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Review

Early-life stress and HPA axis trigger recurrent adulthood depression

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ABSTRACT

It is now broadly accepted that psychological stress may change the internal homeostatic state of an individual. During acute stress, adaptive physiological responses occur, which include hyperactivity of the HPA axis. Whenever there is an acute interruption of this balance, illness may result. The social and physical environments have an enormous impact on our physiology and behavior, and they influence the process of adaptation or 'allostasis'. It is correct to state that at the same time that our experiences change our brain and thoughts, namely, changing our mind, we are changing our neurobiology. Increased adrenocortical secretion of hormones, primarily cortisol in major depression, is one of the most consistent findings in neuropsychiatry. A significant percentage of patients with major depression have been shown to exhibit increased concentrations of cortisol, an exaggerated cortisol response to adrenocorticotropic hormone, and an enlargement of both the pituitary and adrenal glands. The maintenance of the internal homeostatic state of an individual is proposed to be based on the ability of circulating glucocorticoids to exert negative feedback on the secretion of hypothalamic-pituitary-adrenal (HPA) hormones through binding to mineralocorticoid (MR) and glucocorticoid (GR) receptors limiting the vulnerability to diseases related to psychological stress in genetically predisposed individuals. The HPA axis response to stress can be thought of as a mirror of the organism's response to stress: acute responses are generally adaptive, but excessive or prolonged responses can lead to deleterious effects. Evidence indicates that early-life stress can induce persistent changes in the ability of the HPA axis to respond to stress in adulthood. These abnormalities appear to be related to changes in the ability of hormones to bind to GR and MR receptors. First episodes may begin with an environmental stressor, but if the cycles continue or occur unchecked, the brain becomes kindled or sensitized, and future episodes of depression, hypomania, or mania will occur independently of an outside stimulus, with greater frequency and intensity. Generally, HPA axis changes appear in chronic depressive and more severe episodes. Moreover, HPA axis changes appear to be state-dependent, tending to improve upon resolution of the depressive syndrome. Interestingly, persistent HPA dysfunction has been associated with higher rates of relapse and chronicity.

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1. Introduction

The relationship between stress and affective disorders is a strong example of a field of study that can be more fully understood from an integrative perspective. The potential of an integrative approach to contribute to improvements in human health and well-being is more important than historical biases that have been associated with an integrative science approach. Approximately 60% of cases of depressive episodes are preceded by exposure to stressors, especially psychosocial stressors. Among the factors associated with depression in adulthood are exposure to childhood stressors such as the death of a parent or substitute, maternal deprivation, paternal abandonment, parental separation, and divorce. Psychological stress may change the internal homeostatic state of an individual. During acute stress, adaptive physiological responses occur, including increased adrenocortical hormone secretion, primarily cortisol [1,2]. Whenever an acute interruption of this balance occurs, illness may result. Particularly interesting are psychological stress (i.e., stress in the mind) and the interactions with the nervous, endocrine, and immune systems [3]. Childhood maltreatment is a major social problem. It is a complex global phenomenon that does not respect boundaries of class, race, religion, age, or educational level and can occur both publicly and privately, resulting in serious physical injury or even death. Moreover, its psychological consequences can acutely affect a child's mental health well into adulthood [2].

2. Physiology of the HPA axis

The hypothalamic–pituitary–adrenal (HPA) axis constitutes one of the major endocrine systems that maintain homeostasis when the

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organism is challenged or stressed. Activation of the HPA axis is perhaps the most important endocrine component of the stress response [3,4].

Abnormal activation of the HPA axis, as well as increased circulating levels of cortisol, is one potential explanation for many of the features of depression, and many previous studies have described an impaired HPA negative feedback, leading to hypercortisolemia, in the more severe forms of depression [4,5].

Cortisol mediates its action, including feedback regulation of the HPA axis, through two distinct intracellular corticosteroid receptor subtypes referred to as mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) [5,6]. The type-I receptor (MR) has a limited distribution, and it is found in relatively high density in the hippocampus [7] and in sensory and motor sites outside the hypothalamus [8]. The expression of type-II receptors (GR) is more widespread, and they are found in the hippocampus, the amygdala, the hypothalamus, and the catecholaminergic cell bodies of the brain stem [9]. There is a theory that suggests that a GR defect may mediate the impaired negative feedback thought to cause hypercortisolemia in depression [10]. Under basal levels of cortisol, negative feedback is mediated mainly through the MR in the hippocampus, whereas under stress and high cortisol concentrations, feedback is mediated by the less sensitive GR in the hippocampus, hypothalamus, and pituitary gland [5]. The balance in these MR- and GR-mediated effects on the stress system is of crucial importance to the set point of the HPA axis activity [5]. It is proposed that the maintenance of corticosteroid homeostasis and the balance in MR-/GR-mediated effects limit vulnerability to stress-related diseases in genetically predisposed individuals [11].

Stress-induced activation of the HPA axis generally involves stimulated release of corticotropin-releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus into the portal venous circulation, where CRF stimulates the synthesis of proopiomelancortin, the precursor of adrenocorticotropic hormone (ACTH) from anterior pituitary cells. Arginine-vasopressin (AVP) is a potent synergistic factor with CRF in stimulating ACTH secretion [11,12] (see Fig. 1).

In the hypothalamus, the PVN receives fibers from a number of brain areas, notably the brain stem and limbic system (e.g., amygdala and the septal areas). It is thought that these afferents may be important in HPA responses to behavioral and emotional stimuli and may play a role in corticosteroid feedback. Several peptides are released alongside and interact with CRF at the level of the anterior pituitary and alter the stimulatory action of ACTH secretion [13] (see Fig. 2). Increases in circulating ACTH stimulate glucocorticoid release from the adrenal cortex: cortisol is the principal glucocorticoid in humans, and corticosterone is the principal glucocorticoid in other species, such as rats [11,13,14].

The division of the adrenal cortex into separate layers is important since zones produce different steroids [14]. Table 1 summarizes the adrenal steroids. Cortisol is produced by the zona fasciculata at the rate of 12–15 mg/m^2 of body surface area per day [15]. However, more than 90% of the circulating cortisol is bound to corticosteroid-binding globulin (CBG) in humans and rodents [16]. In addition, it has been observed that both exogenous glucocorticoid administration and endogenous increases in plasma cortisol (for example, Cushing's syndrome) result in a 30–40% decrease in the plasma CBG concentration [17]. Thus, CBG levels fluctuate according to glucocorticoid concentration.

Adrenocorticotropic hormone is secreted in irregular bursts throughout the day, and plasma cortisol tends to rise and fall in response to this pulsatile secretion. In humans, the bursts are most frequent in the early morning and least frequent in the evening [18]. The biological clock responsible for the diurnal ACTH rhythm is thought to be located in the suprachiasmatic nuclei of the hypothalamus. Changes in the activity of these neurons increase the release of CRF and AVP by the PVN during usual times of peak activity [19]. Consequently, it is thought that the secretion of CRF and AVP also follows a pulsatile pattern. However, CRF levels in human peripheral plasma are very low and do not exhibit circadian variation [20], and therefore, these levels cannot be used reliably to assess hypothalamic CRF release relevant to the HPA axis. An important feature is the intrinsic rhythmicity of the HPA axis with regard not only to the diurnal variation but also to the pulsatility, which is comparable to the rhythm found within the reproductive and growth hormone axes [21].

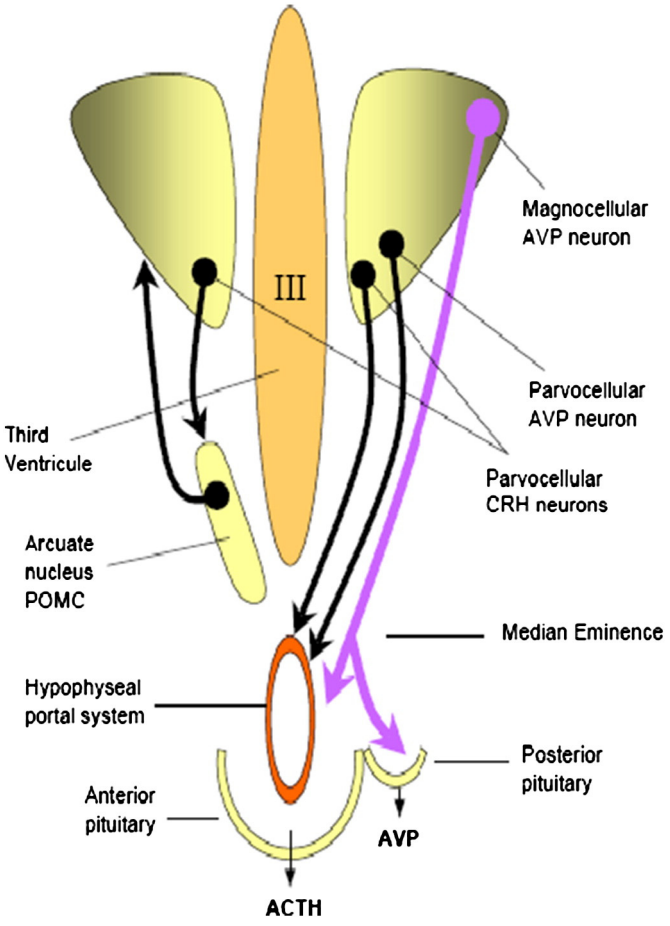

Fig. 1. The paraventricular nuclei of the hypothalamus.
Adapted from [15].

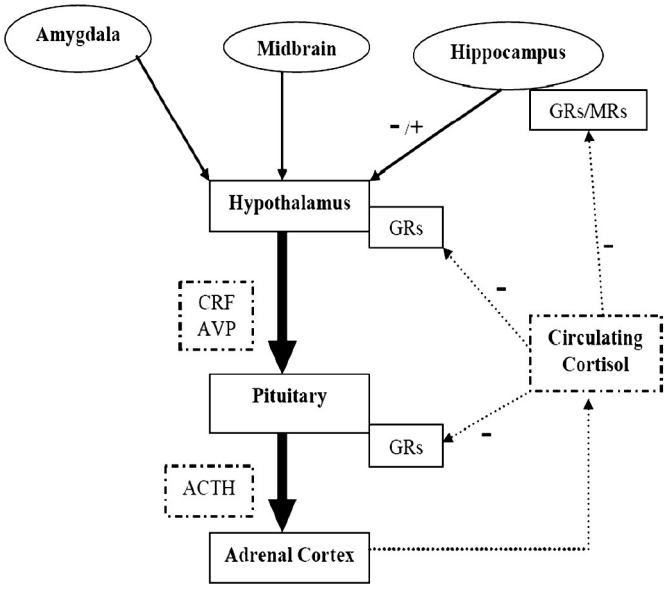

Fig. 2. Schematic diagram of hypothalamic–pituitary–adrenal (HPA) axis. It describes regulation and negative feedback (−) of cortisol via glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs).
Adapted from [13].