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REVIEW

Neuropsychological functioning in health and mood disorder: Modulation by glucocorticoids and their receptors

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Summary Numerous studies have shown that disturbances in hypothalamic—pituitary—adrenal (HPA) axis function and consequent hypercortisolaemia occur in a significant proportion of patients with mood disorders. This dysfunction has been proposed to be an exacerbating factor of depressive symptoms and may predict symptomatic relapse. Glucocorticoids are also known to have a specific role in learning and memory processes. In this review we present a brief overview of the relationship between HPA axis dysfunction and neuropsychological impairment in mood disorders and the specific links between glucocorticoids and cognition in health and illness states. Finally we examine the neuropsychological effects of drugs that specifically target glucocorticoid receptor function.

Contents

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1. Introduction

There is a wealth of evidence demonstrating both neuropsychological impairment and hypothalamic—pituitary—adrenal (HPA) axis dysfunction in patients with mood disorders. However, a direct causal relationship remains difficult to establish. In this review we will first present a brief overview of this evidence before reviewing the literature from healthy subjects and clinical populations in which the direct effects of glucocorticoid manipulation have been examined. Finally we focus on the neuropsychological effects of drugs that directly target glucocorticoid receptors, an area of developing therapeutic research.

1.1. The HPA axis

The HPA axis is one of the primary systems mediating physical and psychological stress responses in humans. Neurones located in the paraventricular nucleus of the hypothalamus secrete corticotropin releasing hormone (CRH) which is transported via the hypothalamo—pituitary portal circulation to the anterior pituitary where adrenocorticotropic hormone (ACTH) is secreted through stimulation of pituitary corticotrophs. ACTH then stimulates the adrenal cortex to secrete glucocorticoids: corticosterone in rats and cortisol in humans.

1.2. Cortisol and corticosteroid receptors

Under basal conditions in healthy humans, cortisol secretion follows a 24-h circadian rhythm where levels are highest at waking and slowly decline to a nocturnal low (Weitzman et al., 1971). As with many hormones cortisol is released in a pulsatile manner throughout this cycle (Young et al., 2004b). A great deal of individual variability can be seen in the secretion of both ACTH and cortisol. Although secretion of the two hormones is not quantitatively linked throughout the day, ACTH has been shown to be the stimulating factor of cortisol release under basal conditions (Follenius et al., 1987; Bornstein et al., 2008). Time-series analysis identifying the periods of the oscillations in plasma levels of cortisol and ACTH in healthy individuals has shown an average periodicity in the oscillations of between 55 and 140 min for ACTH but 95—180 min for cortisol, indicating that a single cortisol peak may be initiated by more than one ACTH peak (Follenius et al., 1987).

Cortisol is involved in the regulation of fat, protein and carbohydrate metabolism, electrolyte balance, body water distribution, blood pressure and has an immunosuppresant anti-inflammatory action (Berne and Levy, 1998). It is also a key regulator of the neuroendocrine stress response, through negative-feedback actions at specific corticosteroid receptors. Two corticosteroid receptor sub-types have been identified; the mineralocorticoid receptor (MR; Type I) and the glucocorticoid receptor (GR; Type II). Both receptors have been implicated in mediating glucocorticoid feedback (Reul and de Kloet, 1985). However there are several differences in the distribution, occupancy and binding properties of the two receptors that affect their physiological role.

GR have been shown to be widely expressed in the central nervous system with highest densities in cortical regions including prefrontal cortex, in limbic areas including hippocampus and amygdala, and in the thalamus and hypothalamus. In the cortex expression is concentrated in pyramidal cells, while in the hippocampus both pyramidal and granule cells express GR (Fuxe et al., 1987; Ahima et al., 1991; Cintra et al., 1994; Patel et al., 2000). Mapping of MR in the CNS has been less comprehensive and data are less consistent. However, a widespread distribution has been noted (Ahima et al., 1991) with particularly high MR density in hippocampal, thalamic and hypothalamic regions (Ahima et al., 1991; Agarwal et al., 1993; Ito et al., 2000). Glucocorticoids bind to the MR with around a 6—10-fold greater affinity than to GR (de Kloet et al., 1999). At basal levels, near complete occupation of MRs occurs while GRs are minimally occupied at this point and only during times of high cortisol secretion, such as the circadian peak or during stress, do MRs become saturated and GR occupancy increases (Reul and de Kloet, 1985; de Kloet and Reul, 1987) (but also see Pace and Spencer, 2005).

2. HPA axis dysfunction in mood disorders

Since the work of Board and colleagues (Board et al., 1956, 1957) over half a century ago, many studies have replicated the findings of raised cortisol levels and HPA dysfunction in patients with mood disorders (Gibbons and McHugh, 1962; Gibbons, 1964; Gallagher et al., 2007b). With more refined techniques it has been established that not only is overall cortisol production increased (Carroll et al., 1976), but also the diurnal profile is altered (Linkowski et al., 1985) with greater waking levels observed during the morning peak (Bhagwagar et al., 2005) and increased levels at the evening nadir, resulting overall in a flattened diurnal rhythm (Deuschle et al., 1997; Posener et al., 2000; Wong et al., 2000).

The most sensitive tests of HPA axis function, however, are 'activating' tests whereby neuroendocrine responses are measured following pharmacological challenge. These are preferred not only because of their increased sensitivity, but also because they elucidate functional changes in the HPA axis at the receptor level (Watson et al., 2006a). The GR agonist dexamethasone has been used widely to examine HPA axis negative-feedback integrity (Rush et al., 1996). An abnormal (non-suppressed) cortisol response to dexamethasone administration has been described in patients with mood disorder (Rush et al., 1996) and may be more