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Sex and stress steroids in adolescence: Gonadal regulation of the hypothalamic–pituitary–adrenal axis in the rat

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ABSTRACT

This review provides an overview of the current understanding of the role of the hypothalamic–pituitary–gonadal (HPG) axis in regulating the hypothalamic–pituitary–adrenal (HPA) axis response to stressors. HPA function is influenced by both organizational (programming) and activational effects of gonadal hormones. Typically, in adult rats, estradiol increases and androgens decrease the HPA response to stressors, thereby contributing to sex differences in HPA function, and sensitivity of the HPA axis to gonadal steroids is in part determined by exposure to these hormones in early development. Although developmental differences in HPA function are well characterized, the extent to which gonadal steroids contribute to age differences in HPA function is not well understood. Deficits in the understanding of the relationships between the HPA and HPG axes are greatest for the adolescent period of development. The critical outstanding questions are, when do gonadal hormones begin to regulate HPA function in adolescence, and what mechanisms precipitate change in sensitivity of the HPA axis to the HPG axis at this stage of life.

1. Introduction

Despite the diverse functions of the hypothalamic–pituitary–adrenal (HPA) axis, it is best known for its role in the stress response. When confronted with stressors, the HPA axis initiates a cascade of signaling that culminates in increased release of glucocorticoids from the adrenal glands, which helps an organism meet the demands of its environment (Sapolsky et al., 2000). Although acute activation of the HPA axis is adaptive, repeated or prolonged activation produces allostatic load and can have deleterious effects on physiology and function (Juster et al., 2010). There is much evidence for differences in HPA function from prenatal life to old age (Lupien et al., 2009), and for sex differences in HPA function (Bangasser and Valentino, 2014; Panagiotakopoulos and Neigh, 2014). Relative to research efforts on the perinatal and adult periods of development, however, far less is known about the HPA axis during adolescence. Even less is known regarding the regulation of the HPA axis by the hypothalamic–pituitary–gonadal (HPG) axis during this time. In this review, we outline what is known from investigations in rats about how gonadal hormones organize and modulate HPA activity at different stages of development, and then focus on adolescence, highlighting the key outstanding questions regarding HPG–HPA interactions during that transitional time of life. Fig. 1 contains the key terms and abbreviations used in the review.

2. HPA signaling

The neuroendocrine stress response is initiated by in the paraventricular nucleus (PVN) of the hypothalamus. Excitatory input to the PVN is derived predominantly from ascending brainstem pathways that respond to physiological challenges (e.g., ether inhalation and hypotension) and from limbic forebrain regions such as the amygdala, which activate the PVN through a multisynaptic pathway during exposure to psychological challenges (e.g., restraint or conditioned fear) (Herman and Cullinan, 1997; Myers et al., 2014). The release of corticotropin releasing factor (CRF) and arginine vasopressin (AVP) into the hypophyseal portal veins to the anterior pituitary triggers the release of adrenocorticotropic hormone (ACTH) into general circulation, which then stimulates the synthesis and release of glucocorticoids (primarily corticosterone in rats) from the adrenal cortex. The release of glucocorticoids is regulated by a negative feedback system that operates at all levels of the axis as well as at upstream brain regions (notably, the hippocampus and medial prefrontal cortex), which dampen further HPA activation and promote a return to basal titers (Herman et al., 2005). In the absence of stressors, basal

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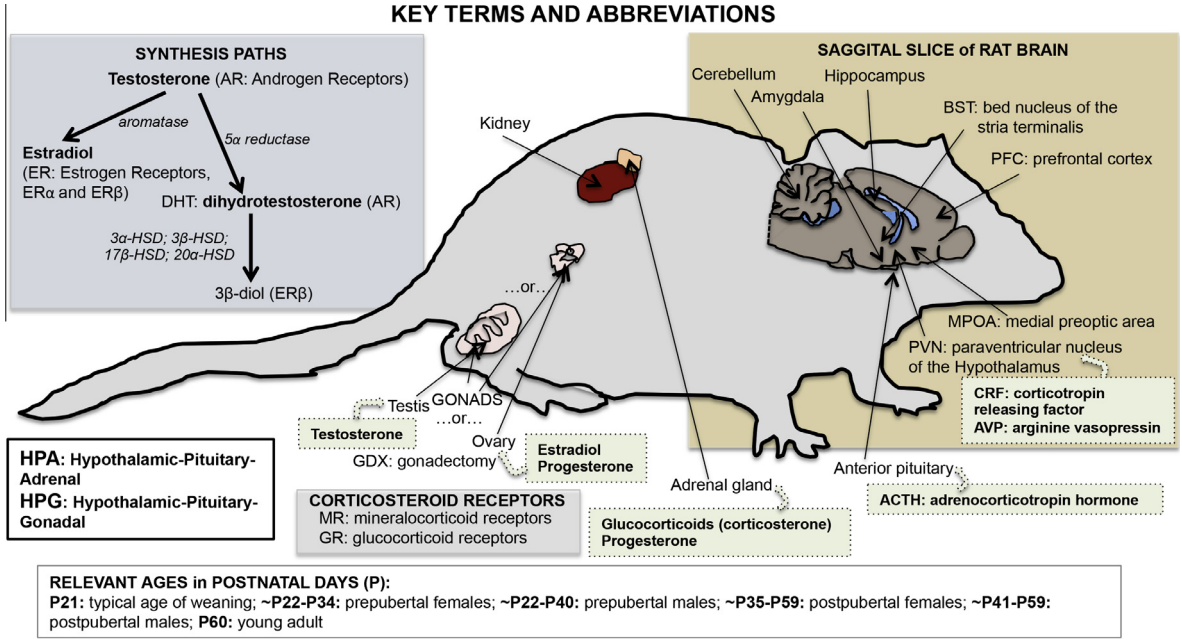

Fig. 1. The figure includes a cartoon outline of a rat depicting relevant structures, a chart of the synthesis pathways of testosterone to estradiol and dihydrotestosterone (receptors for each metabolite are within parentheses; enzymes are italicized), key terms, and abbreviations used in the review (see Handa and Weiser, 2014 for discussion of the synthesis pathways).

concentrations of glucocorticoids are lower and release from the adrenal cortex occurs in pulses (~1 per hour). The extent of release is influenced by the circadian rhythm, with the peak and nadir corresponding to the beginning and end of the active phase each day, respectively.

The effects of glucocorticoids are mediated by mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), ligand-activated transcription factors that reside mainly in the cytoplasm as part of a multimeric complex when unbound (Funder, 1997). Upon binding with glucocorticoids, the receptor translocates to the nucleus and forms a homodimer that binds to glucocorticoid response elements (GREs) in the promoter or intragenic region of GR-/MR-regulated genes, causing transactivation (reviewed in Ratman et al., 2013). Corticosteroid receptors can also cause transrepression by binding to a negative GRE or can alter gene expression at composite GREs or by tethering to other transcription factors (Ou et al., 2001; Biddie et al., 2011). The pleiotropic effect of corticosteroid receptors stems from the existence of multiple receptor isoforms, subtle differences in GRE sequences, cross-talk with other transcription factors, and the recruitment of various co-factors, to name a few (De Bosscher et al., 2008; Meijsing et al., 2009). GR and MR are also differentially expressed within the brain (MR mainly in limbic regions, GR more widespread) and possess different affinities for corticosterone (5–10× higher affinity for MR than for GR) (Reul and De Kloet, 1985). Thus, GR binding is more sensitive to fluctuations in circulating concentrations of glucocorticoids, which leads to the hypothesis that MR predominantly affect basal function (e.g., maintain neuronal excitability, cardiovascular function, and circadian rhythm) and GR predominantly mediate stress effects (e.g., altered immune responses, negative feedback) (Gunnar and Quevedo, 2007).

3. Sex differences in HPA function

There are marked sex differences in HPA activity in rats. For example, basal titers of glucocorticoids are greater in females than males, and their comparable ACTH concentrations suggest that females have enhanced adrenal sensitivity (Atkinson and Waddell, 1997; Babb et al., 2013; Kitay, 1961; Seale et al., 2004a). In addition, relative to males, females have greater concentrations of ACTH and glucocorticoids after acute stress exposure and a slower return to baseline stress levels (Babb et al., 2013; Handa et al., 1994a; Iwasaki-Sekino et al., 2009; Seale et al., 2004a; Viau et al., 2005). Sex differences in PVN activation may underlie the greater stress-induced release of ACTH in females, as studies have shown that expression of the immediate early gene c-fos (marker of neural activation) is upregulated more in females than in males (Babb et al., 2013; Larkin et al., 2010), although others have reported no effect of sex (Viau et al., 2005) or a difference in the other direction (Sterrenburg et al., 2012; Zavala et al., 2011), variability that may be related to the time-points investigated after stress exposures.

Sex-differences in ACTH release may also be mediated by differential expression of HPA-related genes in response to acute stress, with males typically expressing less CRF and AVP messenger RNA (mRNA) in the PVN and less of the ACTH precursor, proopiomelanocortin (POMC), in the anterior pituitary compared with expression in females (Babb et al., 2013; Iwasaki-Sekino et al., 2009; Seale et al., 2004a; Viau et al., 2005). Taken together, there is evidence of sex differences at each level of the HPA axis, with females typically showing a heightened neuroendocrine response. Nevertheless, females may be partially buffered from higher concentrations of glucocorticoids by their greater concentrations than males of corticosteroid binding globulin (CBG) in circulation (Gala and Westphal, 1965; McCormick et al., 2002), which limit the access of corticosterone to MR and GR (Henley and Lightman, 2011).

4. Gonadal hormones modulate HPA function

Sex differences in HPA function in adulthood involve, in part, activational effects of gonadal hormones (i.e., modulatory effects that depend on the concentrations of hormone in circulation). The majority of evidence derived from gonadectomy (GDX) and hormone replacement studies indicates that estrogens increase