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Review

Gonadal steroid hormones and the hypothalamo–pituitary–adrenal axis

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ABSTRACT

The hypothalamo–pituitary–adrenal (HPA) axis represents a complex neuroendocrine feedback loop controlling the secretion of adrenal glucocorticoid hormones. Central to its function is the paraventricular nucleus of the hypothalamus (PVN) where neurons expressing corticotropin releasing factor reside. These HPA motor neurons are a primary site of integration leading to graded endocrine responses to physical and psychological stressors. An important regulatory factor that must be considered, prior to generating an appropriate response is the animal's reproductive status. Thus, PVN neurons express androgen and estrogen receptors and receive input from sites that also express these receptors. Consequently, changes in reproduction and gonadal steroid levels modulate the stress response and this underlies sex differences in HPA axis function. This review examines the make up of the HPA axis and hypothalamo–pituitary–gonadal (HPG) axis and the interactions between the two that should be considered when exploring normal and pathological responses to environmental stressors.

1. Introduction

The origins of the study of stress physiology are rooted in the contributions of the early physiologists, Walter Cannon and Hans Selye. It was Cannon who originally coined the term, "fight or flight", when referring to the physiological responses to acute stressors (Cannon, 1915). He later described the concept of homeostasis as a steady state condition that requires active mechanisms to maintain (Cannon, 1932). These pioneering concepts were further explored by Hans Selye who examined the effect of chronic stressors on an organism's physiology. Selye's studies into the body's reactions to chronic stressors led to his development of the general adaptation syndrome (GAS), a set of nonspecific responses to a stressor which could give rise to pathology after continuous, unrelieved stress.

The pioneering work of Cannon and Selye were closely followed by studies focused on teasing out the biological mechanisms underlying the stress response. These included the demonstration that an anterior pituitary hormone (i.e. adrenocorticotropic hormone; ACTH) can stimulate adrenal glucocorticoid release (Sayers, 1950) and the development of the postulate that pituitary gland function was under neural control (Harris, 1951a,b). The latter hypothesis was based on Harris' observations of the capillary system that existed connecting the ventral hypothalamus with the anterior lobe of the pituitary. In these pioneering studies, Harris demonstrated that disrupting blood flow from the hypothalamus to the pituitary by pituitary stalk section would impair ACTH release (Fortier et al., 1957), whereas electrical stimulation of the rabbit hypothalamus triggered the release of ACTH into the general circulation (De Groot and Harris, 1950). Harris also showed that pituitary explants were non-functional, yet viable (Harris and

Abbreviations: 3ß-diol, 5alpha-androstane-3beta, 17beta-diol; 3α-diol, 5alpha-androstane-3alpha, 17beta-diol; 5-HT, serotonin; 5αR, 5-alpha-reductase; ACTH, adrenocortcotropin releasing hormone; AR, androgen receptor; AVP, arginine vasopressin; BnST, bed nucleus of the stria terminalis; BSA, bovine serum albumin; CBP, CREB binding protein; CORT, corticosterone; CRE, cyclic adenosine monophosphate response element; CREB, CRE binding protein; CRF, corticotropin releasing factor; DES, diethylstilbesterol; DEX, dexamethasone; DHT, dihydrotestosterone; DPN, diarylproprionitrile; ER, estrogen receptor; ERE, estrogen response element; FSH, follicle stimulating hormone; FSL, flinders sensitive line; GABA, gamma-aminobutyric acid; GAS, general adaptation syndrome; GH, growth hormone; GLP-1, glucagon-like peptide 1; GnRH, gonadotropin releasing hormone; GPER, G-protein coupled estrogen receptor; GR, glucocorticoid receptor; HPA, hypothalamo–pituitary–adrenal; HPG, hypothalamo–pituitary–gonadal; HRE, hormone respone element; HSD, hydroxysteroid dehydrogenase; ICV, intracerebroventricular; ir, immunoreactive; ISH, in situ hybridization; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; MPOA, medial preoptic area; MR, mineralocorticoid receptor; NTS, nucleus of the solitary tract; PPT, propylpyrazoletriol; PR, progesterone receptor; PVN, paraventricular nucleus; RAR, retinoic acid receptors; SCN, suprachiasmatic nucleus; SRC, steroid receptor coactivators; T, testosterone; Tfm, testicular feminizing mutation; THR, thyroid hormone receptors; TPH, tryptophan hydroxylase; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone.

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Jacobsohn, 1952). Such studies confirmed the importance of the hypothalamus in controlling anterior pituitary function and helped establish the field of neuroendocrinology as a discipline. Further studies by McCann (1953) and Porter (1953) demonstrated that hypothalamic lesions prevented ACTH release thereby establishing the hypothalamus as the source of the alleged 'releasing factors' that affected pituitary function.

The initial attempts to isolate the putative corticotropin releasing factor (CRF) proved difficult, although initially, the ability of an alternate "CRF", vasopressin, to induce ACTH release was described (McCann and Brobeck, 1954). Hypothalamic releasing factors, such as thyrotropin releasing hormone (TRH), and luteinizing hormone releasing hormone (LHRH, or gonadotropin releasing hormone, GnRH, Schally et al., 1971a) were initially isolated in the late '60s and early '70s (Amoss et al., 1971; Burgus et al., 1970; Nair et al., 1970; Schally et al., 1971b,c), yet, it was a decade later when Vale et al. (1981) isolated, characterized, and described the biological activity of a hypothalamic peptide that caused the release of ACTH from the anterior pituitary gland. Since then, the 41 amino acid CRF, has been shown to be expressed in many brain areas and has been implicated in a wide variety of behaviors and neurobiological functions (Bale and Vale, 2004). We now know that CRF and vasopressin can be co-localized in some neurons of the paraventricular nucleus of the hypothalamus (Sawchenko et al., 1984; Whitnall and Gainer, 1988), that they can be co-released, and that vasopressin acts to enhance the secretogogue properties of CRF at the anterior pituitary gland (Bilezikjian and Vale, 1987; Gillies et al., 1982; Rivier and Vale, 1983).

Of importance for this discussion are the findings that a number of human neuropsychiatric disorders are accompanied by a dysregulation of the HPA axis and that many of these disorders exhibit profound sex differences in risk implicating a modulatory role for gonadal steroid hormones (Kessler et al., 1993; Kessler, 2003). For example, the incidence of major depressive disorder is at least two fold greater in women than in men (Angold and Worthman, 1993; Kessler et al., 1993; Weissman et al., 1993) and this is associated with enhanced HPA activity associated with a reduced ability to feedback regulate the system (Ising et al., 2007; Strohle and Holsboer, 2003). In this review, we first examine the HPA axis and its regulatory elements and follow with a discussion of pre-clinical studies showing sex differences in the function of the HPA axis and the well-described role of gonadal steroid hormones in modulating HPA axis responsivity to stress and stress-related behaviors in adulthood.

2. The hypothalamo–pituitary–adrenal (HPA) axis

2.1. An overview of the HPA axis

Animals respond to real or perceived threats to their welfare by activating neurons that control neuroendocrine responses (e.g. the HPA axis) and the sympathetic autonomic response. For HPA axis activation, the net response is the secretion of glucocorticoids from the adrenal cortex into the general circulation. In humans and many mammals, the main adrenal glucocorticoid is cortisol, whereas corticosterone is the primary glucocorticoid in most rodents. Circulating corticosteroids act on a variety of tissues to mobilize energy stores, induce lipolysis and proteolysis, potentiate vasoconstriction driven by the autonomic nervous system, suppress reproductive function, and alter a number of stress related behaviors; all in an attempt to maintain homeostasis (Herman et al., 2008; Papadimitriou and Priftis, 2009). It is generally thought that many of the responses to acute elevations in glucocorticoids that occur following stressors, such as enhanced cognition and metabolism and inhibition of immune function, are beneficial in the short term as they permit the fight or flight response. By contrast, these same beneficial responses can turn detrimental when the stressor is maintained over long periods of time. Indeed, chronic activation of the HPA axis results in deleterious effects on immune, cardiovascular, metabolic and neural functions and may decrease the viability of neurons and glia to subsequent neurotoxic insults (Jauregui-Huerta et al., 2010; McEwen, 1998; Rajkowska and Miguel-Hidalgo, 2007).

2.2. Anatomy of the paraventricular nucleus (PVN)

The neurons responsible for controlling HPA axis activity reside in the paraventricular nucleus of the hypothalamus (PVN). The PVN represents a collection of neurons in the rostral hypothalamus that is positioned to coordinate neuroendocrine, autonomic and behavioral responses to stressors as well as to maintain energy and water balance (Herman et al., 2008; Levy and Tasker, 2012). The PVN has been most comprehensively studied in the rat brain and reportedly consists of approximately 100,000 neurons in a volume of about 0.5 mm^3. The PVN is arranged in a wing shape structure along the dorsal portion of the third ventricle in the anterior region of the hypothalamus. The initial description of the cytoarchitectural organization of the anterior hypothalamus was made by Gurdjian (1927). Based upon Nissl stained material, he described a medial group of neurons with small cell bodies, a dense lateral group with medium to large cell bodies, and a dorsal group with unique Nissl staining properties in the area that was later included in the hypothalamic paraventricular nucleus. Bargmann (1949) and Bargmann and Scharrer (1951) later identified the densely packed neurons with large cell bodies (i.e. magnocells) as projecting to the posterior pituitary gland.

Later studies described the PVN based on cytoarchitecture and chemoarchitecture using results from tract tracing, Golgi impregnation, and immunocytochemical approaches (Armstrong et al., 1980; Swanson and Kuypers, 1980). Based on such parameters, the neurons of the rodent PVN were grouped into subdivisions with each subdivision associated with specific functions (Biag et al., 2012). Furthermore, while there is some controversy regarding the parcellation of the PVN in humans, it seems likely that similar subdivisions also exist based on criteria used for the rat brain (Koutcherov et al., 2000). Moreover, the neurons of the PVN can be further divided by function into three main types. (1) *Neurosecretory parvocellular* neurons which send their axons to the external zone of the median eminence where they secret releasing factors (e.g. CRF, vasopressin, thyrotropin releasing hormone (TSH), somatostatin) into the hypothalamo–hypophyseal portal vasculature to control the secretion of anterior pituitary hormones such as ACTH, TSH and growth hormone (GH). (2) *Neurosecretory magnocellular* neurons which send projections to fenestrated capillaries in the posterior pituitary where they secrete hormones (e.g. oxytocin, vasopressin) directly into the general circulation. (3) *Long-projecting* neurons which send their axons to brainstem and spinal cord regions involved in controlling autonomic and somatosensory function. Moreover, although PVN neurons are largely classified by output, they can further be subdivided by phenotype, afferent input, cell size, density and dendritic morphology (Armstrong et al., 1980; Ju et al., 1986; Kiss et al., 1991; Rho and Swanson, 1989; Swanson et al., 1986; van den Pol, 1982).

The magnocellular neurons of the PVN are largely distributed into two distinct but adjoining areas. The *medial* magnocellular division lies anteromedially within the PVN and contains mostly oxytocin expressing neurons. The *lateral* magnocellular division is comprised largely of a sphere shaped mass of vasopressin expressing neurons that is surrounded by a loop of oxytocin neurons. The majority of these neurons project to the neurohypophysis and are