host of behavioral changes that are comparable to those seen in depression including alterations in mood, appetite, sleep, locomotor activity and cognition (Nemeroff, 1996).

CRH hyperactivity in major depression is believed to be related, in part, to the failure of cortisol to suppress CRH production through negative feedback regulation (Holsboer, 2000; Pariante and Miller, 2001). This phenomenon is referred to as glucocorticoid resistance. The presence of glucocorticoid resistance in mood disorders is supported by evidence of cortisol non-suppression to dexamethasone in the dexamethasone suppression test (DST) and the more recently developed dexamethasone-CRH (DEX-CRH) test (Holsboer, 2000). Of note, the DEX-CRH test has been shown to be significantly more sensitive than the DST with a sensitivity of up to 80% in patients with major depression, compared to 25% for the DST (Heuser et al., 1994). Failure of dexamethasone to suppress HPA axis responses has also been shown to predict clinical outcome during antidepressant treatment and has been found in first degree relatives of depressed patients (Ising et al., 2005). Aside from abnormal in vivo responses to dexamethasone administration, glucocorticoid resistance in depressed patients has also been demonstrated in vitro. For example, following in vitro glucocorticoid exposure, peripheral blood immune cells from depressed patients have exhibited reduced dexamethasone-induced inhibition of immune cell responses, notably mitogen-induced lymphocyte proliferation and NK cell activity, compared to healthy controls (Pariante, 2004; Pariante and Miller, 2001). Taken together with observations from in vivo glucocorticoid sensitivity measures, these data indicate that glucocorticoid resistance (impaired glucocorticoid sensitivity) is widespread throughout the body in both neuroendocrine and immune tissues and is not