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Glucocorticoids, epigenetic control and stress resilience

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ABSTRACT

Glucocorticoid hormones play a pivotal role in the response to stressful challenges. The surge in glucocorticoid hormone secretion after stress needs to be tightly controlled with characteristics like peak height, curvature and duration depending on the nature and severity of the challenge. This is important as chronic hyper- or hypo-responses are detrimental to health due to increasing the risk for developing a stress-related mental disorder. Proper glucocorticoid responses to stress are critical for adaptation. Therefore, the tight control of baseline and stress-evoked glucocorticoid secretion are important constituents of an organism's resilience. Here, we address a number of mechanisms that illustrate the multitude and complexity of measures safeguarding the control of glucocorticoid function. These mechanisms include the control of mineralocorticoid (MR) and glucocorticoid receptor (GR) occupancy and concentration, the dynamic control of free glucocorticoid hormone availability by corticosteroid-binding globulin (CBG), and the control exerted by glucocorticoids at the signaling, epigenetic and genomic level on gene transcriptional responses to stress. We review the beneficial effects of regular exercise on HPA axis and sleep physiology, and cognitive and anxiety-related behavior. Furthermore, we describe that, possibly through changes in the GABAergic system, exercise reduces the impact of stress on a signaling pathway specifically in the dentate gyrus that is strongly implicated in the behavioral response to that stressor. These observations underline the impact of life style on stress resilience. Finally, we address how single nucleotide polymorphisms (SNPs) affecting glucocorticoid action can compromise stress resilience, which becomes most apparent under conditions of childhood abuse.

1. Introduction

Glucocorticoid hormones play a fundamental role in the adaptation of an organism to stressful events in its life. Research over the past >60 years has shown that glucocorticoid hormone actions at the molecular and cellular level are highly complex with multiple long-term consequences for physiology and behavior (De Kloet and Reul, 1987; De Kloet et al., 1998, 2005; McEwen, 2012a,b). Not surprisingly, research has provided ample evidence that chronic hyper- as well as hypo-secretion of glucocorticoid hormones is involved in the development of a range of metabolic, immune, endocrine and neuro-psychiatric disorders. The psychiatric diseases include stress-related disorders like major depression and anxiety disorders (e.g. post-traumatic stress disorder (PTSD)). During the past 15 years this idea has been supported by evidence that individual differences exist in the vulnerability of developing a major depressive or anxiety disorder during the course of life (Zannas and Binder, 2014). It appears that certain genetic traits, e.g. SNPs in the glucocorticoid receptor (GR; Nr3c1) associated chaperone Fkbp5 (FK506-binding protein 51) gene, in combination with traumatic (early) life events can dramatically increase the likelihood of precipitating psychiatric disease (Klengel and Binder, 2013a,b). Conversely, mechanisms are in place to maintain or increase resilience of the organism to stress and prevent the development of maladaptive responses and disease. Evidence has been accumulating that a physically active life style (exercise) is beneficial in strengthening resilience to stress (Reul and Droste, 2005). Indeed, it has been shown that long-term voluntary exercise in

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rodents such as rats and mice results in changes in HPA axis control, sleep physiology, and anxiety-related behavior (Droste et al., 2003; Lancel et al., 2003; Binder et al., 2004a).

In this article we will review the role of glucocorticoid hormones in resilience. We define resilience as an individual's ability to effectively adapt to stress and adversity, resulting in the prevention of physical and/or psychological disease. We will address recently discovered mechanisms dynamically regulating the biological availability of glucocorticoid hormones. Novel insights into the role of this hormone in epigenetic mechanisms associated with gene transcriptional and behavioral responses to stress will be described. We will review evidence that increasing physical activity in one's life style enhances stress resilience. Finally, we will highlight how early life trauma can affect life-long glucocorticoid action.

2. Glucocorticoid action via MRs and GRs: early findings and concepts

It has been almost 30 years ago since the binding properties of the natural glucocorticoid hormone to receptors in rodent brain have been described (Reul and De Kloet, 1985). Reul and de Kloet discovered that corticosterone binds to two types of receptors, the mineralocorticoid receptor (MR; also termed 'Type 1' in the early days) and the GR (also termed 'Type 2'), in the high-speed soluble fraction ('cytosol') of hippocampus homogenates (Reul and De Kloet, 1985). Highest levels of MRs are typically found in dentate gyrus, CA2 and CA1 of the hippocampus, lateral septum and central amygdala whereas GRs are found throughout the brain with high concentrations in the hippocampus, neocortex and hypothalamic nuclei such as the paraventricular nucleus (PVN) and supraoptic nucleus (Reul and De Kloet, 1985, 1986; Reul et al., 1987; Kiss et al., 1988). This localization pattern was confirmed after the receptor had been cloned (Hollenberg et al., 1985; Arriza et al., 1987) and in situ hybridization and immunohistochemical studies had been performed (Fuxe et al., 1985a,b; Herman et al., 1989a; Van Eekelen et al., 1988; Reul et al., 2000; Gesing et al., 2001). A similar distribution of MRs and GRs as found in the rat and mouse brain was found in the dog brain albeit that the brain localization of MRs is more widespread in this species than in rodents (Reul et al., 1990). Scatchard and Woolf plot analyses showed that MRs bind corticosterone with an extraordinarily high affinity (0.1–0.5 nM) whereas GRs bind the natural hormone with a lower affinity (2.5–5 nM) (Reul and De Kloet, 1985; Reul et al., 1987). As a result of this stark difference in binding affinity, subsequent studies presented a marked difference between MRs and GRs in the degree of occupancy by endogenous glucocorticoid hormone under baseline and stress conditions (Reul and De Kloet, 1985). Under baseline early morning conditions, MRs already showed a high occupancy whereas GRs were hardly occupied. In contrast, at the circadian peak and even more strongly after stress both receptor types showed a high degree of occupancy by endogenous hormone (Reul and De Kloet, 1985).

At the time, the concept of a glucocorticoid-binding receptor, i.e. MR, which under any physiological conditions is highly occupied with endogenous hormone, was rather controversial. As usually receptor signaling is thought to depend on the degree of receptor occupancy by ligand whose concentration is determined by the physiological condition at hand; a receptor like MR that is always substantially occupied would defeat this purpose. Based on the remarkably distinct properties of MRs and GRs in the hippocampus in conjunction with neuroendocrine and other observations, De Kloet and Reul (De Kloet and Reul, 1987; Reul and De Kloet, 1985) developed a concept that amalgamated these properties in a unifying model on glucocorticoid action in this limbic brain structure. In this concept, hippocampal MRs confer tonic inhibitory influences of circulating glucocorticoids that serve to restrain baseline HPA axis activity (De Kloet and Reul, 1987; Reul and De Kloet, 1985). Neuroanatomical, pharmacological and lesion studies indeed showed that the hippocampus exerts a tonic inhibitory influence on the activity of PVN neurons in the hypothalamus, driven transsynaptically through distinct populations of GABA-ergic neurons in the bed nucleus of the stria terminalis (BNST; De Kloet and Reul, 1987; De Kloet et al., 2005; Herman et al., 1989b; Herman and Cullinan, 1997; Herman et al., 2003). In accordance with their responsiveness to elevated glucocorticoid levels and the mediation of the HPA axis-suppressing effects of synthetic glucocorticoids like dexamethasone, GRs are considered to be responsible for the negative feedback action of glucocorticoid hormones (De Kloet and Reul, 1987; Reul and De Kloet, 1985). They do so mainly at the anterior pituitary and PVN level but effects via GRs located in the hippocampus, prefrontal cortex, amygdala and other parts of the brain cannot be excluded (De Kloet and Reul, 1987; De Kloet et al., 2005; Reul and De Kloet, 1985; Herman et al., 2003). The hippocampal MRs and GRs also play distinct roles in the control of sympathetic outflow and in behavioral responses to stressful events (De Kloet et al., 2005). Potent MR- and/or GR-mediated effects of glucocorticoid hormones have been shown in various hippocampus-associated behavioral tests such as the forced swim test, Morris water maze learning and contextual fear conditioning (Jefferys et al., 1983; Veldhuis et al., 1985; Bilang-Bleuel et al., 2005; Gutierrez-Mecinas et al., 2011; Mifsud et al., 2011; Trollope et al., 2012; Reul, 2014; Oitzl et al., 2001; Beylin and Shors, 2003; Zhou et al., 2010). At the cellular level, distinct electrophysiological effects of glucocorticoid hormones via MRs and GRs on hippocampal neurons have been described (Joëls and De Kloet, 1992; Pavlides et al., 1993; Joëls et al., 2009).

In this manner, the dual glucocorticoid-binding receptor system regulates the physiological (including endocrine and autonomic) responses and behavioral responses under baseline and stress conditions thereby maintaining homeostasis and facilitating long-term adaptation, together safeguarding resilience of the organism. The mechanisms underlying resilience are complex and multifaceted. Furthermore, the capacity to cope with and adapt to adverse events is influenced by life style, genetic vulnerability and early life factors. Presently, we are only beginning to understand these mechanisms. Here, we describe several findings that portray the importance and complexity of the role of MRs and GRs in resilience. This is not a complete listing as this would go beyond the scope of this review. The described findings address the diversity and complexity of the mechanisms involved and are regarded as particularly important for future developments.

3. Dynamic control of hippocampal MRs as an instrument of resilience

The high degree of occupancy of hippocampal MRs under any physiological circumstance was a controversial finding because how would such a receptor system be able to adjust signaling to different circumstances? The answer turned out to be: by dynamically adjusting the concentration of receptor molecules in neurons. Serendipitously, we observed that acute stressful challenges that engage the hippocampus like forced swimming and novelty exposure resulted in a significant increase in the concentration of MRs, but not GRs, in the hippocampus of rats (Gesing et al., 2001). The rise was transient and occurred between 8 and 24 h after the challenge. Remarkably, this effect of stress turned out to be mediated by corticotropin-releasing factor (CRF). Intracerebroventricular injection of the neuropeptide resulted in a rise in hippocampal MRs whereas pre-treatment with a CRF receptor antagonist blocked the effect of forced swimming on MRs.