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A comparison between the equine and bovine hypothalamus-pituitary-adrenocortical axis

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ABSTRACT

In this review, we address the function of the hypothalamus-pituitary-adrenocortical (HPA) axis with special emphasis on the comparison between the bovine and equine species. The pars intermedia of the pituitary gland is particularly well developed in horses and cattle. However, its function is not well appreciated in cattle yet. The Wulzen's cone of the adenohypophysis is a special feature of ruminants. Total basal cortisol concentration is much higher in horses than that in cows with similar free cortisol fractions. Corticotropin-releasing factor (CRF) concentrations in equine pituitary venous blood are lower compared with other species, whereas plasma ACTH concentrations in cows are higher than those in horses. A CRF challenge test induced a more pronounced cortisol response in horses compared with cattle, whereas regarding ACTH challenge testing, the opposite seems true. Based on data from literature, the bovine species is characterized by relatively high basal blood CRF and ACTH and low cortisol and glucose concentrations. Obviously, further lowering of blood cortisol in cattle is easily prevented by the high sensitivity to ACTH, and as a consequence, subsequent increased gluconeogenesis prevents imminent hypoglycemia. Hypoglycemia is less likely in horses given their high muscle glycogen content and their relatively high cortisol concentration. When assessing HPA axis reactivity, response patterns to exogenous ACTH or CRH might be used as a reliable indicator of animal welfare status in cows and horses, respectively, although it is emphasized that considerable caution should be exercised in using measures of HPA activity solely to assess animal welfare.

1. Introduction

Animals respond to stress by activating a wide array of behavioral and physiological responses that are collectively referred to as the stress response [1]. The two main physiological components of the response to a stressor are mediated by the hypothalamus-pituitary-adrenocortical (HPA) axis and by the locus coeruleus and/or norepinephrine autonomic nervous systems to provide a stress response, respectively, resulting in elevation of glucocorticoids and catecholamines in plasma [1–3] primarily involved in metabolic homeostasis [4]. Hypothalamic corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), pituitary adrenocorticotropic hormone, and adrenal glucocorticoids comprise the HPA axis. As the top-level hormone in this cascade, CRF plays a central role in the stress response by regulating the pituitary-adrenocortical axis. Stress is commonly defined as a state of real or perceived threat to homeostasis [1]. As such, glucocorticoids are produced in response to disturbances of the homeostasis and are themselves necessary to mobilize the energy required to restore

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this homeostasis [5,6]. The great number of physiological and behavioral effects exerted by glucocorticoids has an important (patho) physiological impact. As a result, several mechanisms have evolved to control HPA axis activation and integrate the stress response. Glucocorticoid feedback inhibition plays a prominent role in regulating the magnitude and duration of glucocorticoid release. In addition, the HPA axis is regulated at the level of the hypothalamus by a diverse group of afferent projections from limbic, midbrain, and brain stem nuclei [1].

The immunohistochemical presence of neuropeptides and cytokines in endocrine and/or immune cells of the human adrenal medulla and cortex as well as specific binding sites on steroidogenic cells make the presence of additional short-paracrine and ultrashort-autocrine feedback loops on cortical cell proliferation and steroid metabolism likely [7]. Furthermore, genetics contributes to the individual variation in basal and stimulated plasma glucocorticoid levels and also to adrenal gland mass that increases in response to prolonged adrenal stimulation [5]. Recent studies have supported the notion that exposure to glucocorticoids and stress in various forms, durations, and intensities during different periods of development can lead to long-lasting maladaptive HPA axis responses in the brain. These results demonstrate that this maladaptive response is comprised of persistent epigenetic changes in the function of HPA axis-associated genes that govern homeostatic levels of glucocorticoids. Thus, glucocorticoid signaling and its ability to alter the epigenetic landscape is one of the key mechanisms that alter the function of the HPA axis and its associated cascades [8–10]. This response, in turn, stimulates other endocrine glands (anterior and posterior pituitary, adrenal cortex, thyroid, parathyroid, pancreas, and kidney) to secrete secondary hormones, which potentiate fuel mobilization and regulate water and electrolyte concentrations [11]. In animals, the stress reactivity of the HPA axis is consistently greater in females compared with males [12,13].

Although the essential HPA response to stress appears to be conserved in vertebrates, the manner in which it is activated and its effects and consequences vary [14–16]. In this review, we address the function of the HPA axis with special emphasis on the comparison between the bovine and equine species (for a summary see Table 1). The aim of the review was to compare the HPA axis of a veterinary relevant species characterized by a very low basal blood cortisol concentration with a relevant veterinary herbivorous species characterized by a regular blood cortisol concentration, respectively.

2. The hypothalamus-pituitary-adrenocortical (HPA) axis

The HPA axis regulates circulating levels of glucocorticoid hormones thereby rapidly responding to stressors [17]. As such, glucocorticoids are the downstream effectors of the HPA axis, playing essential roles in development, energy balance, immune function and behavior, and feedback actions on the activity of the HPA axis [15,18,19]. The body strives to maintain glucocorticoid levels within certain boundaries, and interference at any level of the axis will influence the other components via feedback loops [20].

Under basal conditions (ie, unstressed with the dynamics of the HPA axis characterized by both a circadian and an ultradian rhythm of hormone secretion), glucocorticoids are released with a pronounced circadian rhythm [17]. In general, the peak in hormone levels occurs toward the end of the dark period in diurnal animals, whereas in nocturnal species, there is a peak toward the end of the light period. In diurnal species (including most farmed animals), a peak is observed in the morning and a trough during the evening and at night [4]. Compared with the horse, circadian rhythm is weak in the bovine species [4]. When studied in more detail, it becomes clear that the circadian rhythm of the HPA axis is characterized by a pulsatile release of glucocorticoids from the adrenal gland that results in rapid ultradian oscillations of hormone levels both in the blood and within target tissues, including the brain. Of note, a circadian rhythm in ACTH release is often undetectable. This dissociation between ACTH and corticosteroids during the circadian cycle suggests a diurnal variation in the adrenal sensitivity to ACTH, with higher responsiveness during the peak phase of glucocorticoid secretion. Indeed, it has been proposed that, in addition to the regulatory effect on CRF secretion, the suprachiasmatic nucleus (SCN) can also regulate adrenal activity independently from hypothalamus-pituitary drive by modulating adrenal sensitivity to ACTH [17]. It should be realized that besides diurnal and ultradian rhythms even seasonal rhythms have been described in several species [4]. Accumulating evidence supports the concept that there is a strong interrelation between the clock system and the HPA axis at multiple levels. The light-activated central clock, within the SCN, controls the activity of the HPA axis through synapses between the SCN and the paraventricular nucleus, thereby providing the basis for the circadian release of glucocorticoids, which in humans reach their zenith concentrations early in the morning and their nadir concentrations late at night. Moreover, the central clock system seems to influence the secretion of glucocorticoids from the adrenal cortices by altering the sensitivity of the zona fasciculata to ACTH, an effect that has been attributed to the activation of the autonomic nervous system by the SCN and/or to the presence of an adrenal peripheral clock. The peripherally expressed clocks receive regulatory information from the central clock through neural and humoral signals and also contribute to the rhythmic release of glucocorticoid hormones [3].

3. The hypothalamus

The paraventricular nucleus of the hypothalamus, where neurons expressing CRF and AVP reside, is central to HPA function. These neurons are a primary site of integration leading to graded endocrine responses to stressors [21,22]. Corticotropin-releasing factor is the primary hypothalamic neurohormone regulating the HPA axis in all vertebrates studied [15,18,23]. Arginine vasopressin is primarily a neurohypophysial hormone, produced in magnocellular neurones of the hypothalamic paraventricular and supraoptic nuclei, but parvocellular CRF neurones also coexpress AVP, which acts as a second “releasing factor” for