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The neuronal mineralocorticoid receptor: From cell survival to neurogenesis

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ABSTRACT

Mineralocorticoid receptor (MR), a hormone-activated transcription factor belonging to the nuclear receptor superfamily, exerts widespread actions in many tissues such as tight epithelia, the cardiovascular system, adipose tissues and macrophages. In the mammalian brain, MR is present in the limbic areas where it is highly expressed in neurons of the hippocampus and mostly absent in other regions while the glucocorticoid receptor (GR) expression is ubiquitous. MR binds both aldosterone and glucocorticoids, the latter having a ten-fold higher affinity for MR than for the closely related GR. However, owing to the minimal aldosterone transfer across the blood brain barrier and the absence of neuronal 11β hydroxysteroid dehydrogenase type 2 as an intracellular gate-keeper, neuronal MR appears to be fully occupied even at low physiological glucocorticoid levels while GR activation only occurs at high glucocorticoid concentrations, i.e. at the peak of the circadian rhythm or under stress. This defined a one hormone/two receptors system that works in balance, modulating a large spectrum of actions in the central nervous system. MR and GR are involved in the stress responses, the regulation of neuron excitability, long term potentiation, neuroprotection and neurogenesis in the dentate gyrus. MR thus constitutes a key factor in the arising of higher cognitive functions such as memorization, learning and mood. This review presents an overview of various roles of MR in the central nervous system which are somewhat less studied than that of GR, in the light of recent data obtained using cellular models, animal models and clinical investigations.

1. Introduction

The mineralocorticoid receptor (MR, or NR3C2), which belongs to the nuclear receptor superfamily and mainly acts as a ligand-dependent transcription factor [1,2], is highly expressed in neurons within the limbic structures of the brain, especially in the hippocampus, although MR is almost absent in most other brain areas. The closely related glucocorticoid receptor (GR or NR3C1) is ubiquitously expressed in the central nervous system. The limbic system, which encompasses the hippocampus, the amygdala, and the prefrontal cortex, is crucial in the arising of cognitive functions such as emotions, mood, behavior, memorization and learning [3]. Hippocampus is constituted of several structures such as Cornus Ammonis subdivided in CA1, CA2 and CA3 subregions and the dentate gyrus, the latter being the major site of neurogenesis in adult mammals [4] (see Fig. 1).

As hormone-dependent transcription factors, MR and GR share the same specific DNA response elements termed glucocorticoid response elements (GRE) to which they bind as homo- or heterodimers [5]. While MR displays a high affinity for both the mineralocorticoid hormone aldosterone and the glucocorticoid cortisol (in human) as well as corticosterone (in rodents), glucocorticoid hormone concentrations are at least a hundred times higher in the plasma than that of mineralocorticoids [6]. In archetypal MR target cells, mainly in tight epithelial cells of the distal nephron in the kidney, the 11β hydroxysteroid dehydrogenase type 2 (11βHSD2) enzyme converts corticosterone and cortisol into inactive metabolites (11-dehydrocorticosterone and cortisone, respectively), allowing MR occupancy by aldosterone [7] and subsequently the regulation of ionic transports [2]. Neurons in the hippocampus do not express this enzyme, thus MR should be mainly considered as a glucocorticoid-activated receptor in the central nervous system (CNS). This situation is similar in many other non-epithelial target cells such as in cardiomyocytes and adipocytes [8–11].

Glucocorticoid secretion is tightly regulated by the hypothalamic–pituitary-adrenal axis (HPA). Stressful changes in the

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environment or the circadian clock modulate the production of corticotrophin releasing hormone (CRH) in the paraventricular nucleus (PVN) of the hypothalamus that in turn controls the secretion of adrenocorticotropin hormone (ACTH) in the anterior pituitary triggering glucocorticoid release from the cortex of the adrenal gland. Thus, glucocorticoid as well as mineralocorticoid hormones are sometimes referred to as corticosteroid hormones. The HPA axis is itself controlled by the limbic system that acts on the PVN activity (Fig. 1) [12]. As a consequence, this endocrine system activity is strongly linked to cognitive, behavioral and emotional occurrences. Besides, glucocorticoids exert a well-described, negative regulatory feedback loop on HPA axis activity [13].

Plasma glucocorticoid concentration is maximal at awakening, when the organism needs to mobilize energy resources from the body and slowly decreases afterward to reach a nadir before the start of the inactive period, then rises again during late sleep. This cyclical variation of glucocorticoid release is superimposed with ultradian hourly pulses [14]. Of note, this cyclic pattern is inverted between nocturnal species (rodents) and diurnal species (human).

MR exhibits a 10-fold higher affinity for glucocorticoids than the GR (e.g., for corticosterone, Kd = 0.5 nM and 5 nM, respectively). As a consequence, MR is very likely fully occupied by glucocorticoids even at the trough of the circadian rhythm. Besides, the GR is only significantly occupied and activated under high glucocorticoid concentrations that prevail at the peak of the circadian rhythm or under stress [6] (Fig. 2). The physiological relevance of MR function in neurons, as a receptor which is permanently activated by its ligands is somewhat puzzling but interestingly, evidence suggests that MR and GR in the brain may also act as membrane receptors exerting rapid non-genomic actions, although with a lower affinity for corticosterone [15,16]. This paradigm provides an additional level of complexity in corticosteroid receptor signaling in the CNS.

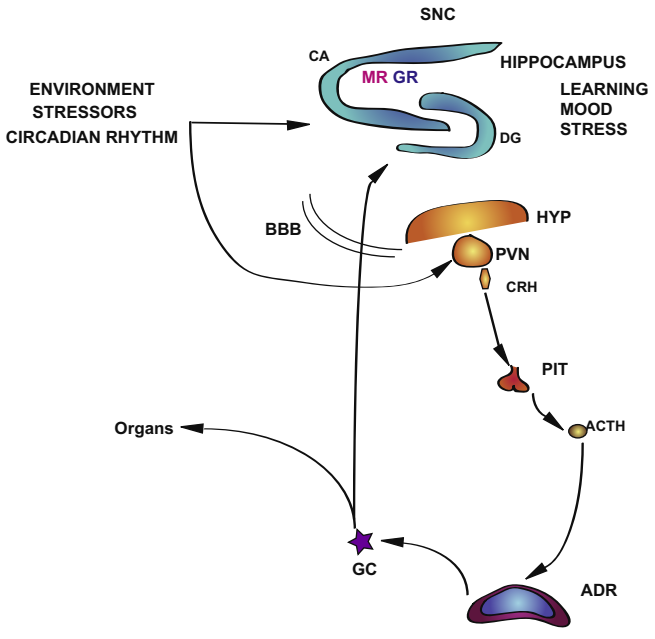

Fig. 1. Schematic representation of the hypothalamic–pituitary-adrenal (HPA) axis. The paraventricular nucleus (PVN) in the hypothalamus (HYP) secretes the corticotrophin releasing hormone (CRH) under the control of the environment, various stressors and the circadian/ultradian rhythm. CRH in the portal blood stimulates adrenocorticotropin hormone (ACTH) that triggers the secretion of glucocorticoids (GC) by the adrenal glands (ADR). GC exerts widespread actions on many organs and able to cross the blood brain barrier to act on the central nervous system (CNS), where the hippocampus, encompassing the cornus ammonis (CA) and the dentate gyrus (DG), expresses both MR and GR.

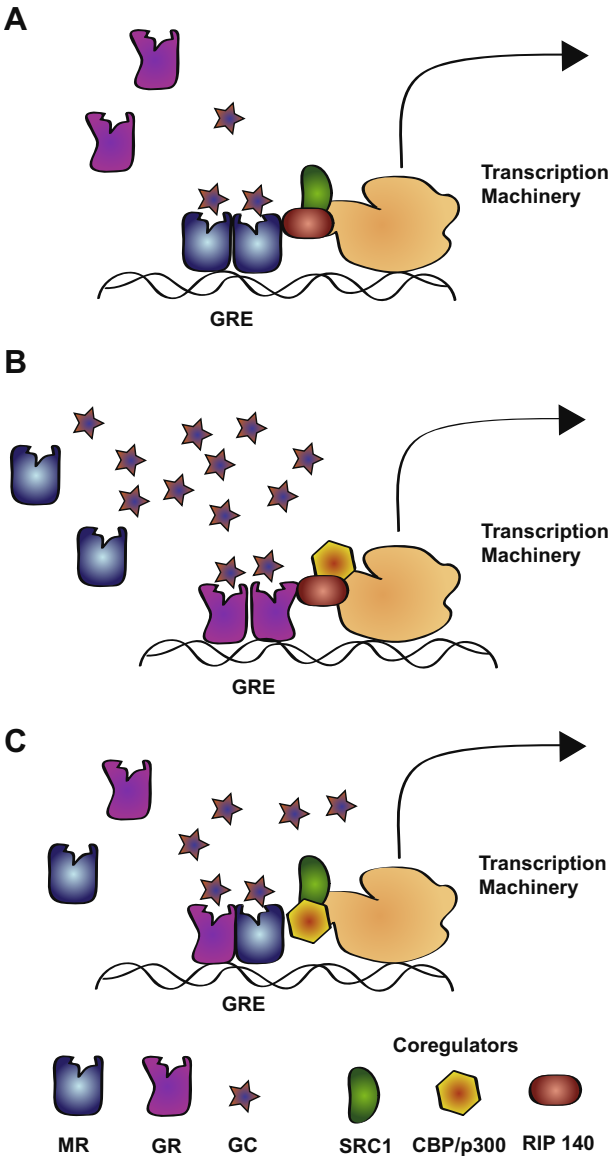

Fig. 2. Simplified illustration of the mechanisms of glucocorticoid actions on the CNS. (A) at low glucocorticoid (GC) concentration, such as at the trough of the circadian rhythm, MR is already fully occupied by GC, recruits a distinct set of coregulators (e.g., SRC1, CBP/p300, RIP 140 [108]), binds to glucocorticoid response elements (GRE) on the DNA to activate transcription of a specific set of genes. (B) at high GC concentration, liganded GR binds to its own set of GRE, interacts with coactivators (red and orange) to stimulate transcription. (C) At intermediary levels of GC, MR and GR likely form heterodimers on some target gene regulatory sequences.

Many studies on corticosteroid actions in the CNS have mostly focused on the GR, while the role of MR remains somehow neglected. In this review, we mostly focused on MR-mediated responses to corticosteroid hormones in the limbic system. We will give an overview of the transcriptional regulation of MR, of its role in stress responses, memorization, behavior, mood, neurogenesis and in neuroprotection/apoptosis. We will also describe the molecular, cellular and physiological events involved in a wide array of animal and cellular models.

2. MR expression in the CNS

NR3C2 gene was cloned in several species and encodes for a protein that exhibits the classical structure of members of the nuclear receptor superfamily. Indeed, MR is composed of an N-terminus