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Review

Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder

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ABSTRACT

Both hyper- and hypo-activity of the hypothalamus–pituitary–adrenal (HPA) axis activity are a consistently reported hallmark feature of stress-related disorders, such as major depression and posttraumatic stress disorder (PTSD), respectively. In this manuscript, however, we are summarizing evidence pointing to altered glucocorticoid (GC) sensitivity in relevant target tissues for HPA axis hormones. Specifically, we provide a summary of GC effects on cognitive functions, as an emerging marker for central nervous system GC sensitivity, and of GC effects on peripheral inflammatory responses. With regard to depression and PTSD, evidence thereby points to decreased GC sensitivity of the cognitive and inflammatory systems in depression, and increased GC sensitivity of both systems in PTSD. Taken together, these data support the hypothesis that both psychiatric disorders are characterized by inefficient GC signaling, although through dysregulations at different levels. Potential underlying pathways and implications are discussed.

Contents

1. Introduction

Glucocorticoids (GC), the end hormones of the hypothalamus–pituitary–adrenal (HPA) axis, play a major role in human health and disease. Traditionally, excess secretion of GCs has been viewed as an important factor in immune suppression, the metabolic syndrome, and stress-related psychiatric disorders (e.g. Sapolsky et al., 1986). However, given the importance of sufficient GC

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concentrations for the regulatory control of damaging forces, mainly the inflammatory response system, as well as reports of hypocortisolism in some psychiatric conditions and during chronic stress, deficient GC signaling recently has received increasing attention (e.g. Raison and Miller, 2003; Fries et al., 2005; Heim et al., 2000).

In this review, we will investigate data on the efficiency of glucocorticoid signaling within two target systems that are of particular importance for health and well-being in stress-related psychiatric diseases, specifically in depression and posttraumatic stress disorder (PTSD). One of these target systems is the innate immune system, more specifically the inflammatory cascade, because of its central role in a large number of diseases (e.g. cardiovascular and metabolic diseases (Hansson and Libby, 2006; Hotamisligil, 2006). The second glucocorticoid responsive functional area reviewed here is the central nervous system, more specifically brain regions involved in cognitive processes, like the limbic system and the prefrontal cortex (Lupien et al., 2009; Wolf, 2009).

We will describe possible associations or dissociations of these two systems' glucocorticoid sensitivities and the relevance for human health. Furthermore, evidence for enhanced GC sensitivity in PTSD and reduced GC sensitivity in depression will be discussed. Moreover, possible underlying mechanisms will be briefly highlighted, before a conclusion and a look into the future of this rapidly growing research area is presented.

2. Regulation of glucocorticoid sensitivity in target tissues

Glucocorticoids mediate their effects by binding to cytosolic receptors, of which two subtypes have been described: The type-1 or mineralocorticoid receptor (MR) and the type-2 or glucocorticoid receptor (GR; de Kloet et al., 2005; McEwen et al., 1997). The two receptors differ in their affinity for cortisol (with the MR having a ten-fold higher affinity). In addition they differ in their localization within the CNS and in the periphery (Miller et al., 1990). Although both receptors reside in the cytoplasm, recent evidence suggests the existence of a membrane bound form of the MR characterized by a lower affinity compared to its intracellular counterpart (Joels et al., 2008). Since the MR appears to have a limited role in the influence of GCs on the immune system (Lim et al., 2007), and due to the fact that most CNS effects of increased GCs on memory have been attributed to GR mediated effects (Roozendaal et al., 2006) we focus on the GR in this review. However, preliminary evidence pointing to involvement of the MR in the processes described in the following will be presented.

Generally, the GR is found in the cytoplasm as part of an assembly consisting of the receptor itself, the chaperones heat shock protein 90 (HSP90), HSP70, as well as co-chaperones, such as FK506 binding protein 5 (FKBP5), and other proteins, such as p23 (Pratt, 1993). This GR heterocomplex undergoes constant conversion from a non-steroid binding back to a steroid binding state. Upon ligand binding, the GR dissociates from the chaperone protein complex, undergoes a conformational change, and translocates to the nucleus. Within the nucleus, hormone-activated GR homodimers can act in two ways, either by interacting with specific DNA sequences (glucocorticoid response elements, GREs) in the promoter region of glucocorticoid responsive genes, thereby enhancing (GRE) or inhibiting (negative GRE, nGRE) transcription, or by interaction with other transcription factors (McKay and Cidlowski, 1999). Given the complexity of the glucocorticoid signal transduction pathway, it is conceivable to expect various mechanisms and modulators to interfere at different levels and thus to change the transcriptional output (for an overview, see Bamberger et al., 1996). For example, GR number and function can be regulated ligand-dependently, by the concentration of GCs themselves (Silva et al., 1994), or ligand-independently, by factors such as pro-inflammatory and type-1 cytokines that are found to up-regulate transcription of the GR (e.g. Pariante et al., 1999). One pathway might be the specific up-regulation of the non-ligand-binding beta isoform of the GR (GR-beta), which is thought to act as an endogenous inhibitor of GC action (Bamberger et al., 1995; Webster et al., 2001) resulting in the down-regulation of glucocorticoid sensitivity of target cells (for more details on cytokine effects on GR function, see Pace et al., 2007).

Given the number of steps and the plethora of already documented, as well as probably yet undiscovered influences on the GC signaling cascade, it is not surprising that studies conducted in the last decade were able to report inter- and intra-individual differences in the ability of target tissues to respond to glucocorticoid signals (DeRijk et al., 1996; Miller et al., 2002a; Rohleder et al., 2003). Furthermore, some of these factors are constant within one organism (e.g. GR polymorphisms), while others can differ between target tissues. Some modifications of the signaling cascade are dynamic, for example, leading to GC sensitivity alterations during acute stress (Rohleder et al., 2003), while others can be better described as relatively static or as long-term alterations, for example, due to early life experiences or chronic stress (e.g. Miller et al., 2002a; Weaver et al., 2004; Rohleder et al., 2009a). Because of the potential variability of different target tissues' sensitivity to vital GC signaling, it has been concluded that assessment of GC concentrations alone is not sufficient to draw conclusions about the efficiency of HPA signaling. Hence, in the following two sections, we will describe methods to assess glucocorticoid sensitivity in two tissues, the central nervous system (CNS) and the immune system.

2.1. Assessment of glucocorticoid sensitivity in CNS structures relevant for cognition

With regard to the CNS, electrophysiological measures have been used to investigate central GC sensitivity in animals (e.g. in vitro changes in neuronal excitability in hippocampal slices; Diamond et al., 2007; Joels, 2001). However, in humans, such invasive approaches are not feasible. Hence, human research has to address the issue of central GC sensitivity via indirect approaches.

One approach is to utilize GCs, negative feedback action on the pituitary and the hypothalamus (Dallman et al., 1994; de Kloet et al., 2005). The sensitivity of these target regions can be assessed using well-established pharmacological challenge protocols such as the dexamethasone (DEX) suppression test (DST; The APA Task Force on Laboratory Tests in Psychiatry, 1987) or the combined DEX/CRH Test (Ising et al., 2005). The DST primarily tests feedback at the level of the pituitary (de Kloet, 1997), while the DEX/CRH test might assess feedback sensitivity of supra hypothalamic regions (Ising et al., 2005).

GCs also act on a range of other brain structures that are involved in HPA control, but are also crucially important for learning and memory. In this context, the hippocampus, the amygdala, and the prefrontal regions have received attention (de Kloet et al., 2005; Diamond et al., 2007; Joels et al., 2006; Wolf, 2008). For hippocampus mediated long-term memory, GCs enhance memory consolidation but impair memory retrieval. These behavioral effects are caused by GC effects on neurons in the amygdala and hippocampus (Joels et al., 2006; Roozendaal et al., 2006; Wolf, 2009). In addition, there is evidence that GCs impair cognitive functions mediated by the prefrontal cortex (e.g. working memory; Lupien et al., 1999).

Experimental studies investigating central nervous system effects of GCs regularly observe a substantial inter-individual variation in the size of the GC effect on memory. This variation