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Review

Neuroendocrine mechanisms of innate states of attenuated responsiveness of the hypothalamo-pituitary adrenal axis to stress

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Abstract

Neuroendocrine responses to stress vary between sexes and reproductive states and are influenced by the type of stressor. Stress responses are attenuated in some physiological states, such as lactation and conditions of low visceral adipose tissue. Moreover, some individuals within a species characteristically display reduced stress responses. The neuroendocrine mechanisms for stress hyporesponsiveness are likely to include reduced synthesis and secretion of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus as a result of enhanced glucocorticoid negative feedback and/or reduced noradrenergic stimulatory input from the brain stem. A major limitation of research to date is the lack of direct measures of CRH and AVP secretion. Attenuated stress responsiveness is also commonly associated with reduced pituitary responsiveness to CRH and AVP. The possible roles of inhibitory central inputs to CRH and AVP neurons and of oxytocin and prolactin in attenuating the HPA axis responses to stress are unknown.

Keywords: Stress; Stress hyporesponsiveness; Hypothalamo-pituitary adrenal axis; Stress responsiveness; Lactation; Visceral adiposity; CRH; AVP; Glucocorticoids; Norepineprhine

1. Introduction

Stress is a complicated physiological mechanism that embodies a range of integrative physiological and behavioral processes that occur when there is a real or perceived threat to homeostasis. While it is generally accepted that these processes are adaptive, designed to re-establish homeostasis and allow coping, it is also apparent that inadequate or excessive and/or prolonged activation of stress systems can disturb normal physiological and behavioral function. This can result in a range of adverse consequences such as depression, impaired cognition, cardiovascular disease, impaired immune function with increased vulnerability to disease, impaired growth and reproductive function, osteoporosis, diabetes, dementia and reduced life expectancy [22,24,220,221,236,238]. Despite a vast literature on stress responses in a range of species, there is still much to be learned about the mechanisms of stress responses so that strategies can be developed to prevent and overcome stress-induced disorders.

Under some physiological conditions, responses to stress are naturally attenuated while still being adequate to allow adaptation to adverse threats to homeostasis. There are various physiological states where this occurs but one of the best known examples is seen in the female during late pregnancy and lactation. It is also apparent that stress responses vary between humans and animals with differing amounts of visceral adipose tissue. Lean individuals generally display reduced responses to stress. Furthermore, neuroendocrine and behavioral responses to stress often vary substantially between individuals, within the same species, such that some individuals inherently display reduced responsiveness of the stress systems, including the hypothalamo-pituitary adrenal (HPA) axis. An understanding of the neuroendocrine mechanisms that underlie natural physiological states of reduced stress responsiveness, defined here as stress hyporesponsiveness, will provide knowledge that could be utilized to generate

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physiological treatments for people at risk of illness due to chronic stress and/or disorders of the stress systems. This is conceptually attractive because the most effective mechanisms to suppress stress responses will undoubtedly be those that the body itself uses. In this review we explore some of the mechanisms of stress hyporesponsiveness in lactating females, lean individuals and individuals that display naturally attenuated neuroendocrine responses to stress. Our focus is upon the regulation of the HPA axis.

2. Physiological responses to stress

The intrinsic or extrinsic stimuli, whether real or perceived, that challenge homeostasis, are commonly termed stressors. Stressors are many and varied (e.g. psychological, physical, surgical trauma, strenuous exercise, undernutrition) and activate a range of physiological systems, the most commonly studied being the HPA axis (Fig. 1) and the sympathoadrenal system. Activation of the HPA axis results in stimulation of parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus and the release of the neuropeptides corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal blood system. The combined action of CRH and AVP on the corticotropes of the anterior pituitary gland stimulates the secretion of peptides derived from pro-opiomelanocortin which include adrenocorticotropin (ACTH), the opioid peptide β-endorphin and α-melanocyte-stimulating hormone [38,49,74,123,179]. Although the physiological importance of the secretion of β-endorphin and α-melanocyte-stimulating hormone in response to stress is not well understood, ACTH acts on the cortex of the adrenal glands to stimulate the synthesis of glucocorticoids. Glucocorticoids regulate the secretion

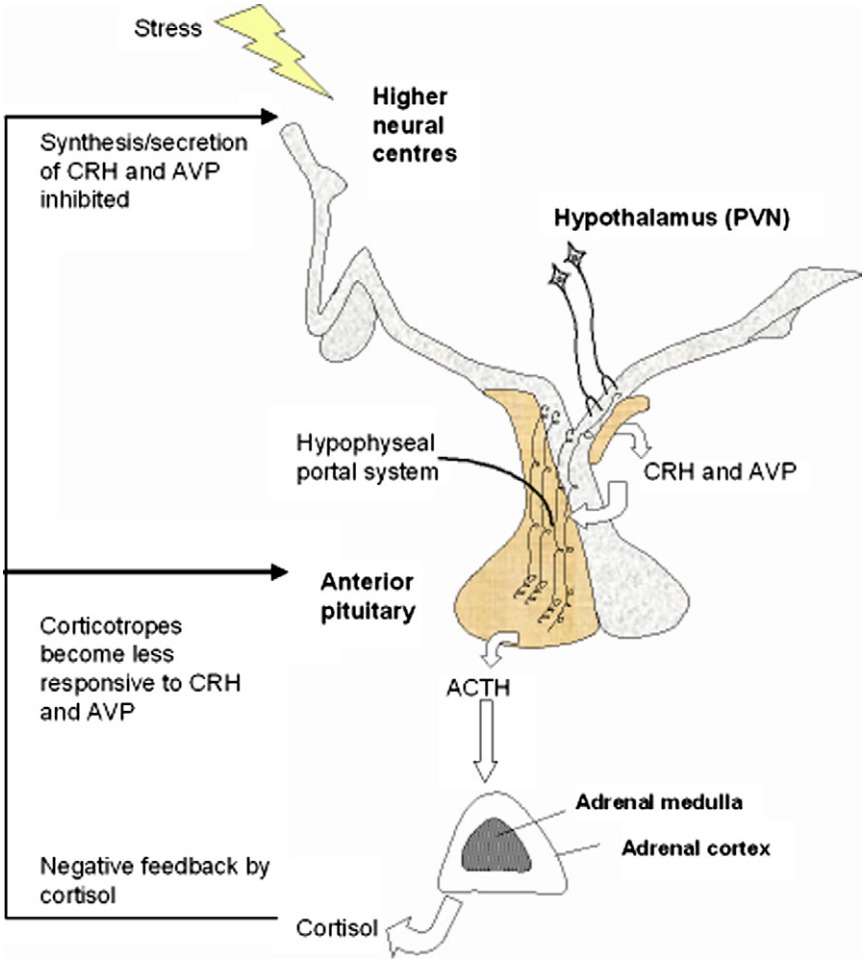

Fig. 1. Schematic representation of the hypothalamo-pituitary adrenal (HPA) axis. Stress causes activation of parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus and the consequent release of the neuropeptides corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system. The combined action of CRH and AVP on corticotrope cells of the anterior pituitary gland stimulates the secretion of peptides derived from pro-opiomelanocortin which include adrenocorticotropin (ACTH), the opioid peptide β-endorphin and α-melanocyte-stimulating hormone (not shown). ACTH acts on the cortex of the adrenal glands to stimulate the synthesis of glucocorticoids. Glucocorticoids regulate the secretion of CRH, AVP and ACTH through negative feedback actions in the brain, to ultimately inhibit the synthesis and secretion of CRH and AVP, and anterior pituitary gland, where corticotropes become less responsive to CRH and AVP. In humans and many mammalian species, the predominant glucocorticoid is cortisol (illustrated here), whereas in rodents and avian species the key glucocorticoid is corticosterone.