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Review

Development of the HPA axis: Where and when do sex differences manifest?

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ABSTRACT

Sex differences in the response to stress contribute to sex differences in somatic, neurological, and psychiatric diseases. Despite a growing literature on the mechanisms that mediate sex differences in the stress response, the ontogeny of these differences has not been comprehensively reviewed. This review focuses on the development of the hypothalamic–pituitary–adrenal (HPA) axis, a key component of the body's response to stress, and examines the critical points of divergence during development between males and females. Insight gained from animal models and clinical studies are presented to fully illustrate the current state of knowledge regarding sex differences in response to stress over development. An appreciation for the developmental timelines of the components of the HPA axis will provide a foundation for future areas of study by highlighting both what is known and calling attention to areas in which sex differences in the development of the HPA axis have been understudied.

1. Introduction

The stress response provides the necessary metabolic realignment essential for survival when faced with a challenge (Fig. 1). However, the stress system evolved to respond to physical challenges and the inclusion of modern-day non-physiological chronic stressors has led to the increased manifestation of stress-induced disorders. The increased incidence of stress-induced disorders facilitated the observation of distinct sex differences in stress-induced pathology and has led to the investigation of differences in the types of stressors that males and females respond to behaviorally (Matthews et al., 1991) and the observations that chronic stress induces changes in physiology and behavior (Chrousos and Gold, 1992) for both sexes. The hypothalamic–pituitary–adrenal (HPA) axis mediates a portion of the stress response and is aptly named to describe three of the major structures of the axis. Sex differences in the HPA axis, and the portion of the stress response that it mediates, largely arise during puberty; however, the initial development of the structures of the HPA axis is relevant to the means by which sex differences later manifest. Therefore, this review discusses embryological development of HPA axis components, pubertal changes, and ultimately sex differences in HPA axis function across the lifespan.

2. The hypothalamus

2.1. Embryology/anatomy

The HPA axis begins at the hypothalamus, which, like the rest of the brain, is derived from the neural tube. The neural tube is the vertebrate embryo's precursor to the spinal cord and brain structures (Muller and O'Rahilly, 1988; Sadler, 2005). From the open cranial end of the neural tube, the prosencephalic vesicle (ultimately the cerebrum, optic vesicle, and hypothalamus) develops and folds, the caudal fold becomes the diencephalon (Sadler, 2005). The lateral walls of the diencephalon extend anteriorly and give rise to a groove called the hypothalamic sulcus, which is the primitive origin of the mature hypothalamus (Altman and Bayer, 1986). In its final size, the hypothalamus occupies a minute portion of brain volume, smaller than 2% (Rubin et al., 2007) which is remarkable given its critical role in endocrine function. Anatomical boundaries of the hypothalamus are the anterior commissure and lamina terminalis anteriorly, the mammillary bodies and midbrain posteriorly, and thalamus superiorly (Netter, 2010). Hence, it is derived from the Greek words for "under" (hypo-) the thalamus

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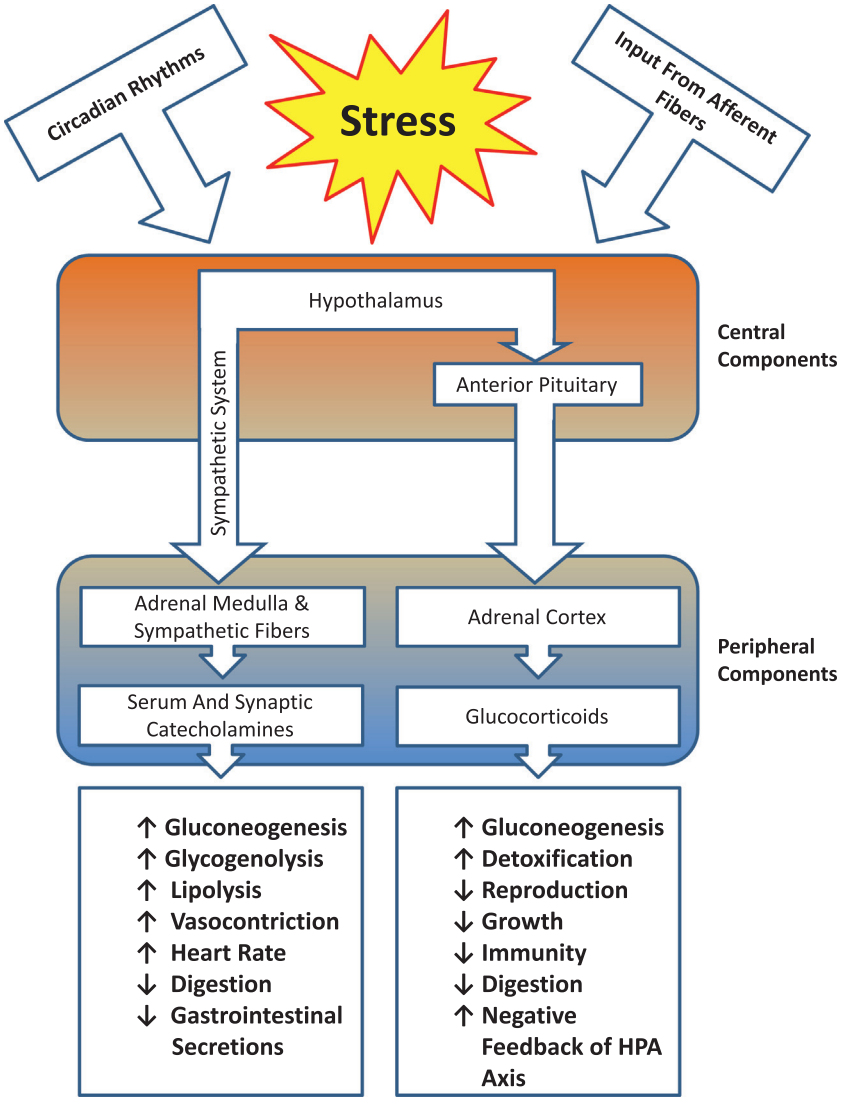

Fig. 1. Overview of the stress response – Integration of inputs from sensory afferent fibers, innate circadian rhythms and stressful stimuli occurs at the level of the hypothalamus. Propagation of the stress response is mediated through stimulation of the anterior pituitary corticotrophs and information carried in efferent sympathetic fibers. The peripheral effectors of the system, the adrenals and peripheral sympathetic terminals are the final pieces of a complicated and well integrated system.

(thalamus = "a room"). Caudally, the surface of the hypothalamus gives rise to a prominence (called the tuber cinereum), which later descends anterior–caudally to form the pituitary infundibulum. Axons within the infundibulum run downwards and terminate inside the posterior pituitary gland. The infundibulum and the pars tuberalis of the anterior pituitary together form the pituitary stalk (Rubin et al., 2007). The secretory products carried in terminal axons of hypothalamic neurons are secreted in the hypophyseal portal blood system, a collection of capillaries on the surface of the base of the hypothalamus (Netter, 2010).

The primary hypothalamic output, relevant to the HPA axis, is Corticotropin Releasing Factor (CRF). The major outputs of CRF, the initiating hormone of the stress response, are the paraventricular nuclei (PVN), adjacent to the ventricular ependymal cell layer, which lines the third ventricle (Rubin et al., 2007). During development and folding of the neural tube, embryonic neuroblasts that give rise to hypothalamic neurons remain close to the ependymal cell layer. As the fetal brain matures, products of further cell divisions move laterally and end in their final destination in the PVN (Altman and Bayer, 1978a,b,c). To date, information regarding sex differences in the embryological development of the hypothalamus is limited and future research is necessary to develop an understanding of potential contributions of hypothalamic development towards sex-specific responses to stress in the infantile period.

2.2. CRF production and receptors

As mentioned above, release of CRF from the PVN of the hypothalamus initiates the HPA axis response (Fig. 2). In its mature form, CRF is a 41-amino-acid peptide hormone (Vale et al., 1981), and the main stimulator of Adrenocorticotropic Hormone (ACTH) secretion from the anterior pituitary (Rivier et al., 1982; Rivier and Plotsky, 1986), the next step in the HPA axis response. The initial translation product of the *CRF* gene, preproCRF, is a large pre-cursor molecule (196 amino acids in length) with a hydrophobic signal sequence, and thus, destined for extracellular secretion (Robinson et al., 1989). Post-translational modifications include cleavage of the basic amino acids on either end of the molecule (Shibahara et al., 1983). CRF is synthesized by parvocellular neurons of the PVN of the hypothalamus (Swanson et al., 1983), and the hormone is carried caudally in axons from the PVN to the base of the hypothalamus (median eminence), where it is

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