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Review article

Does mineralocorticoid receptor play a vital role in the development of depressive disorder?

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ABSTRACT

Depression is a leading cause of disability worldwide. However, the biological and molecular mechanisms underlying this disease remain unclear. Stress, a disposing factor in the development of depression, leads to hypothalamic-pituitary-adrenal (HPA) axis activation and glucocorticoids release. Glucocorticoids at physiological concentrations activate two types of steroid receptors including the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). During the past decades, lots of studies have confirmed the role of GR in depression. An increasing number of studies, in recent years, indicate that abnormal function of MR is also a crucial component of the pathophysiology of depression. Thus, this review summarizes the role of MR in the HPA axis dysregulation, inflammation, decreased neurogenesis and stress-related behaviors in depression. All of which will provide more information about MR in depression.

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Contents

1. Introduction

Depression is the most common psychiatry disorder in the world. It's reported that the lifetime prevalence of major depression is about 17% in the USA [74]. According to the report from World Health Organization, more than 350 million people suffered from depression. Various symptoms including anhedonia, depressed mood, abnormalities in sleep, increased stress sensitivity, thought of worthlessness, inappropriate guilt, helplessness and high tendency to suicide can be found in this disorder. The core symptoms are anhedonia and depressed mood in depressive patients [89]. Nowadays, monoamine hypothesis, neurotrophins and neurodegeneration, incorporate gene-environmental interactions, neuroendocrine and epigenetic forms of plasticity reveal the possible pathophysiology of depression [45,46,71]. However, the specific pathological mechanisms underlying this disorder remain unclear.

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Stress is a predisposing factor in the development of depression. Exposing to stress results in the release of glucocorticoid via the hypothalamic-pituitary-adrenal (HPA) axis activation. Glucocorticoids (cortisol in humans and corticosterone in rats and mice) can bind to two types of receptors in the brain: the mineralocorticoid receptor (MR)and the glucocorticoid receptor (GR). Wherein, the GR is expressed in the whole brain, and the MR is mainly existed in the limbic areas such as the hippocampus, amygdala and neocortex [76], the structures which are essential for learning, memory and emotional behavior. Remarkably, the hippocampus exhibits a relatively high level of MR gene [78]. Moreover, the affinity of the endogenous hormones corticosterone and cortisol for MR is approximately 10-fold higher than the affinity for GR [29]. Therefore, variations in the circulating level of glucocorticoids lead to shifts in the balance between MR and GR activity [55]. A high MR occupancy can be observed under basal conditions in order to maintain low basal glucocorticoid levels, while full GR occupancy can be only achieved under high glucocorticoid concentrations. In basal (non-stressed) physiological state, (low glucocorticoid concentration) MR is activated and localized in the nucleus, where it exerts the function of tonic inhibitory effect on the HPA axis. Once the glucocorticoid concentration increases under the circadian peak or exposure to stress, GRα(only GRαsubtype has a genomic effect ,others such as GRβ,GRγ, GR-A and GR-P are inactive) [53] translocate into the nucleus where it exerts genomic effects [17,52]. Though the role of GR in the aetiology of stress-related diseases is fully studied [36,81,84], MR may also play a vital role in the development of depression.

The MR is believed to be a genomic cytoplasmic nuclear transcription factor. Upon glucocorticoid binding, the receptor-ligand MR complex translocates into the nucleus, affecting transcription of many genes including growth factors, cell-adhesion molecules and neuropeptides [65]. The genomic MR is believed to have a more regulatory function on the HPA axis as it can determine HPA axis sensitivity and set the threshold for stress reactivity. However, in addition to the slower genomic effects, the MR is capable of rapidly responding to elevated cortisol levels which has been ascribed to a membrane-bound MR [32]. The membrane-bound MR can process the rapid effects of stress-induced glucocorticoid level elevation and influence the appraisal of an acute stressful situation in the initial phase via nongenomic effects of MR. Genomic MR and nongenomic MR (membrane-bound MR) work together to determine the stress susceptibility [40]. Over the past decade, it was focused on the role of MR in HPA-axis activity, neurotransmission, synaptic plasticity, and stress-related behavior [40]. All of these have put the MR forward as an important stress moderator. Therefore, we review the current evidence for the role of MR in the pathophysiology of depression. We will summarize the role of MR in the HPA axis dysregulation, inflammation, decreased neurogenesis and stress-related behaviors in depression.

2. Role of MR and GR in HPA-axis activity

2.1. MR and HPA-axis activity

A lot of studies have confirmed that the MR controls the neuroendocrine activation of the HPA axis not only in basal condition but also under stress context [13,70]. In animal studies, transgenic mice lacking the MR in the forebrain displayed an altered basal and stress-induced corticosterone secretion, with especially enhanced corticosterone levels in response to restraint stress. This phenomenon demonstrates that MR in forebrain may regulate the HPA axis by inhibiting the corticosterone secretion [39]. In addition, transgenic mice with increased levels of MR in the forebrain exhibit gender-dependent differences in the HPA axis activity in response to stress. Female transgenic mice exhibited a moderate suppression of the corticosterone response to restraint stress, while similar basal and stress-induced HPA axis activity was found in male mice [82]. Furthermore, MR overexpression in basolateral amygdala reduces stress-induced plasma corticosterone levels and has no significant effect on basal corticosterone levels [61].

Clinical studies also have demonstrated that HPA axis can be inhibited by fludrocortisone, a MR agonist, in depressed patients [73]. The majority of these studies are focused on evaluating the interaction of MR agonists and antagonists with the HPA axis activity. It was reported that MR plays a clear role in HPA axis regulation in humans. The administration of a MR antagonist increases the cortisol secretion during the quiescent phase of the circadian rhythm. [14]. Moreover it has been reported that systemic administration of canrenoate enhances spontaneous cortisol secretion by inhibiting central γ-aminobutyric acid (GABA) ergic receptors during the nadir phase of the circadian rhythm [30], further demonstrating the fact that MR has a role on the regulation of the basal activity of the HPA axis. On the other hand, the acute administration of the MR agonist, fludrocortisone, significantly inhibits nocturnal HPA axis activity in healthy people [7].

One of the characteristics of major depression is the dysregulation of the HPA axis with a flattened circadian rhythm of cortisol [11]. Recent evidence suggests that MR is highly involved in this process. In postmortem brains of depressed patients, when compared with controls, a significant reduction of MR expression in the anterior hippocampus [69] and prefrontal cortex could be found [100]. Furthermore, in brain tissues from depressed patients, MR transcripts were detected with low levels in hippocampus, inferior frontal gyrus and cingulate gyrus when compared to the non-depressed subjects [47,54]. In addition, it is reported that modulation of MR by its agonist, fludrocortisone, can accelerate the response to SSRI (selective serotonin reuptake inhibitor) treatment when compared with the effect observed in the group with the addition of placebo or spironolactone [72]. It is believed that the improvement of circadian rhythm of HPA axis by MR may contribute to the SSRI treatment acceleration. All these data suggest that MR may occupy a crucial role in the regulation of circadian rhythm of the HPA axis.

2.2. MR and GR balance in depression

2.2.1. MR and GR balance in the regulation of HPA-axis activity

The GR is believed to be important in the regulation of the response to stress when endogenous levels of glucocorticoids are high. GR activation is necessary for the HPA feedback regulation when levels of glucocorticoid are high. GR has a low affinity but high capacity for glucocorticoids and are very responsive to changes in glucocorticoid concentrations. While MR is thought to be involved in the tonic inhibitory activity within the HPA axis, GR appears to “switch off” glucocorticoid production at times of stress.

Many reports have documented that the HPA axis system was dysregulated in depressed patients as evidenced by higher baseline cortisol values and an overactive response to psychological stressors ([12,60]). Several mechanisms are involved in this dysregulation of HPA axis including the central nervous system (CNS) and immune-endocrinology alterations. MR and GR play an important role in these processes [97].

The balance in MR/GR is a prerequisite for adaptation, homeostasis and health in the regulation of stress response. It is reported that imbalance of MR and GR may contribute to HPA axis hyperactivity and thus to depression etiology [80]. In stress, MR and GR operate in complementary fashion in control of adaptation to environmental demands. Under stress, MR is activated and modulates appraisal processes and retrieval of stored information, which can help to take decisions in crucial questions underlying the onset of a stress and emotional reactions. GR is involved in the redistribution of energy resources, which have a role in the termination of the stress response and management of later adaptations [66]. The cellular response patterns to this MR/GR balance upon stress have been documented. The activated MR rapidly enhances excitatory transmission by a nongenomic mechanism and stimulates the presynaptic release of glutamate. On the contrary, glutamate release and excitation is suppressed by GR [57]. Initially, this rapid transient increase in excitability helps the individual to appraise environmental input and

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