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How to measure glucocorticoid receptor's sensitivity in patients with stress-related psychiatric disorders

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ABSTRACT

Stress is a state of derailed homeostasis and a main environmental risk factor for psychiatric diseases. Chronic or uncontrollable stress may lead to a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is a common feature of stress-related psychiatric disorders. One of the key mechanisms underlying a disturbed HPA axis is an impaired function of the glucocorticoid receptor (GR) with an enhanced or reduced feedback sensitivity for glucocorticoids and subsequently altered concentrations of peripheral cortisol. GR function is regulated by a multiprotein complex including the different expression of the hsp90 co-chaperone FK 506 binding protein 51 (FKBP5) that may be genetically determined or acquired in response to stressful stimuli. Specific patterns of a dysregulation of the HPA axis and GR function are found in different stress-related psychiatric entities e.g. major depression, job-related exhaustion or posttraumatic stress disorder. GR challenge tests like the dexamethasone-suppression test (DST), the dexamethasone-corticotropin-releasing hormone (dex-CRH) test or most recently the analysis of the dexamethasone-induced gene expression are employed to sensitively measure HPA axis activity in these disorders. They provide information for a stratification of phenotypic similar but neurobiological diverse psychiatric disorders.

In this review we present a synopsis of GR challenge tests with a focus on the application of the DST, the CRH test and the dex-CRH test as well as the dexamethasone-induced gene expression in stress-related psychiatric entities.

1. Introduction

Since Walter Cannon developed further Claude Bernard's concept of homeostasis in the early 20th century (Cannon, 1933) and Hans Selye introduced the "term general adaption syndrome" in the 1950s (Selye, 1950) the concept of stress is defined as a nonspecific response of the body comprising behavioral and physical adaptive reactions to meet the needs of the posed threat to homeostasis. The "nonspecific response" has ever since been associated with the activation of the hypothalamic-pituitary-adrenal (HPA) axis, climaxing in hyper-cortisolism via an increased production of corticotropin-releasing hormone (CRH) in the hypothalamus and a consecutive increase in ACTH in the pituitary followed by glucocorticoids secreted from the adrenal glands. If this non-specific response persists it leads to an impaired adaption and ultimately results in pathological changes of the endocrine and immune system (Leonard and Myint, 2009).

Psychosocial stress seems to play a crucial role in the development of psychiatric disorders. Short increases of stress hormones compile mostly protective effects against other stress-activated bodily systems, whereas if the stress response persists over a longer period of time it induces long-term alterations of the HPA axis as observed in subjects afflicted with unemployment and job-related exhaustion or after traumatic events such as war, sexual abuse or accidents (Morris et al., 2012).

In the past decades there has been growing evidence of a dysregulation of the HPA axis not only in major depression, but also in other stress-related psychiatric entities (Holsboer and Ising, 2010). The frequency of psychiatric symptoms in states of endocrine rearrangements e.g. during pregnancy, post partum or in the perimenopausal phase, was described as early as in the 1940s by psychiatrist Manfred Bleuler, who also noted endocrinological changes in psychiatric states and psychiatric symptoms e.g. mood changes in diseases of the hormone system (Steinberg et al., 2015).

A dysregulation of the HPA axis is one of the most robust laboratory finding in a variety of psychiatric entities. Changes in glucocorticoid sensitivity and the levels of mediators of the stress response, catecholamines, glucocorticoids and cytokines, may not only be the sequence of allostatic load, but be the sine qua non of an illness-specific

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psychopathology. However, the measurement of baseline concentrations of the endocrine hormones did not produce consistent patterns of the HPA axis function in different stress-related psychiatric disorders (Holsboer, 2000). Moreover, tests challenging the HPA axis via an activation of the glucocorticoid receptor (GR) or the CRH type 1 receptor (CRHR1) produced more reliable evidence of reproducible alterations of the HPA axis. In this review we give an overview of tests challenging the HPA axis with a focus on glucocorticoid signaling in stress-related psychiatric disorders. Common features and different endocrine patterns in response to the application of the dexamethasone-suppression test (DST), the CRH test and the dexamethasone-corticotrophin releasing hormone (dex-CRH) test as well as the dexamethasone-induced gene expression in major depression, posttraumatic stress disorder and job-related exhaustion are described. Major depression represents a stress-related psychiatric disorder with a high prevalence, a severe burden for patients, a major socioeconomic impact and robust alterations in HPA function. Posttraumatic stress disorder is also associated with robust HPA axis alterations, but with a contrary pattern as major depression, and is provoked by a clear environmental hit. Although job-related exhaustion is not a clinical diagnosis according to DSM-5 or ICD-10, but it combines clinical features of major depression and is promoted by an unfavorable environment.

2. Physiological and pathological functioning of the HPA axis

2.1. Physiological functioning of the HPA axis

The HPA axis is the key element of stress response in the central nervous system (CNS) (Holsboer and Ising, 2010). Physical stressors act on the brainstem and the hypothalamic regions; psychological stressors on brain regions that are involved in emotions, the memory of emotionally arousing experiences and fear (amygdala), memory (hippocampus) as well as executive functions (prefrontal cortex, PFC) (Arnsten, 2009; Joels and Baram, 2009; Roozendaal et al., 2009; Popoli et al., 2011). Firstly, a stressful stimulus promotes the release of the monoamines noradrenaline, dopamine and serotonin from the hippocampus, the amygdala, the prefrontal cortex (PFC) and the nucleus accumbens amongst others. The paraventricular nucleus (PVN) of the hypothalamus synthesizes CRH, arginine vasopressin (AVP) and other neuropeptides to operate broad and yet distinct autonomic, humoral and behavioral effects. CRH itself is also a neuroregulator in extra-hypothalamic circuits (Gallagher et al., 2008). It is involved in immune functions, cognition, regulation of vegetative functions e.g. decreased sleep, libido and appetite as well as increased anxiety (Holsboer and Ising, 2010), motility of the gastrointestinal tract, development and regulation of cardiac function and vascular tone (Quintanar and Guzman-Soto, 2013). In the amygdala CRH is part of regulatory function of behavioral and autonomic responses to stress including stress-related anxiety and structural plasticity (McEwen, 2006).

CRH bind to CRH receptors 1 and 2 in the anterior pituitary and induce the synthesis and release of ACTH in the circulation (Fig. 1; (Holsboer and Ising, 2010). ACTH activates the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. GCs are omnipresent in the body in almost every tissue. In the blood they are bound to corticoid binding globuline (CBG), which regulates the availability of cortisol for biological action. GCs comprise multiple functions involving regulation of homeostasis, energy metabolism (e.g. gluconeogenesis, lipolysis, protein degradation), cellular differentiation, as well as neuronal survival and neurogenesis (Pariante and Lightman, 2008). They are involved in the acquisition of new memories and appraisal of events (Gold, 2015), and regulation of higher functions such as sexuality and mood (Anacker et al., 2011). GCs have direct effects on immune functions and inflammation (Padgett and Glaser, 2003). Infections stimulate–apart from adaptive and innate immune functions–the HPA axis and prevent an overshooting of the immune response (Rosenblat et al., 2014). Cortisol is secreted at a wide concentration range following a circadian rhythm acting at multiple targets. The highest concentrations of cortisol are measured in the morning, the nadir at about midnight (Chan and Debono, 2010). Homeostasis of the HPA axis however is guaranteed by balanced feedback mechanisms allowing to adapt to acute and chronic stressors (Holsboer, 2000). Under stressful conditions the amplitude and frequency of the pulsatile release of GCs increases (Holsboer and Ising, 2010). The negative feedback inhibition of the HPA axis is induced by endogenous glucocorticoids. Pivot of the HPA feedback mechanism are mainly the GRs expressed within the hypothalamus and pituitary. Specifically, glucocorticoids bind to the GRs of the hippocampus, the PVN and cells of the anterior pituitary gland and thus inhibit the synthesis and secretion of CRH in the PVN and ACTH in the pituitary via mostly GABA-ergic interneurons (Pariante and Lightman, 2008). The activated GRs inside and outside the brain induce a feedback inhibition leading to a reduction of the HPA axis activity. Mechanisms regulating the GR feedback inhibition involve GR expression and GR function and the availability of cortisol influenced by the blood-brain barrier and its transporters (Pariante and Lightman, 2008).

The genomic effects of GCs are primarily induced by two related receptor molecules, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). MRs are highly expressed in neurons of the hippocampus and the lateral septum, moderately expressed in the amygdala, the PVN and the locus coeruleus. GRs are ubiquitously expressed in the brain with a high density in the hippocampus, the lateral septum and the PVN. Both receptors bind primarily cortisol, but with a tenfold difference in affinity (Reul and de Kloet, 1985). The higher affinity MR is almost completely occupied with basal glucocorticoid concentrations under physiological circumstances, the lower affinity GR is progressively activated during stress- and circadian-related increases in the frequency and amplitude of cortisol secretory bursts (de Kloet et al., 2005).

2.2. Critical components of the HPA axis –GR and FKBP5

GCs enter cells by passive membrane passing and bind to the cytosolic glucocorticoid receptors (GR; Fig. 1). Chaperone-assisted folding determines conformational changes and thereby the binding capacity of the GR, but also trafficking and turnover of the GR (Holsboer, 2000). The GR is a ligand-activated transcription factor. The most common pathway of an activated GR is a dimerization and translocation into the nucleus where GR homodimer bind to glucocorticoid response elements (GREs) in the promotor region of glucocorticoid-responsive target genes on the DNA and activate gene transcription (transactivation). By binding to negative GREs (nGREs) GR homodimer may also cause repression of gene transcription (transrepression) (Zhou and Cidlowski, 2005).

When inactive the GR is part of a multiprotein-complex consisting of heat-shock proteins (hsp) and immunophilins Fig. 1; (Pratt and Toft, 1997). The formation of a heterocomplex consisting of hsp90, and hsp70 as essential chaperones and hsp70-organizing protein (hop), hsp 40 and p23 (Pratt et al., 2006) is a prerequisite for a cytosolic high-affinity steroid-binding conformation (Bresnick et al., 1989). Above all the hsp90 co-chaperone FK506 binding protein 51 (FKBP5) (Binder, 2009) is crucial for the determination of GR sensitivity and has been associated with disturbances of the HPA axis in stress-related psychiatric disorders (Binder, 2009; Zannas et al., 2016). FKBP5 is supposed to modulate the stress response of the GR by regulating gene-environment-epigenetic interactions (Zannas et al., 2016).

The co-chaperone FKBP5 is an important glucocorticoid-induced functional regulator of the GR complex (Fig. 1). FKBP5-binding induces a confirmation of lower binding affinity for cortisol (Jaaskelainen et al., 2011). After glucocorticoid binding FKBP5 is exchanged against FK506 binding protein 52 (FKBP4) which can then bind dynein. Subsequently the translocation of the GR-complex into the nucleus is allowed and then GR activation promotes FKBP5 mRNA and protein expression