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Influence of chronic stress on brain corticosteroid receptors and HPA axis activity

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Abstract:
Background: Disruption of the glucocorticoid negative feedback system evoked in animals by chronic stress can be induced by downregulation of glucocorticoid receptors (GRs) in several brain regions. In the present study, the dynamics of the changes in GRs, in brain structures involved in stress reactions, prefrontal cortex, hippocampus and hypothalamus was compared with the peripheral hypothalamo-pituitary-adrenocortical (HPA) axis hormones response to chronic stress.
Methods: Rats were exposed to 10 min restraint or restrained twice a day for 3, 7 or 14 days, and 24 h after the last stress session exposed to homotypic stress for 10 min. Control rats were not restrained. After rapid decapitation at 0, 1, 2, and 3 h after stress termination, trunk blood for plasma adrenocorticotropic hormone (ACTH) and corticosterone determinations was collected and prefrontal cortex, hippocampus and hypothalamus were excised and frozen. Plasma hormones were determined using commercially available kits and glucocorticoids and mineralocorticoids protein levels in brain structure samples were determined by western blot procedure.
Results: Restraint stress alone significantly decreased glucocorticoid receptor (GR) level in prefrontal cortex and hippocampus, and increased mineralocorticoid receptor (MR) level in hypothalamus. Prior repeated stress for 3 days significantly increased GR protein level in hippocampus and diminished that level in hypothalamus in 7 days stressed rats. Acute stress-induced strong increase in plasma ACTH and corticosterone levels decreased to control level after 1 or 2 h, respectively. Prior repeated stress for 3 days markedly diminished the fall in plasma ACTH level and repeated stress for 7 days moderately deepened this decrease. Plasma ACTH level induced by homotypic stress in rats exposed to restraint for 3, 7, and 14 days did not markedly differ from its control level, whereas plasma corticosterone response was significantly diminished. The fast decrease of stress-induced high plasma ACTH and corticosterone levels was accompanied by a parallel decline of GR level only in prefrontal cortex but not in the hippocampus or hypothalamus.
Conclusions: Comparison of the dynamics of changes in plasma ACTH and corticosterone level with respective alterations in GR and MR in brain structures suggests that the buffering effect of repeated stress depends on the period of habituation to stress and the brain structure involved in regulation of these stress response.

Key words:
glucocorticoid receptors, mineralocorticoid receptor, chronic stress, HPA axis, adaptation, brain structures

Introduction

Stressful stimuli release corticotropin releasing hormone (CRH) and vasopressin from CRH neurons in paraventricular nucleus (PVN) to axon terminals in the basal hypothalamus and into the pituitary portal circulation. Portal CRH and vasopressin stimulate anterior pituitary corticotrophs to release ACTH, which

causes the synthesis and secretion of corticosteroid from adrenal cortex [21, 23]. Systemic corticosteroids induce both rapid and protracted actions in peripheral tissues and the brain. Circulating glucocorticoids (GCs) can control the HPA axis activity by negative feedback directly at the hypothalamus level and in pituitary or hippocampus and prefrontal cortex [4, 10, 38, 40]. The control of circulating levels of glucocorticoids to prevent oversecretion and maintain their homeostatic range is achieved by multiple types of feedback which use different intracellular mechanisms [30] in numerous brain areas that influence the inhibition of the stress response [25].

Acute stress-evoked rapid and powerful glucocorticoid hypersecretion may induce three types of feedback: fast, intermediate and delayed feedback [7, 9, 12, 22]. Rate-sensitive or fast feedback is active in seconds to turn off CRH and ACTH secretion following application of a brief stressor. The negative GC feedback to the HPA axis response is specific to stimulation of higher limbic structures by psychological stressor. Rapid GC regulation of hypothalamic CRH neurons as well as hippocampal and prefrontal cortex pyramidal neurons is largely mediated by modulation of excitatory or inhibitory synaptic inputs to these neurons [20]. Although MRs are predominantly expressed in the brain limbic structures, mainly in the hippocampus, they are also found at the hypothalamic level [13, 19]. Hippocampal MRs control the proactive feedback involved in the maintenance of the basal HPA activity during the circadian rhythms. MRs play a role in the subtle control of the HPA axis in humans [2, 8, 17, 32]. GR distribution is ubiquitous, although uneven, in neurons and glial cells. GR density is the highest in the parvocellular PVN of the HPA axis, in neurons of ascending aminergic pathways and in limbic neurons that modulate PVN activation trans-synaptically. Abundant coexpression of MR and GR is found in hippocampal pyramidal cells also in the dentate gyrus and some cortical areas of almost all species [8, 38].

The chronic stress-induced attenuation and disruption of the glucocorticoid negative feedback system exerts different abnormal changes in the higher centers of the HPA axis which are also observed in human depression [8, 11, 27, 33]. GCs play a key regulatory role in the neuroendocrine control of the HPA axis and on the terminations of the stress response by exerting negative feedback at the levels of hypothalamus and pituitary and in some supra-hypothalamic structures. Activation of MR receptors in the hippocampus inhibits the activity of the HPA axis [27, 30]. In the brain, endogenous cortisol displays higher affinity for MRs than GRs and under basal conditions glucocorticoids primarily bind to MRs, and GRs are occupied when glucocorticoid levels increase in response to stress. Glucocorticoid hormones from the adrenal cortex released in response of HPA axis to stress act on peripheral target tissues to restore homeostasis of the organisms and engage GRs in the CNS to control the intensity and duration of the stress response [25]. Hippocampal formation contains high number of receptors for GCs and modulates the release of these hormones *via* negative feedback loop inhibiting the LHPA system [13]. Hippocampal activity suppresses CRH release from the neurons in PVN, whereas suppression of the hippocampal activity disinhibits CRH release [28]. Under basal conditions, corticosterone extensively binds to hippocampal MR receptors. The GR is occupied during high concentration of circulating glucocorticoids under stress and is suggested to be the primary mediator of autoregulatory feedback inhibition, whereas the MR exerts tonic actions on the brain [36]. Although tonic elevation of plasma GC level may inhibit HPA axis *via* a negative feedback mechanism, HPA axis usually retains responsiveness to new acutely applied stressors. The stress-induced negative feedback effect of GC may be reduced by inhibiting some of a variety of neurons, mainly noradrenergic *via* CRH neurons in the PVN [16]. Glucocorticoids, by negative feedback at the hypothalamus and pituitary, inhibit rapidly the synthesis and secretion of CRH and POMC/ACTH, respectively, through nongenomic mechanisms. Glucocorticoids, by similar feedback at the hippocampus and due to a high density of GR, inhibit the PVN and HPA activity [36]. Corticosteroids may, by genomic action, slow translation of mRNA important for generation of various neurotransmitters and neuropeptides. In addition, steroid action on membrane associated receptor protein, *via* monoamine and opioid mediation, may rapidly modulate the stress-induced effects [6, 9]. Corticosteroids acting through balanced stimulation of GRs and MRs play a crucial role for health. Dysfunction of prefrontal cortex or hippocampus is implicated in the pathogenesis of depression. Alterations in GC sensing system may underlie the HPA axis changes associated with psychiatric diseases [9, 25].

Virtually all effective disorders are associated with alterations in HPA axis activity and are influenced by