Chapter

View on Aldosterone and the Brain Revisited

Natasa Hlavacova and Damiela Jezova

Abstract

The mineralocorticoid hormone aldosterone has been investigated almost exclusively with respect to cardiovascular function, as the main effects of aldosterone are related to water-electrolyte balance and the control of the blood pressure. This overview is focused on less traditional and long-time neglected effects of aldosterone on the brain and behavior. Preclinical studies by our research group brought evidence on causal relationships between aldosterone and anxiety as well as aldosterone and depression-like behavior. Aldosterone was found to be anxiogenic and depressogenic in a rat model. Preclinical studies also indicate that aldosterone may be an early marker of depression onset. Aldosterone is known to be an important component of the stress response, and we have shown that its role is particularly important during early postnatal period in pups. Studies in patients with major depressive disorder revealed that an unfavorable therapy outcome is predicted by a higher salivary aldosterone/cortisol ratio. Our clinical studies showed that salivary aldosterone concentrations reflect the severity, duration of the depressive episode, and treatment outcome in patients with major depressive disorder. Moreover, the patients with depression fail to exert known daily rhythmicity of aldosterone release.

Keywords: aldosterone, anxiety, depression, stress, rhythm

1. Introduction

The mineralocorticoid hormone aldosterone is typically viewed as the principal regulator of sodium and potassium balance thus playing a major role in maintaining extracellular volume homeostasis. The classical genomic actions of aldosterone are mediated by mineralocorticoid receptor (MR). The MR and its kin, the glucocorticoid receptor (GR), evolved from an ancestral corticoid receptor in a cyclostome (jawless fish) throughout gene duplication and divergence. Distinct orthologs of the MR and GR initially appeared in cartilaginous fishes, such as sharks, skates, rays, and chimeras. Aldosterone first appears in lungfish, lobe-finned fish that are forerunners of terrestrial vertebrates [1, 2]. The evolution of the relationship between aldosterone and MR likely occurred in response to dramatic changes associated with transition from aquatic to terrestrial life. In the ocean, aquatic organisms had the burden of fighting constant salt loading, whereas the prospect of a terrestrial existence presented the opposite problem, preventing their emergence from the sea. It is likely that the aldosterone-MR relationship was a part of the solution to maintain ion balance during this transition from water to land [3]. Further sequence divergence of the MR and GR in terrestrial vertebrates led to emergence of aldosterone as a selective ligand for the MR [4]. The first studies with recombinant human MR

yielded an unexpected discovery [5] that human MR has strong binding affinities for several corticosteroids (aldosterone, cortisol, corticosterone, and 11-deoxycorticosterone) and for progesterone. Although these steroids show similar affinity for human MR, transcriptional activation of human MR by these steroids is different. Compared to glucocorticoids, aldosterone is a stronger activator of the MR [6]. The ability of aldosterone to activate human, rat, and mouse MRs is complicated by the substantially higher concentration of glucocorticoids.

Given the fact the glucocorticoids circulate at much higher concentrations than aldosterone, glucocorticoids would be expected to predominantly occupy the MRs under most conditions [7]. In the peripheral epithelial tissues, the specificity of MR for aldosterone is achieved by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) which converts glucocorticoids to inactive metabolites, thus allowing aldosterone to bind to the MR. In the brain, the situation is much more complicated. Central action of aldosterone via MR is limited due to almost negligible levels of 11β-HSD2 in the brain. The lack of 11β-HSD2 in MR-rich regions suggests that the majority of brain MRs are likely to be fully occupied by glucocorticoids [8]. From these reasons, possible central effects of aldosterone have been neglected for a long time. Nevertheless, over the last 20 years, there is growing body of evidence that certain brain areas contain MRs that bind preferentially mineralocorticoids. This was demonstrated in the nucleus tractus solitarius, the subcommissural organ, and the ventrolateral subdivision of the ventromedial nucleus of the hypothalamus [9–13]. Importantly, nonclassical effects of aldosterone mediated via nongenomic actions [14] and de novo synthesis of aldosterone within the brain should also be considered [15].

Studies by Ron De Kloet group published more than 30 years ago were not in favor of aldosterone effects on exploratory activity or forced extinction paradigm of a passive avoidance response in rats [16]. Pretreatment with aldosterone blocked the serotonin response to corticosterone [17]. It should be noted, however, that aldosterone was administered in a single injection to acutely adrenalectomized rats. The authors concluded that that the time interval between acute aldosterone administration and behavioral testing (1 hr) was too long for the appearance of behavioral effects of aldosterone. Until 2008, nothing was known about repeated or chronic aldosterone treatment on behavior related to anxiety or depression in normal intact rodents.

Writing this overview was motivated by the new evidence on atypical effects of aldosterone gathering during the last few years, when we have started our research on aldosterone and the brain. In spite of the generally accepted view on the absence of the central effect of aldosterone, we have decided to perform research in the field. The main focus of this mini-review is given on aldosterone action in the central nervous system from two points of view, namely, the pathophysiology of mood disorders from translational point of view and the significance of aldosterone during the development.

2. Nothing dared nothing won

The scientific work is based on testing the hypotheses formulated on the basis of thoroughly verified facts obtained in several laboratories using various experimental approaches. It might happen, however, that even not yet satisfactory confirmed evidence evokes the desire to lead the research in a new direction. This happened to us, and we have to formulate a hypothesis on anxiogenic and depressogenic action of aldosterone about 10 years ago. At that time, the arguments to formulate such a hypothesis were rather vague and certainly inadequate, but we were full of enthusiasm and courage.

Our scientific interest in atypical effects of aldosterone on mental functions was motivated by scattered data published 15 years ago by the authors Murck et al. [18] and Emanuele et al. [19]. In small groups of depressed patients, they observed increased plasma aldosterone concentrations. However, causal relationship between aldosterone and mood disorders has not been approached. Our first original data on this topic were obtained in animal studies.

In the first series of experiments, we have tested the hypothesis that prolonged elevation of circulating aldosterone induces increased anxiety-like behavior in rats. Subchronic treatment with aldosterone (2 μg/100 g body weight/day for 2 weeks) via subcutaneous osmotic minipumps was applied to induce a mild hyperaldosteronism. Rodents do not, of course, tell the researchers that they feel anxious, but there are behavioral tests in which anxiety level can be assessed. In these tests, we have shown that aldosterone-treated animals exhibited increased anxiety-like behavior [20]. Anxiogenic effect of aldosterone was manifested by a significantly reduced frequency of entries and time spent in the open arms in the elevated plus maze test as well as reduced number of entries and time spent in the central area of the open-field test in aldosterone-treated rats compared to controls. Aldosterone treatment negatively influenced both the conventional spatiotemporal measures of anxiety and the ethological parameters related to anxiety and risk assessment behavior [20].

The role of aldosterone in anxiety-like behavior was supported by the results obtained using a different approach, demonstrating an anxiolytic action of an aldosterone antagonist. As an aldosterone antagonist, the selective MR blocker eplerenone, a clinically used drug for the treatment of heart failure and hypertension, was used [21]. Mild anxiolytic effects were observed after a single administration of eplerenone at the dose of 100 mg/kg body weight [22]. Anxiolytic effects of MR blockade were completely demonstrated following repeated treatment with eplerenone [23]. Eplerenone administered for 11 days (50 mg/kg body weight twice daily) influenced ethological indicators of anxiety. More importantly, significant differences were found in classical spatiotemporal measures, as the eplerenone-treated rats entered more often and spent more time in the open arms of the elevated plus maze. Another original finding is the effect of subchronic MR blockade on hippocampal concentrations of brain-derived neurotrophic factor (BDNF), a marker of brain plasticity. Stress-induced alterations in BDNF have been identified as a strong candidate modulating stress-related pathology [24, 25]. On the contrary, chronic treatment with antidepressants was shown to increase BDNF levels [26]. We have demonstrated that eplerenone treatment prevented stress-induced decrease in hippocampal concentrations of BDNF, suggesting a positive influence of MR blockade on brain plasticity [23].

In the next series of experiments, we focused our attention on depression-like behavior. We have used the same rat model of hyperaldosteronism previously and assessed symptoms of depressive behavior using the sucrose preference test and the forced swim test. The results clearly demonstrated that the subchronic increase in circulating aldosterone exerts depressogenic effects [27]. Aldosterone treatment induced an anhedonic state manifested by decreased sucrose preference. Depressogenic action of aldosterone was confirmed also in the forced swimming test. Animals treated with aldosterone spent significantly longer time in immobility and showed significantly decreased latency to become immobile [27]. Our results on depression-like behavior induced by aldosterone treatment in rats were confirmed by the authors Bay-Richter et al. [28]. As a result of our collaboration with colleagues from the USA, we revealed that hyperaldosteronism induces changes in expression of genes that have been shown to be associated with a major depressive disorder in humans [27].

Supporting data on the role of aldosterone in the development of depressive behavior have also been obtained in another animal model of depression. We have established a new and novel animal model of depression based on diet-induced tryptophan depletion in female rats [29]. Diet-induced tryptophan depletion resulted in a significant reduction of brain serotonin and induction of depression-like behavior manifested by increased immobility in the forced swim test [30]. Interestingly, the depression-like state was associated with a significant increase in serum aldosterone concentrations. We showed that aldosterone secretion had increased already after 4 days of tryptophan depletion, prior to the rise in serum corticosterone. This finding suggests that aldosterone may be more important than corticosterone in the development of a depression-like state and aldosterone may constitute an early marker for the onset of depression-like behavior [30].

In a very recent study by Geerling et al. [13], the authors characterized a hallmark of aldosterone-sensitive HSD2 neurons in the nucleus of the solitary tract. They showed that axons of HSD2 neurons project to the parabrachial complex/pre-locus coeruleus and the ventrolateral bed nucleus of the stria terminalis, two neural hubs with a crucial function in salt appetite (salt hunger) and accompanying arousal. They suggested that downstream targets of HSD2 neurons promote sodium appetite, but they may also influence stress coping and mood circuits to produce dysphoric, anhedonic, and anorexic symptoms of hyperaldosteronism.

Our evidence of a causal relationship between hyperaldosteronism and anxiety- and depression-like behaviors in animals represents a breakthrough in the research on aldosterone action in the central nervous system and reveals a new area of research with potential clinical significance.

3. Translation of experimental data to clinical research

Animal models can be useful tools in biomedical research, but undoubtedly, it has frequently been observed that effects found in animal models cannot be translated to the clinic [31]. It is therefore essential that knowledge gained from animal studies should be carefully confirmed in human studies.

To be able to translate the knowledge obtained in animal models to clinical research, we have initially introduced a methodology to measure aldosterone concentrations in saliva [32]. Determination of steroids in saliva has become a valuable alternative due to the noninvasiveness and laboratory independence of sampling. While assays for salivary cortisol are widely used, the availability of assays for measurement of aldosterone in saliva has been limited. Concentrations of aldosterone in saliva represent approximately one-third of the total level in plasma, and they correlate well with plasma values [33, 34]. We have modified the methodology of aldosterone radioimmunoassay by concentrating the saliva and validated the method by a low-dose ACTH test and by confirmation of daily rhythm and sex differences [35].

We have provided the first original data on the relationship between aldosterone and trait anxiety in humans. We have shown that the relationship between aldosterone and trait anxiety is determined by sex and the phase of the menstrual cycle in women [32]. Negative correlation between salivary aldosterone concentrations and trait anxiety was observed in women in the luteal phase, while a positive association was found in women in the follicular phase of the menstrual cycle.

In recent years, we have performed several studies to clarify the role of aldosterone in depressive disorder. We have conducted a pilot study in patients with a major depressive disorder in collaboration with Marburg University, Germany. Biomarkers of MR function were examined in order to characterize their relationship to clinical treatment outcome after 6 weeks in 30 patients with major

depression [36, 37]. Although the number of patients was not very high, there was a significant association between salivary aldosterone concentrations and the severity of depressive symptoms. A negative correlation between aldosterone concentrations in saliva and improvement in clinical state of patients was revealed. Interestingly, a higher ratio of aldosterone to cortisol concentrations at baseline was predictive for poorer clinical outcome after 6 weeks of treatment [36].

Supporting data came also from other researcher groups. In patients with primary hyperaldosteronism, a higher occurrence of anxiety and depressive symptoms compared to healthy volunteers was demonstrated [38–40]. A population study in humans revealed that the combination of the chronic stress of living alone and depressive symptomatology was accompanied by high levels of aldosterone [41]. On the other hand, Hallberg et al. [42] found lower concentrations of aldosterone in patients with major depression with suicidal behavior than suicidal patients without depression and non-suicidal depressive patients.

The most complete results so far have been obtained by examining 60 patients with major depressive disorder in a study performed in collaboration with clinical psychiatrists, particularly the Department of Psychiatry, Faculty of Medicine, Comenius University and University Hospital Bratislava, Slovakia [43]. The sample consisted of 37 postmenopausal women and 23 men suffering from major depressive disorder. Morning and evening samples of saliva were obtained during depressive episode (admission to the hospital) and after reaching clinical remission (discharge). Results showed several notable original findings. Salivary aldosterone concentrations were higher at the time of admission to the hospital than those at the time of discharge, i.e., after improvement of the clinical state. It is well known that aldosterone secretion shows a daily rhythm [35, 44, 45] with the highest values in the morning and the lowest at evening. The patients with depression failed to exert known daily rhythmicity of aldosterone release [43]. An intriguing finding was the observation of the relationship between morning aldosterone concentrations and the duration of the current depressive episode. When patients were stratified according to the length of the depressive episode, women with a shorter duration of the depressive episode (up to 12 weeks) exhibited significantly higher aldosterone concentrations than women with a longer episode (over 16 weeks). In men, this difference was not observed. We have also demonstrated that morning salivary aldosterone concentrations are particularly higher in patients with severe depressive episode than those with moderate depressive episode. These findings strongly support the role of aldosterone in the pathophysiology of depressive disorder. Concentrations of aldosterone in the saliva appear to reflect the clinical outcome, duration, and severity of depressive episode in a sex-dependent manner [43].

4. Aldosterone during the development

In pups, the main physiological role of the renin-angiotensin-aldosterone system is to maintain water-electrolyte balance, while the hypothalamic-pituitary-adrenocortical (HPA) axis regulates energy metabolism. Prenatal and early postnatal brain development is a very complex process that can be endangered by a number of endogenous and exogenous stimuli. This is a serious problem given the neurodevelopmental background of several psychiatric disorders [46, 47]. Environmental stimuli that may interfere with the normal development of the central nervous system include excessive exposure to stressful situations. Exposure to stressors at the time of brain development may cause a repeated elevation in concentrations of glucocorticoids which are known to exert negative effects. Of the stress hormones, the neurotoxic effect is attributed, in particular, to glucocorticoids. Increased levels of glucocorticoids adversely affect neurogenesis and brain plasticity [25].

As was already mentioned, animal models represent a useful tool in the research in the field of neurodevelopmental disorders. Long time ago, scientists have discovered that there is a physiological mechanism in the rodents protecting the developing brain from neurotoxic glucocorticoids. During the first 2 weeks of life (from about days 2–14), rat pups show reduced capacity to secrete corticosterone in response to several stimuli [48–50]. This period was called the stress non-responsive period. Later, after introducing more sophisticated analytical methods for plasma corticosterone analysis, it has been found that a small increase occurred and the period was renamed to stress hyporesponsive period. In this period, corticosterone response to stress stimuli is several times lower than that in adult rats. This phenomenon is associated with dramatically reduced corticosteroid-binding globulin (CBG) levels [51, 52]. This occurs as a result of reduced half-life of CBG in plasma and decreased CBG production by the liver in the neonates [53, 54]. Thus, corticosterone circulates mainly in the free form during the stress hyporesponsive period, since CBG levels are negligible. During the stress hyporesponsive period, the adrenal gland is hyporesponsive to adrenocorticotropic hormone. Numerous studies have demonstrated that maternal factors, such as maternal care and feeding, are critical for the regulation of the pup's HPA axis and the maintenance of the stress hyporesponsive period [50]. It has been demonstrated that maternal deprivation during the stress hyporesponsive period causes a rapid rise in corticosterone concentrations [50] and profoundly affects GR epigenetics [55]. This type of studies would be welcome for aldosterone and the MR as well, since these are understudied. No information on possible similar reduction of aldosterone in response to stressors during the stress hyporesponsive period was available.

In a joint project with the Institute of Experimental Medicine, Hungarian Academy of Sciences, we have demonstrated that 10-day rat pups showed increased rather than reduced response of aldosterone to several acute stress stimuli. Stress-induced rise in aldosterone concentrations was significantly higher in pups compared to that in adulthood as well as compared to the rise in corticosterone [56]. In adult rats, the response was quite opposite; the increase in stress-induced aldosterone concentrations was only mild, whereas the elevation of corticosterone was much more pronounced. The physiological significance of increased aldosterone secretion during stress in the early postnatal period is supported by our findings of altered expression of mineralocorticoid and glucocorticoid receptors in the hypothalamus, hippocampus, and prefrontal cortex and in particular by increased expression of 11β-HSD2 [56].

It may be suggested that the main physiological importance of higher aldosterone secretion in pups is related to the maintenance of water-electrolyte balance during the perinatal period. MRs are present in the heart, blood vessels, adipocytes, and macrophages. It is possible to assume that during the perinatal period, aldosterone takes over the regulatory role of glucocorticoids in certain cellular processes and molecular mechanisms. Experiments in vasopressin-deficient Brattleboro rats excluded the possible important role of vasopressin. It appears that the shift from a more pronounced aldosterone to corticosterone rise during stress occurs after 40 postnatal days [57]. It is therefore clear that during rodent development, aldosterone is the more important stress hormone of the adrenal cortex than corticosterone.

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