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Review

Dynamics of adrenal glucocorticoid steroidogenesis in health and disease

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ABSTRACT

The activity of the hypothalamic–pituitary–adrenal (HPA) axis is characterized by an ultradian (pulsatile) pattern of hormone secretion. Pulsatility of glucocorticoids has been found critical for optimal transcriptional, neuroendocrine and behavioral responses. This review will focus on the mechanisms underlying the origin of the glucocorticoid ultradian rhythm. Our recent research shows that the ultradian rhythm of glucocorticoids depends on highly dynamic processes within adrenocortical steroidogenic cells. Furthermore, we have evidence that disruption of these dynamics leads to abnormal glucocorticoid secretion observed in disease and critical illness in both humans and rats.

Contents

1. Introduction

Glucocorticoids (cortisol in humans and corticosterone in rodents) are vital hormones produced by the activity of the hypothalamic–pituitary–adrenal (HPA) axis that play a key role for homeostatic regulation. Glucocorticoids are released rapidly in response to both internal and external stressors to facilitate homeostatic regulation by exerting metabolic, anti-inflammatory and immunosuppressive effects, and by affecting mood and cognitive function. Glucocorticoids are synthetized in the adrenal gland cortex in response to adrenocorticotropic hormone (ACTH) release from the anterior pituitary (Dallman and Jones, 1973; Dallman et al., 1987a), which, in turn, is regulated by the secretion of the neuropeptides corticotropin releasing hormone (CRH) and vasopressin from the paraventricular nucleus of the hypothalamus (PVN). Once released from the adrenal glands into the blood circulation, glucocorticoids access target tissues, such as the liver, the heart and vascular tissues, to exert metabolic and cardiovascular effects respectively, and the brain to promote, for example,

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cognitive processes necessary to cope with a threatening situation (De Kloet, 2004). Glucocorticoids also regulate the activity of the HPA axis, and thus their own production, through feedback mechanisms acting at the level of the PVN and the pituitary gland, where they inhibit the release of CRH and AVP (Dallman et al., 1987a, 1987b; Jones et al., 1977), and ACTH (Jones et al., 1977) respectively. Furthermore, glucocorticoids can indirectly regulate HPA axis activity via modulation of other brain structures, including the hippocampus, the amygdala and the prefrontal cortex, which, in turn, regulate the activity of the PVN (Ulrich-Lai and Herman, 2009).

Under basal (i.e., unstressed) conditions, ACTH and glucocorticoids display a highly dynamic pattern that is characterized by both a circadian and an ultradian rhythm of hormone secretion. Indeed, circadian variations in glucocorticoids levels over the 24-hour cycle are not made up of a smooth change in hormone levels, but is in fact characterized by a rapid ultradian, pulsatile pattern of hormone secretion, with a periodicity of approximately 1 hour in the rat (Fig. 1). The ultradian rhythm of glucocorticoids was first described in the rat by Jasper and Engeland (1991). By using intra-adrenal microdialysis techniques in non-stressed freely behaving animals they observed that, in addition to the hourly corticosterone pulse frequency, both the ultradian frequency and amplitude of the pulses were modulated in a circadian manner (Jasper and Engeland, 1994). The ultradian rhythm of corticosterone has been also investigated in the rat plasma by using an automated blood-sampling system (Clark et al., 1986) that allows collection of small blood samples at a high frequency (e.g. every 5–10 minutes) for an extended periods of time (Windle et al., 1998b) in unstressed and freely moving rats over the whole 24-hour cycle. During the last 25 years our group has used this automated sampling system to show that, consistent with previous findings, the pulsatile corticosterone rhythm is maintained in the blood, with an ultradian frequency similar to that observed in the adrenal gland. Further, analysis of corticosterone pulse characteristics using the PULSAR algorithm (Merriam and Wachter, 1982) has shown that the pulse amplitude varies in a circadian manner, with low amplitudes in the morning and higher amplitudes in the evening (Windle et al., 1998a).

Our studies in the rat have shown a marked sexual diergism (Seale et al., 2004a, 2004b) and genetic variation (Windle et al., 1998a) in both the circadian and the ultradian pattern of corticosterone. Disruption of ultradian corticosterone dynamics has been also shown in a number of pathological states. For example, rats exposed to chronic inflammation have a hyperactive HPA axis, characterized by increased corticosterone pulsatility throughout the 24-h cycle that results in flattening of the hormone circadian rhythm (Windle et al., 2001).

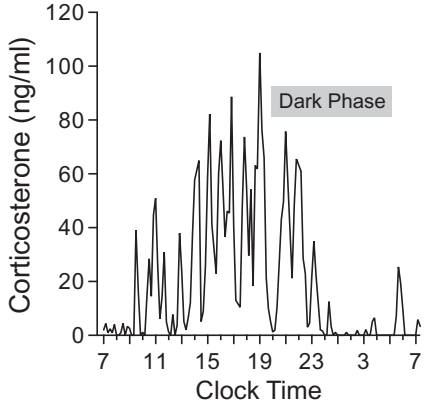

Fig. 1. Ultradian rhythm of corticosterone in the rat. Under basal (unstressed) conditions, the dynamics of corticosterone secretion is characterized by both a circadian and an approximately hourly ultradian rhythm. In the rat, peak levels of corticosterone occur prior to the active dark phase (gray bar). The figure shows an individual corticosterone profile: blood samples were collected from a male Sprague Dawley adult rat every 10 min for 24 hours using an automated blood sampling system; corticosterone levels were measured by radio-immune assay.

In addition to the rat, an ultradian rhythm of glucocorticoids has been reported in numerous species, including rhesus monkey (Holaday et al., 1977; Tapp et al., 1984), sheep (Fulkerson, 1978), and human (Henley et al., 2009a; Lewis et al., 2005; Weitzman et al., 1971).

The functional interaction between glucocorticoid pulsatility and the neuroendocrine and behavioral response to stress has been investigated in a number of studies. For example, in rats exposed to stress, the timing of the stressor relative to the phase of the underlying ultradian rhythm is crucial in determining the magnitude of the ACTH and corticosterone response to the stressor (Sarabdjitsingh et al., 2010; Windle et al., 1998a). This neuroendocrine response is also associated with a different behavioral response to the stressor, such as grooming, locomotion, and risk assessment, which are higher in rats that are stressed during the rising phase of corticosterone, compared to rats exposed to stress during the falling phase of the hormone pulse (Sarabdjitsingh et al., 2010). Furthermore, corticosterone pulsatility is also important for social behavior, as seen in resident rats that are more aggressive during the rising phase of a corticosterone than during the falling phase, when exposed to an intruder rat (Haller et al., 2000).

Ultradian rhythmicity of glucocorticoids in the plasma is paralleled by pulses of free hormone in the tissue, including subcutaneous tissue (Bhake et al., 2013; Qian et al., 2012) and saliva (Trifonova et al., 2013), and in the brain (Droste et al., 2008). Studies in vitro and in adrenalectomized rats, in which the endogenous hormone was replaced by either pulsatile or constant infusion of corticosterone, have shown that normal gene expression of glucocorticoid-target genes is only achieved with pulsatile corticosterone infusion, whereas the transcriptional response is disrupted when the tissue is exposed to constant glucocorticoid (Conway-Campbell et al., 2010; Stavreva et al., 2009). Indeed, ultradian corticosterone pulses are paralleled by rapid GR nuclear translocation (Conway-Campbell et al., 2007), cyclic GR binding to the DNA in the promoter sequences of glucocorticoid-responsive genes (e.g. Period (Per) 1) (Conway-Campbell et al., 2010; Stavreva et al., 2009), and by a rapid and transient increase in hnRNA for several GR-regulated genes. In contrast constant exposure to corticosterone is associated with a continuous increase in hnRNA and accumulation of higher levels of mature RNA (mRNA) and protein (Stavreva et al., 2009), which is consistent with data predicted by mathematical modeling of this system (Scheff et al., 2012). Interesting, this transient activation that is typical of normal ultradian rhythmic only occurs in response to the endogenous glucocorticoids such as corticosterone and hydrocortisone, whereas a single pulse of the synthetic glucocorticoid analog dexamethasone results in a prolonged GR activation profile (Stavreva et al., 2009). Pulsatile secretion of glucocorticoids is necessary to maintain a state of constant dynamic equilibration preventing down-regulation of signaling processes and/or abnormal prolonged activation of glucocorticoid responsive genes. It is therefore clear that abnormal constant exposure of glucocorticoids in target organs, as seen in several diseases in humans, and during treatment with long-lasting synthetic glucocorticoids, can have biological consequences such as glucocorticoid resistance and immune dysregulation.

Details of the importance of pulsatility for the genomic and non-genomic effects of glucocorticoids have been recently reviewed (Spiga et al., 2014). In this review article, we will focus on the mechanisms underlying the origin and regulation of pulsatility in the adrenal gland, and how these mechanisms become disrupted in disease and critical illness.

2. The origin of CORT ultradian rhythm

2.1. Ultradian rhythms of the HPA axis

A number of studies have shown that, in addition to endogenous glucocorticoids, an ultradian pattern underlies other