HHS Public Access

Author manuscript

Trends Endocrinol Metab. Author manuscript; available in PMC 2019 May 02.

Published in final edited form as:

Trends Endocrinol Metab. 2006 ; 17(4): 124–125. doi:10.1016/j.tem.2006.03.002.

Reduced glucocorticoid receptors: consequence or cause of depression?

Gretchen N. Neigh and **Charles B. Nemeroff**

Department of Psychiatry & Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle, Suite 4000 Atlanta, GA 30322, USA

Abstract

Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis is common in patients with major depression. A recent study demonstrates that reduced expression of the glucocorticoid receptor in mice causes depression-like behaviors and HPA axis dysfunction following stressor exposure. This model offers a novel system for the study of the pathophysiology that underlies depression-like behaviors. It also adds to the growing evidence that implicates glucocorticoid receptor dysfunction in depression.

Glucocorticoid receptor hypothesis of depression

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis is a frequent feature of patients with syndromal major depression [1], and successful treatment with antidepressants is associated with normalization of HPA axis activity [2]. Reduction in the number or function of glucocorticoid receptors (GRs) might lead to the pattern of HPA axis dysfunction reported in depressed patients. Consistent with this, peripheral tissues of depressed patients have been reported to exhibit a reduction in GRs [3]. Also of note are recent reports that mifepristone, a glucocorticoid receptor antagonist, can successfully treat the psychotic component of delusional depression [4], characterized by profound HPA axis hyperactivity. Furthermore, data from laboratory animal studies support a role for GR in depression-like behaviors. Some of the most elegant demonstrations of this hypothesis originate from deletion or inactivation of GR. Ridder *et al*. [5] have recently published a noteworthy study of the role of GR in depression-like behaviors. Homologous recombination was used to generate mice that were heterozygous for GR deletion. This resulted in ~50% reduction in the expression of GR (GR+/ −) and a stress-sensitive phenotype, in that these mice only demonstrated HPA axis dysfunction and depression-like behaviors following exposure to a stressor. Although the data presented by Ridder *et al*. [5] are compelling and demonstrate that a reduction in GR is sufficient to induce depression-like behaviors following stressor exposure, the necessity of reduced GR for the expression of depression-like behaviors is not addressed, leading to the question: are reduced GRs a consequence or cause of depression?

Corresponding author: Nemeroff, C.B. (cnemero@emory.edu).

Face validity of reduced GR expression as a model of depression

The GR manipulation described by Ridder *et al.* [5] exhibits face validity. Heterozygous GR deletion causes a partial reduction in GR, as opposed to a complete deletion or silencing of the gene, a condition more consistent with probable clinical manifestation of an alteration in GR. Also of note is the consistency of the model with the clinical characteristics of the disease, which means that an environmental perturbation (exposure to footshock in this case) is necessary to elicit both depression-like behavior and HPA axis dysfunction. This is consistent with the observation that asymptomatic first-degree relatives of depressed patients demonstrate some degree of HPA axis dysfunction, suggesting an underlying structural or functional change that increases the susceptibility to depression [6] and, moreover, that a stressful life event often precipitates an episode of major depression.

Potential window into the neurochemical mediators of depression-like behaviors

Mice with reduced GR demonstrate a decrease in brain-derived neurotrophic factor (BDNF) [5], reduction of which might be critical in the pathogenesis of depression [7]. The reported change in BDNF is of particular interest because, although GR changes occur in depression, they are probably not the sole mechanism for the manifestation of depression-like behaviors, as suggested by the prevalence of cases of depression without hypercortisolemia [8]. Alterations in growth factors, such as BDNF, or neurotransmitters, which lead to altered synaptic function and structural changes, such as altered neurogenesis or pathogenic dendritic pruning, have been posited to underlie depression-like behaviors [7]. This does not negate the value of the GR+/ − mouse for the study of depression-like behaviors, but rather illustrates another valuable aspect of the model. Through the characterization of neurochemical and structural changes demonstrated in the GR+/ − mouse, especially following stressor exposure, additional candidates that contribute to the cause of depression-like behaviors might be identified.

What about the rest of the HPA axis?

Although the Ridder *et al.* [5] findings illustrate the sufficiency of reduced GR for the expression of depression-like behaviors, GR manipulations have not consistently reproduced these findings. Thus, mice with a GR point mutation that prevents GR dimerization exhibit no change in emotional behaviors [9], mice with a brain-specific GR knockout exhibit reduced depression-like behaviors [10], and mice with a forebrain-specific GR knockout show depression-like behaviors in the absence of a stimulating event [11]. Variations in the transgenic manipulation employed to alter GR might account for these variable results; however, it is also plausible that changes in GR are not directly responsible for the manifestation of depression-like behaviors but represent a concurrent epiphenomenon of a yet unidentified alteration in the central nervous system.

Hypercortisolemia and disturbances of GR function are not always present during the clinical manifestation of depression [12] and, even when present, do not occur at all times during the episode [13]. This suggests that, although changes in GR function might be

involved in the etiology of depression-like behaviors (at least in some cases), other aspects of the HPA axis might also be altered. More specifically, elevations in corticotropin releasing factor (CRF) have been reported in depressed patients in both CSF and postmortem studies [14], and CRF receptor 2 knockout mice and CRF overexpressing transgenic mice demonstrate depression-like behaviors [15]. Indeed, CRF changes could underlie the effects of a GR manipulation [16].

This leads to the dreaded 'chicken or egg' argument, but it might not matter which disruption occurs first but, rather, the crucial point might be the HPA axis dysfunction that the initial perturbation sets in motion. Causation of depression can be as multifactorial as the manifestation of symptoms among individuals, but the identification of common underlying neuronal mechanisms for the depression-like behaviors will undoubtedly open new avenues for pharmacological intervention. Additional studies of GR+/ − mice, as well as mice with other transgenic manipulations of the HPA axis and CRF system, are necessary to better understand the pathogenesis of depression. This includes characterization of other measures of HPA axis function in the GR+/ − mice and assessment of the effects of antidepressant treatment. In short, Ridder *et al.* [5] elegantly demonstrate the sufficiency of a reduction in GR for the manifestation of depression-like behaviors and HPA axis dysfunction following a severe stressor, and add to the body of evidence that links HPA axis dysfunction with depression. However, they do not address the necessity of a reduction in GR for the manifestation of depression-like behaviors. A clear cause–effect relationship cannot be extrapolated from these novel data. A seminal role for HPA axis dysfunction in some forms of depression cannot be denied, but the precise mechanism(s) of action has yet to be ascertained. Elucidation of the underlying mechanism should catapult our understanding of depression and depression-like behaviors forward and finally determine whether a reduction in GR is a consequence or cause of depression.

Acknowledgements

This work was funded by the National Institute of Health (NIH) MH-42088, NIH MH-52899, and a NIH Institutional Research and Academic Career Development grant K12GM00680–05.

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