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Modulation of c-Jun N-terminal kinase signaling and specific glucocorticoid receptor phosphorylation in the treatment of major depression ☆

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ABSTRACT

Glucocorticoid resistance is a common finding in major depressive disorder. Increased glucocorticoid receptor (GR) phosphorylation at serine 226 is associated with increased glucocorticoid resistance. Previously we have demonstrated that depressed patients exhibit higher levels of GR phosphorylated at serine 226 compared to healthy controls. The enzyme that is involved in this specific GR phosphorylation is c-Jun N-terminal kinase (JNK). We propose that modulation of glucocorticoid phosphorylation at serine 226, by targeting JNK signaling pathway, could be a potential strategy for antidepressant treatment. We base this assumption on the results of previous research that examined GR phosphorylation and JNK signaling in animal models and human studies. We also discuss the potential challenges in targeting JNK signaling pathway in depression.

Introduction

The etiology of depression is still poorly understood, and present treatment strategies fail to alleviate the symptoms of 10–40% of depressed individuals [1]. Current trends in mood disorders research highlight the need of distinguishing between the specific syndromes that fall under the wide "umbrella" of major depression, in order to personalize treatment and achieve better therapeutic response. This notion found support in basic research, which demonstrated significantly different gene expression profiles between stress-related depression models and endogenous depression models [2].

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has long been associated with stress-related depression [3]. Namely, a significant percentage of depressed patients exhibit increased blood cortisol levels, and this effect is higher in those with comorbid anxiety [4,5]. Effects of cortisol are mediated through the glucocorticoid receptor (GR), including the feedback regulation of the HPA axis. Therefore, the impairment of GR signaling is suggested to play a pivotal role in the HPA axis dysregulation in stress-related depression [6,7].

The GR regulates the expression of a variety of genes, including ones that are involved in metabolism and immunity, neuronal survival, neurogenesis and regulation of HPA axis [8]. Therefore, in addition to its role in the neuroendocrine system, GR signaling is strongly involved in immune system response. Cortisol is one of the most potent anti-inflammatory hormones in the body, and pathways coupled with glucocorticoid resistance may conspire during chronic stress to contribute to chronic activation of inflammatory responses [9]. Namely, a large body of research supports the notion of inflammatory disturbance in depression [10,11]. Chronic stress, through glucocorticoid resistance (i.e. decreased sensitivity to anti-inflammatory effects of glucocorticoids), may contribute to chronic activation of immune system in major depressive disorder [12].

Considering the complex interplay between glucocorticoid and inflammatory signaling (in both physiological and pathological conditions), as well as evidence of dysfunction of both these systems in major depression, targeting one or both systems could be a potential therapeutic strategy for this disorder [13].

The glucocorticoid receptor signaling

GR is a ligand-dependent transcriptional factor that resides in the cell cytoplasm in its inactive form. After ligand binding it

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