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Review

Corticosteroid–serotonin interactions in the neurobiological mechanisms of stress-related disorders

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ABSTRACT

Among psychiatric disorders, depression and generalized anxiety are probably the most common stress-related illnesses. These diseases are underlain, at least partly, by dysfunctions of neurotransmitters and neurohormones, especially within the serotoninergic (5-HT) system and the hypothalamo–pituitary–adrenal (HPA) axis, which are also the targets of drugs used for their treatment. This review focuses on the nature of the interactions between central 5-HT and corticotrope systems in animal models, in particular those allowing the assessment of serotoninergic function following experimental manipulation of the HPA axis. The review provides an overview of the HPA axis and the 5-HT system organization, focusing on the 5-HT_{1A} receptors, which play a pivotal role in the 5-HT system regulation and its response to stress. Both molecular and functional aspects of 5-HT/HPA interactions are then analyzed in the frame of psychoaffective disorders. The review finally examines the hippocampal neurogenesis response to experimental paradigms of stress and antidepressant treatment, in which neurotrophic factors are considered to play key roles according to the current views on the pathophysiology of depressive disorders.

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1. Introduction

Stress, originally defined by Hans Selye as a "non-specific response of the body to a demand", may also be described as any environmental change, either internal or external, that disturbs the maintenance of homeostasis (Leonard, 2005). The term "stress" can be used in two ways: either to identify events or circumstances that are perceived adversely ("stressors") or to describe the state induced by such events or circumstances (the "stress reaction") (Glue et al., 1993). The purpose of the stress response is to maintain homeostasis (Sapolsky, 2003), which include a series of physiological reactions such as endocrine activation (especially of the hypothalamo–pituitary–adrenal – HPA axis) and cardiovascular changes, which, *per se*, do not produce pathological changes. It is only when a prolonged and sustained stimulation exceeds the body capacity to maintain homeostasis that stress can have psychopathological sequelae. Indeed, consequences of exposure to repeated stressors are multiple. After an acute reacting phase, long-term symptomatology emerges and encompasses anxiety, irritability and a feeling of being unable to cope which may ultimately result in depression.

Depression is probably the most common stress-related disorder. However, repeated stress *per se* is not sufficient to cause depression. Interactions between a genetic predisposition and some environmental stressors are probably necessary to induce this disease (Caspi and Moffitt, 2006). In addition, not only the HPA axis, but also brain neuronal systems, including the monoaminergic systems and in particular the serotoninergic (5-hydroxytryptamine, 5-HT) one, are clearly involved in stress-related disorders. Limbic brain regions, such as the hippocampus and the septum, which play a key role in mood control, are abundantly innerved by serotoninergic projections and are also particularly sensitive to glucocorticoids (Moore and Halaris, 1975; Hugin-Flores et al., 2004). The HPA axis and the 5-HT system are closely cross-regulated under normal physiological conditions in mammals (Chaouloff, 1993; Lopez et al., 1998). In addition, their interactions are of particular relevance when considering pathological conditions such as depression, in which dysfunctioning actually concerns both the HPA axis and the 5-HT system (Lesch et al., 1990; Barden, 1999; Porter et al., 2004). A deficiency in brain serotoninergic activity has been proposed to increase vulnerability to major depression (Asberg et al., 1986). This could notably be the case when a diminished availability of the 5-HT precursor, L-tryptophan, impairments in 5-HT synthesis, release or metabolism, and/or 5-HT receptor abnormalities occur (Maes and Meltzer, 1995). On the other hand, increased tonic activity of the HPA axis has been consistently reported in major depression. This change results from a deficit in the negative feedback regulation of HPA axis as shown by the failure of glucocorticoid receptor (GR) activation to decrease plasma levels of ACTH and cortisol in the "dexamethasone suppression test" (Montgomery et al., 1988). Interestingly, lesions of 5-HT nerve terminals in animals have been found to potentiate the stress-induced rise in plasma corticosterone, in line with the hypothesis that a low 5-HT tone is, at least in part, involved in the etiology of depression, through resulting increased tonic activity of the HPA axis (Richardson, 1984).

This review aims at synthesizing recent progress in the knowledge of the neurobiological mechanisms of stress-related disorders, especially depression, with a particular focus on the 5-HT system and the HPA axis. Indeed, interactions between this monoamine system and the stress axis appear to be critical regarding both the onset and maintenance of a depressive episode. After a brief overview of the HPA axis and the 5-HT system, we will analyze the molecular and functional aspects of their interactions, to finally examine how alterations in these interactions can underlie, at least in part, psychoaffective disorders such as depression.

2. Hypothalamo–pituitary–adrenal axis and corticosteroids

2.1. Hypothalamo–pituitary–adrenal axis

When an organism is exposed to a stressor, several mechanisms are activated to restore homeostasis. Stress initiates processes in the central nervous system (CNS), particularly in the paraventricular nucleus (PVN) of the hypothalamus. When this brain region is stimulated by stress, it releases corticotropin-releasing hormone (CRH) and its co-secretagogue arginine–vasopressin (AVP). CRH and APV reach the anterior pituitary gland, where they cause the release of adrenocorticotropin hormone (ACTH) into the circulation. At the level of adrenal glands, ACTH stimulates glucocorticoid-producing cortex cells, which ends with the secretion of cortisol (in human) or corticosterone (in rodents) in blood (Palkovits, 1987) (Fig. 1). These hormones, the corticosteroids, exert numerous actions at the periphery and in the CNS. At the periphery, corticosteroids are involved in energy mobilization (glycogenolysis), and exert modulatory controls on the immune system, bone and muscle growth, epithelial cell growth, erythroid cell production and the cardiovascular system (McEwen and Stellar, 1993; Tronche et al., 1998).

Corticosteroids act through binding onto two types of intracellular steroid receptors, the mineralocorticoid (MR) or type I, and the GR or type II, receptors (de Kloet et al., 1998; Gass et al., 2001). These receptors are abundantly expressed in the limbic brain areas where they mediate distinct and complementary actions. They have identical structure both in the periphery and in the brain (Patel et al., 1989). The MR is a high-affinity receptor which binds corticosterone at low concentration (Kd ~0.5 nM). Its affinity for corticosterone is 10-fold higher than that of GR (Kd ~5 nM). Therefore, in vivo, MR is almost completely occupied (90%) by basal corticosterone levels and this contributes to maintaining homeostasis. In contrast, GR is occupied at only ~10% under such basal ("resting") conditions (Reul and de Kloet, 1986). But when the level of corticosterone rises up to its circadian maximum or during stress, GR becomes substantially occupied by the hormone ligand (de Kloet et al., 1998). Due to this differential occupation of MR and GR, a difference in function has been proposed, with a more tonic inhibitory control function for the MR and a role for the GR in the negative feedback regulation of the HPA axis during stress or at circadian peak (Bradbury et al., 1994; de Kloet et al., 1998). Indeed, under physiological conditions, HPA axis activity is mainly determined by two factors, stress (either physical or psychological) which increases its activity, and the normal circadian rhythm (de Kloet, 2000). Both factors can be dysregulated in a number of diseases and disorders.