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REVIEW

The brain mineralocorticoid receptor and stress resilience

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Summary Stress exposure activates the HPA-axis and results in the release of corticosteroids which bind to two receptor types in the brain: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). While the role of the GR in stress reactivity has been extensively studied, the MR has received less attention. Nevertheless, pioneering in-depth studies over the past two decades have shown the importance of the brain MR in the processing of stressful information. Moreover, a membrane-bound MR mediating the rapid effects of cortisol was recently discovered. This review summarizes how the MR may play a role in stress resilience. Both preclinical and clinical studies suggest that the MR is an important stress modulator and influences basal as well as stress-induced HPA-axis activity, stress appraisal, and fear-related memories. These MR effects are mediated by both genomic and non-genomic MRs and appear to be at least partially sex-dependent. Moreover, the majority of studies indicate that high MR functionality or expression may confer resilience to traumatic stress. This has direct clinical implications. First, increasing activity or expression of brain MRs may prevent or reverse symptoms of stress-related depression. Second, individuals with a relatively low MR functionality may possess an increased stress susceptibility for depression. Nevertheless, the number of clinical MR studies is currently limited. In conclusion, the recent emergence of the MR as a putative stress resilience factor is important and may open up new avenues for the prevention and treatment of psychiatric disorders.

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1. Introduction

Exposure to stress results in the release of (nor)adrenaline via the sympatho-adrenomedullary system and the release of corticosteroids via the hypothalamic-pituitary-adrenal (HPA)-axis. Both systems act in concert to enable an individual to successfully adapt to a changing environment (de Kloet et al., 2005). Corticosteroid hormones (cortisol in humans and corticosterone in rodents) ensure that sufficient energy is available and dampen the immune function. At the same time, cortisol exerts negative feedback on the HPA-axis and prevents a damaging overshoot. An efficient and adaptive stress response requires a rapid activation of the HPA-axis after stress exposure but also an effective termination once the stressor has subsided (McEwen, 2004). Prolonged or excessive HPA-axis activity following chronic stress can exceed an individual's allostatic load and may subsequently result in the development of psychiatric and somatic disorders (Juster et al., 2010). Indeed, exposure to traumatic stress is a major risk factor for many psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders (Heim et al., 2008).

Corticosteroids bind to two receptors in the brain: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These receptors operate in a complementary fashion to regulate HPA-axis activity (de Kloet, 2013; Harris et al., 2013). Activation of the GR and MR triggers a signalling pathway involving a cascade of cellular, immunological and physical changes via genomic transcriptional regulation (Joëls et al., 2009). Whereas the GR is expressed throughout the brain, the MR is predominately expressed in limbic areas such as the hippocampus and amygdala (Patel et al., 2001; Reul and de Kloet, 1985; Seckl et al., 1991). In the hippocampus, MRs are co-localized with GRs (Patel et al., 2001). Compared to the GR, corticosteroids have a 10-fold higher MR affinity (Grossmann et al., 2004; Rupprecht et al., 1993). These high-affinity characteristics result in a high MR occupancy rate even under basal (non-stressful) conditions in order to maintain low basal corticosteroid levels through negative feedback (de Kloet and Reul, 1987; Reul and de Kloet, 1985). In contrast, full GR occupancy is only reached when cortisol concentrations peak, for example after awakening or as a result of stress. It is therefore not surprising that the GR has dominated endocrine stress research. With regard to the relation between the MR and GR, both receptors have complementary roles in the regulation of HPA-axis functionality (de Kloet et al., 2007). In contrast to the MR, the genomic GR facilitates recovery and adaptation and normalizes brain functioning some hours after stress exposure when corticosteroid levels have returned to baseline due to negative feedback (Joëls et al., 2012). The high affinity of MR for cortisol has been reason to believe that the MR mainly facilitated GR functionality by binding cortisol rather than having an independent role in stress reactivity. Pioneering in-depth studies over the past