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Review

Temporal control of glucocorticoid neurodynamics and its relevance for brain homeostasis, neuropathology and glucocorticoid-based therapeutics

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ABSTRACT

Glucocorticoids mediate plethora of actions throughout the human body. Within the brain, they modulate aspects of immune system and neuroinflammatory processes, interfere with cellular metabolism and viability, interact with systems of neurotransmission and regulate neural rhythms. The influence of glucocorticoids on memory and emotional behaviour is well known and there is increasing evidence for their involvement in many neuropsychiatric pathologies. These effects, which at times can be in opposing directions, depend not only on the concentration of glucocorticoids but also the duration of their presence, the temporal relationship between their fluctuations, the co-influence of other stimuli, and the overall state of brain activity. Moreover, they are region- and cell type-specific. The molecular basis of such diversity of effects lies on the orchestration of the spatiotemporal interplay between glucocorticoid- and mineralocorticoid receptors, and is achieved through complex dynamics, mainly mediated via the circadian and ultradian pattern of glucocorticoid secretion. More sophisticated methodologies are therefore required to better approach the study of these hormones and improve the effectiveness of glucocorticoid-based therapeutics.

Contents

Abbreviations: 11βHSD, 11β-hydroxysteroid dehydrogenase; ACTH, corticotrophin; AD, alzheimer disease; AGs, adrenal glands; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP, anterior pituitary; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BNST, bed nucleus of stria terminalis; CBG, cortisol binding globin; CCR, cortisol to corticosterone ratio; CNS, central nervous system; CRH, corticotrophin-releasing hormone; CYP2D, cytochrome P450 2D; D1, dopamine receptor type 1; D2, dopamine receptor type 2; GABA, gamma-aminobutyric acid; $GABA_A$, GABA receptor type A; GC, glucocorticoid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal (axis); IL-1β, interleukin 1beta; LTP, long term potentiation; MR, mineralocorticoid receptor; NFκB, kappa-light-chain-enhancer of activated B cells nuclear factor; NO, nitric oxide; P450c11β, cytochrome P450 11-beta-hydroxylase; P450c21, cytochrome P450 21-hydroxylase; PD, parkinson disease; PFC, prefrontal cortex; PGP, P-glycoprotein; PVN, paraventricular nucleus; TBI, traumatic brain injury; TNFα, tumour necrosis factor alpha; SCN, suprachiasmatic nucleus.

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1. Introduction: Glucocorticoids and their clinical significance

The hypothalamic-pituitary-adrenal (HPA) axis, whose significance in human and animal physiology and pathology has been extensively studied for many decades, is crucially involved in regulating internal homeostatic mechanisms (many of which have a circadian pattern) and coordinating the organisms' stress responses. Many of these phenomena are regulated in man by one of the main end-products of the axis, the glucocorticoid (GC) cortisol, and to a lesser extent by corticosterone (which additionally constitutes the primary GC type in rodents and other non-human primates). These adaptation processes, which are characterized by great diversity, involve regulation of developmental (Allen, 1996; Jobe et al., 1998) and metabolic pathways (van Rossum and Lamberts, 2004), immune system components (Sorrells and Sapolsky, 2007) as well as modulation of human cognition and behaviour.

It is well known that GCs are biosynthesized for immediate release in the cortical *zona fasciculata* of the adrenal glands (AGs), and due to their lipophilic nature they rapidly diffuse across cell membranes, and are distributed via the systemic circulation predominantly – approximately 95% – bound to carrier proteins, mainly cortisol binding globin (CBG), and albumin, throughout the body (Lightman and Conway-Campbell, 2010) and cleared through liver (bile acids) and kidneys (urine) (Glantz et al., 1976). As indicated by these dynamic physicochemical properties as well as by more recent studies on endogenous GC dynamics (Hughes et al., 2010), GC abundance in the various tissues is primarily regulated by: (i) the pattern of their release into the systemic circulation from the adrenal cortex (i.e. the mode and integrity of activity of the HPA axis) (Henley et al., 2009a), (ii) the ratio of the circulating free to bound form (which is temperature-dependent and together with the concentration of CBG determines the availability of the biologically active cortisol) (Lentjes and Romijn, 1999), (iii) the tissue-specific existence of enzymes that locally modulate active GC levels (cortisol conversion to inactive cortisone and *vice versa*) (Tomlinson et al., 2004), (iv) the capacity of some tissues (for instance the brain) to locally produce/regenerate steroids (Mellon et al., 2001), (v) the activity of the P-glycoprotein (PGP) pump across the blood-brain barrier (BBB) and (vi) the clearance rate of GCs from liver and kidneys. Processes (i), (ii) and (vi) determine the temporally-fluctuating, biologically active systemic GC concentrations.

The wide spectrum of GC-related biological actions, apart from indicating their generic significance in human (and many other animal species') physiology, has been exploited in the field of therapeutics of various disorders; natural or synthetic GCs are prescribed/used in several clinical conditions for instance inflammatory-oedematous diseases like serious allergies, asthma, serious bacterial infections (in combination with antibiotics) and primarily autoimmune disorders (Hill et al., 1990; Rhen and Cidlowski, 2005). Other therapeutic indications of GCs include conditions like chronic pain (in combination with first line pain killers under multi-drug schemes) and neoplastic lesions (again in combination with first line anti-neoplastic drugs under multi-drug schemes), as well as adrenal insufficiency (replacement therapy) (Crown and Lightman, 2005a).

Unfortunately, treatment with GCs is often only partial effective and also results in adverse effects (Boling, 2004; Crown and Lightman, 2005b). In the field of applied clinical neurosciences, GC-based therapeutics present two major challenges; the reduction of the neuropsychiatric adverse effects that accompany their high-dose or long-term use (Klein, 1992; Tavassoli et al., 2008; Ricoux et al., 2013) and good scientific evidence for their effectiveness (in neurological cases occasionally prescribed). To overcome these challenges, as well as to further explore possible applications of GCs in other neurological processes including diagnosis, discrimination between disease subtypes, prognosis, treatment strategies of neuropsychiatric conditions, it is important to conceptualize the multi-level regulatory dynamics of GCs in stress regulation and health preservation (Young et al., 2004).

The purpose of this article is to discuss how the new concept of HPA pulsatility can provide a methodological and clinically significant advance for our understanding of stress physiology and pathology. We place GCs' effects on brain's functional phenotypes into the context of HPA rhythmicity, as well as highlight some important concepts related to GC neurodynamics in brain physiology and pathology.

2. Inconsistencies in our understanding of GC therapeutics in neurology

There is a characteristic discrepancy between the preclinical evidence that support the utilization of GC-based therapeutics or prognostic markers in various pathological cases and the poor results in terms of their efficiency or appropriateness when they are actually applied in clinical practice. This is also the case in neurological conditions.

Association of GCs with stroke evolution and prognosis has for instance been highlighted in clinical terms, since cortisol levels were found high during the first post-stroke week and such concentrations were associated with higher prevalence of systolic blood hypertension and night-time blood hypertension 24-h after stroke (Ahmed et al., 2004), and with increased dependency, delirium incidences, depression and mortality rates in post-stroke patients (though these conclusions are not necessarily independent of stroke severity and thus GC levels cannot be used as independent prognostic markers) (Barugh et al., 2014). Nevertheless, there is serious scientific confusion on whether GC levels can be used for short- and/or long-term prognosis of post-stroke patients, as well as at what stage of the post-stroke clinical evaluation these data should be acquired and interpreted (Christensen et al., 2004; Johansson et al., 2000; Marklund et al., 2004). There is also a debate on the causal origin of these raised GC concentrations, whether