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Mineralocorticoid receptors in the brain and cardiovascular regulation: minority rule?

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Abstract

A small proportion of brain mineralocorticoid receptors (MR) mediate control of blood pressure, water and electrolyte balance, sodium appetite, and sympathetic drive to the periphery. Circulating inflammatory cytokines modulate MR-mediated changes in sympathoexcitation. Aldosterone binding to MR in the brain occurs, despite concentrations that are 2–3 orders of magnitude less than those of cortisol and corticosterone, which have similar affinity for the MR. The possible mechanisms for selective MR activation by aldosterone, the cellular mechanisms of MR action and the effects of brain MR on hemodynamic homeostasis are considered in this review. MR antagonists are valuable adjuncts to the treatment of chronic cardiovascular and renal disease; the crucial need to discover targets for development of selective therapy for specific MR functions is also discussed.

Perspective

Mineralocorticoids are aptly named for their enhancement of vectorial transport of Na^+ and water in one direction, and K^+ and H^+ in the other, across epithelial barriers such as that of the renal tubule and choroid plexus. In the adrenal zona glomerulosa, synthesis of the primary mammalian mineralocorticoid, aldosterone, is increased by angiotensin II via the AT1 receptor, and is also increased by high potassium levels, and a low-salt diet. Aldosterone synthesis is suppressed, although not completely, by a high-salt diet [1]. Mineralocorticoids act through mineralocorticoid receptors (MR), which are expressed on many non-epithelial cells, as well as in transport epithelia, including cells in the heart, vessels and brain [2]. The extent of occupation and activation of brain MR by mineralocorticoids in competition with glucocorticoids is cell-specific and as yet not resolved. MR are amply expressed in several specific areas of the brain; however, only a minority of these mediate functions that relate directly to blood pressure or electrolyte and fluid homeostasis [3–5]. In this review, I briefly address the complex issue of the cardiovascular consequences of the central actions of aldosterone. Addition of MR antagonists to the standard treatment for chronic heart failure has greatly improved patient outcome, including quality-of-life measures that do not clearly derive from cardiovascular function [6–9]. Although these aspects will not be addressed in this review, MR in the brain that are not directly involved in hemodynamic regulation should be considered in the future as the use of MR antagonists becomes more common.

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Molecular mechanisms of MR activity

MR is a member of the steroid nuclear receptor family of transcription factors, with basic structural similarities to other members of the steroid nuclear receptor family, particularly that of the glucocorticoid receptor (GR). Ligand-free MR are primarily, but not exclusively, located in the cytosol in association with chaperone and cell scaffolding proteins that alter the conformation of the molecule and anchor it in proximity to interacting proteins [10–13]. Upon ligand binding, chaperone proteins are shed, and MR translocate to the nucleus where they associate with coactivator proteins and form dimers that bind to hormone response elements (HRE) to repress or activate promoters of gene transcription [14]. Activated MR can form heterodimers with GR, as well as homodimers [15–18]. The MR shares a HRE with GR [16,19], adding to the difficulty in separating GR and MR function. Cell-specific expression of different co-activator proteins, such as different splice variants of the steroid receptor coactivator-1 protein, also influence the HRE to which the activated MR and GR will bind [20,21]. Expression of the two receptor types in the brain overlaps, but is distinct, with the relative expression of MR and GR differing between neurons even among those in the hippocampus [3]. The effects of heterodimerization on transcriptional activity *in vivo* are not yet clear, but are presumed to have implications for both MR- and GR-mediated actions.

MR ligand specificity

Understanding MR transcriptional activity has been further complicated by its similar intrinsic affinity for the primary glucocorticoids cortisol and corticosterone (in rats and mice) and aldosterone. Cortisol and corticosterone circulate at 100 (free) to 1000 (total) times the concentration of aldosterone. The affinity of the GR for cortisol and corticosterone is approximately one-tenth that of the MR for these glucocorticoids, and GR affinity for aldosterone is approximately one-tenth that of cortisol and corticosterone. Most MR, including those of the brain, are at least partially occupied by non-stress levels of glucocorticoids under normal steroid concentrations [3,22] and GR are thought to be occupied by cortisol or corticosterone only at the zenith of the circadian cycle and during stress.

Using autoradiography, aldosterone binding has been demonstrated in many discrete areas of the brain of the adrenalectomized rat, and this binding overlaps with, but is different from, corticosterone and dexamethasone binding [23–25]. Binding studies in animals pretreated with a GR agonist to limit steroid binding to MRs also demonstrated more widespread binding of aldosterone than of corticosterone, particularly in the cortex and hypothalamus, with the exception of the hippocampus, to which corticosterone and aldosterone bind to a similar degree [25]. Interpretation of these studies, however, is complicated by the use the adrenalectomized animals. Yongue and Roy measured aldosterone and corticosterone by radioimmunoassay in cell nuclei after cell fractionation of different portions of brains from rats. They confirmed that the heaviest site of endogenous corticosterone occupation *in vivo* was the hippocampus and, notwithstanding the stoichiometric odds of normal circulating steroid concentrations, found aldosterone in cell-nucleus fractions of all brain sites tested, with the highest concentration in the hypothalamus. Although the amounts of corticosterone in the cell nuclei of brain tissue reflected changes in plasma corticosterone, the amount of aldosterone did not vary with different plasma aldosterone concentrations produced by altering the sodium intake of the rats, suggesting that endogenous aldosterone binding was saturated even during a high-salt diet when circulating aldosterone levels are low [26].

MR specificity for aldosterone in mineralocorticoid target cells is thought to be determined extrinsically by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (Box 1).

In addition to its detection in transport epithelia of the colon and select renal tubular epithelia, 11β-HSD2 mRNA has been detected by *in situ* hybridization in the brain, including in circumventricular nuclei [27]. Using immunohistochemistry, 11β-HSD2 and MR have been shown to colocalize in aldosterone target neurons of the nucleus tractus solitarius (NTS) [5,28,29]. 11β-HSD2 is thought to convert cortisol and corticosterone to the inactive steroids cortisone and 11-dehydrocorticosterone, to create a microenvironment in which aldosterone can effectively compete with glucocorticoids for MR binding [30]. Rapid conversion of corticosterone to 11-dehydrocorticosterone from both endogenous and tritiated precursors by minced whole brain from adrenal-intact rats and adrenalectomized rats has been demonstrated [30].

Although the result of MR binding in some tissues, including the brain [31,32], depends on whether the ligand is aldosterone or a glucocorticoid, MR in transport epithelial cells mediate similar functions whether activated by aldosterone or a glucocorticoid. Inactivating mutations of the *Hsd11b2* (11βHSD2) gene and pharmacologic inhibition of the enzyme produces apparent mineralocorticoid excess, while suppressing the renin–angiotensin–aldosterone system, presumably by allowing cortisol or corticosterone to bind and activate aldosterone target MRs. Similarly, the high amounts of cortisol attained in ectopic adrenocorticotrophic hormone (ACTH) syndrome are thought to saturate the 11β-HSD2, resulting in inappropriate activation of the MR by cortisol [33].

Based in part upon binding studies performed in whole tissues, it has been suggested that conversion of active to inactive glucocorticoid would not suffice to confer aldosterone selectivity to the MR, even in the kidney [22]. Interpretation of these studies is difficult because only a small proportion of total the MRs in the kidney (that in the cortical collecting, distal convoluted and outer medullary tubules) are in aldosterone target cells expressing 11β-HSD2 [2,34]. Unfettered binding by corticosterone of the majority of MR expressed was not considered. 11β-HSD2 requires NAD^+ as cofactor for dehydrogenase activity, and generates NADH in the process [35]. An alternative hypothesis for the mechanism of action of 11β-HSD2 in aldosterone target cells is that MR in these cells are bound by glucocorticoid, and that the NADH generated by 11β-HSD2 stabilizes the MR:glucocorticoid conformation to limit transcriptional activity. When 11β-HSD2 is inhibited, NAD^+ accumulates, producing a change in conformation of the glucocorticoid-bound MR that allows it to have the same transcription activity as the MR bound by aldosterone [36]. Accumulation of reactive oxygen species in injured or hypoxic tissues (e.g. in the infarcted myocardium), is hypothesized to have a similar effect on the MR:glucocorticoid complex to that of NAD^+, triggering the activation MR by glucocorticoids [36]. This is a compelling, if yet unproven, explanation for how MRs in non-epithelia tissues that do not express 11β-HSD2 become activated during pathologic conditions, despite low to normal aldosterone levels. An argument against this postulate is the activation by high levels of cortisol in ectopic ACTH syndrome [33].

In addition to its transcriptional activity, the MR mediates rapid non-genomic effects through second-messenger systems including the phosphorylation of extracellular signal-regulated kinase 1 (ERK)1 and ERK2 and c-Jun NH_2-terminal kinase (JNK) 1 and 2 kinases, [37–39]. G-protein receptor 30 (GPR30), a seven-transmembrane spanning G protein receptor, has been postulated to be responsible for activation of phosphatidylinositol 3-kinase-dependent contraction and ERK activation in vascular smooth muscle cells by aldosterone [40]. These effects are not separated from the transcriptional activity of MR in this review. MR might also be activated in a steroid-independent manner through transactivation by other signal transduction pathways, in particular that of angiotensin II [41]. Although beyond the scope of this review, the potential activation of MR by an angiotensin II signaling pathway is germane to central hemodynamic control, as angiotensin

II, in addition to aldosterone, is an important mediator of blood pressure and of fluid and electrolyte homeostasis in hypothalamic centers.

Central nervous system blood pressure, electrolyte and water control centers

The anterior hypothalamus and brain stem were identified as general areas of prominent aldosterone binding, using autoradiography and measurement of aldosterone in the cell nucleus as a reflection of receptor binding [23–26]. These areas comprise several centers that are important for hemodynamic and fluid/electrolyte homeostasis, including the organum vasculosum lamina terminalis (OVLT), subfornical organ (SFO), area postrema (AP), subcommissural organ, magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON), and select neurons of the NTS and of the rostral lateral ventral medulla (RVLM) of the brain. The OVLT, SFO and AP are circumventricular organs that have incomplete blood brain and ependymal barriers, which allow detection of changes in osmotic pressure, sodium concentration, and hormones and cytokines in the blood and cerebrospinal fluid [42]. The area anteroventral to the third ventricle, the AV3 V area, comprises the OVLT, ventral portion of the median preoptic nucleus, anteroventral periventricular nucleus and the periventricular nucleus, plus nerve fibers that relay information between these structures and areas receiving and integrating hemodynamic information. Among these are the NTS and lateral parabrachial nucleus in the medulla, and PVN, SON and median preoptic nucleus of the hypothalamus [43]. Lesions of the AV3 V area prevent mineralocorticoid/salt and renovascular forms of hypertension by disrupting multiple regulatory systems, some of which might not involve direct MR effects, including those for osmoreception, water and sodium homeostasis (thirst and sodium appetite), integration of baroreceptor and autonomic nervous system information, and secretion of vasopressin and natriuretic factor [44,45].

The chronic lateral intracerebroventricular (ICV) infusion of aldosterone or the mineralocorticoid deoxycorticosterone acetate, at doses too small to increase sodium appetite or to have an effect when infused systemically, produces hypertension associated with an increase in vascular tone, and in the release of vasopression and decrease in baroreceptor sensitivity [4]. The effect is accelerated by decreasing renal mass and increasing salt intake, but it also occurs on a standard rodent diet (0.3% Na) in intact rats [46]. ICV infusion of an MR antagonist at a dose too small to have an effect when infused systemically prevents mineralocorticoid excess/salt hypertension [47]. ICV infusion of a selective GR agonist did not alter the blood pressure, nor did ICV infusion of an equimolar amount of corticosterone, but the concomitant infusion of increasing concentrations of corticosterone decreased the hypertension produced by ICV aldosterone infusion in a dose-related fashion [31]. It has not been ascertained whether this is was a result of the increased formation of transcriptionally inactive MR:glucocorticoid complexes, differential transcription of different genes with competing functions by the MR:aldosterone and MR:glucocorticoid complexes, or increased GR:glucocorticoid transcriptional activity and interactions with GR-mediated functions. Recent work in which small interfering RNAs for the MR and AT1a angiotensin II receptor (AT1aR), and pharmacologic antagonists of the MR and AT1aR were infused ICV, confirmed and extended these studies [48]. These experiments clearly demonstrated a significant synergism between angiotensin II and aldosterone signaling through the AT1aR and MR, with inhibition of either MR or AT1aR suppressing the hypertension and increase in sodium appetite in response to the central infusion of angiotensin II or aldosterone [48].

The lesioning and ICV infusion studies of MR agonists and antagonists have been tremendously informative, but blunt instruments, in the study of brain MR regulation of

blood pressure. Using more refined immunohistochemical techniques, a small number of neurons of the NTS, which express both MR and 11β-HSD2, have been identified and found to be crucial to the response to sodium deprivation and sodium repletion [5,49]. These aldosterone-target neurons receive information about sodium intake and plasma concentration from the vagus nerve [50], and about osmolality from AP neurons [5,49], and project to neurons in the parabrachial nuclei, which in turn project to the central nucleus of the amygdala, another area of the brain crucial for salt appetite [51]. Inhibition of MR in the amygdala either by infusion of an antagonist or antisense oligonucleotides inhibits the salt appetite produced by mineralocorticoid excess [52]. Aldosterone binding of MR in the NTS activates some of the neuronal pathways involved in motivational and reward behavior, including those in the nucleus accumbens, ventrolateral bed nucleus of the stria terminalis and, indirectly, the amygdala [5,29,53]. Mineralocorticoid excess and sodium deprivation are both associated with signs of depression in humans and experimental animals [5,54,55]. This might explain the difficulty experienced by patients in complying with a low-salt diet, as well as reports of the amelioration of depression and cognition in patients with primary aldosteronism after resolution of their disease [56,57]. Given the prevalence of primary aldosteronism, inappropriate MR activation in the brain might be significant in up to 12% of patients with hypertension [1].

Clinical relevance

Primary aldosteronism, the most frequent cause of secondary hypertension, is caused by an aldosterone-producing tumor or idiopathic hyperplasia and unregulated aldosterone production by adrenal zona glomerulosa cells [1].It is associated with hypertension, suppression of renin, hypokalemia, alkalosis, and cardiovascular remodeling with hypertrophy [1,4]. It should be noted that even in primary aldosteronism, concentrations of aldosterone are still at least two orders of magnitude less than those of cortisol. Notwithstanding, aldosterone values in the highest quartile of the normal range predict the future development of hypertension in normotensive subjects, demonstrating the importance of seemingly insignificant increases in aldosterone in the development of high blood pressure [58].

Although increased central sympathetic drive is part of the mechanism of mineralocorticoid hypertension in experimental animals [59,60], its role in primary aldosteronism has been controversial, in part because many studies in patients have been acute and relied upon indirect arm-cuff blood pressures and inappropriate control groups [61,62]. When intra-arterial pressure was monitored continuously and plasma norepinephrine was sampled hourly for 24 hours, providing data for regression curves that reflect dynamic changes in blood pressure and norepinephrine, it was found that the sympathetic nervous system was a greater influence on blood pressure in patients with primary aldosterone before, compared with after, removal of their aldosteronoma and remediation of their disease [63]. Both primary aldosteronism and essential hypertension were associated with significantly greater muscle sympathetic nerve activity compared with non-hypertensive subjects, and the sympathetic activity was normalized in the patients with primary aldosteronism after surgical resolution of their disease [64]. In a study of 26 human volunteers who served as their own controls, it was shown that a fourfold increase in plasma aldosterone, which is in the pathophysiologic range, increased muscle sympathetic nerve activity and impaired baroreflex responses, similarly to results from experimental animal studies [65].

The MR and cardiovascular inflammation

Vascular and myocardial remodeling in hypertension was once thought to be a simple response to increased force and shear stress. However, in a number of studies, patients with

primary aldosteronism were shown to have increased left ventricular hypertrophy compared with patients with essential hypertension of similar severity and duration, demonstrating the importance of elevated aldosterone levels in addition to blood pressure 1,4]. Heart and vessel remodeling as a result of chronic mineralocorticoid or angiotensin II excess in experimental animals is independent of blood pressure, preceded by increases in markers of oxidative stress and inflammation, and mitigated by MR antagonists [4,66,67]. However, as has been demonstrated in myocardial infarction (MI) models and clinical studies, inappropriate activation of MR contributing to cardiovascular inflammation and remodeling also occurs in conditions in which circulating levels of aldosterone are not increased. The mechanisms for the activation of non-aldosterone target tissue MR are still uncertain, as already discussed [68,69].

Role of hypothalamic MR in inflammation and sympathoexcitation in cardiovascular damage

It has been assumed that pathologic changes in the injured heart that are mediated by the prolonged and inappropriate activation of MR are caused by MR within the heart. However, recent studies suggest that brain MR also have a significant effect. Coronary ligation causing an MI in rats is associated with an increase in tumor necrosis factor α (TNF)-α and interleukin (IL)-1β levels in the blood and heart, neuronal activity and TNF-α and IL-1β synthesis within the PVN, and sympathetic drive to the heart [70,71]. The progression of cardiac dysfunction to heart failure in this model is mitigated by MR antagonists targeted to the AV3 V area and PVN. Treatment with an MR antagonist significantly reduced cerebrospinal fluid prostaglandin E, plasma norepinephrine, TNF-α, IL-1β and IL-6, and hypothalamic cyclooxygenase-2 (COX-2) and corticotrophin-releasing hormone (CRH) protein expression. The MR antagonist also decreased immunohistochemical staining for TNF-α, IL-1β, IL-6 and CRH in PVN neurons in these rats [70–72]. The effect of the MR antagonist on the inflammatory response in the hypothalamus induced by myocardial injury was similar to that of the anti-cytokine drugs etanercept and pentoxifylline [72].

Blood-borne proinflammatory cytokines do not act directly on neurons. They signal to neurons by inducing COX-2 activity and synthesis of prostaglandin E2 (PGE2) by perivascular macrophages in the brain. For example, the hypothalamic-pituitary-adrenal axis is stimulated and glucocorticoid synthesis is increased by circulating TNF-α via activation of the PVN neurons that release CRH by this mechanism. PGE2 synthesis also mediates excitation caused by circulating IL-1β of neurons within the AV3 V area, which project to the medial preoptic area and PVN [73]. Central administration of a COX-2 inhibitor after ICV administration of a lipopolysaccharide blunted the increase in sympathetic activity and decreased levels of PGE-2 in the CSF, further demonstrating the connection between inflammation and sympathoexcitation [74].

ICV infusion of a macrophage toxin (clodronate) 1 day after coronary ligation eliminated perivascular macrophages and COX-2 immunoreactivity within the PVN, and significantly reduced PVN excitation and levels of PGE2 and norepinephrine in the CSF, without reducing the increased levels of TNF-α and IL-1β in plasma or PVN. Depletion of macrophages also decreased blood pressure, renal sympathetic activity and heart-rate responses to injection of TNF-α into the carotid artery, compared with MI rats that did not receive the clodronate, presumably as a result of the reduced neuronal excitation within the PVN [75].

As in the periphery, NADPH oxidase-dependent super-oxide generation within the PVN was also found to be involved in the release of inflammatory cytokines. In addition it was associated with an increase in sympathetic drive upon inflammatory insult [74]. ICV

infusion of apocynin (an NADPH oxidase inhibitor) and tempol (a reactive oxygen species scavenger) decreased the hypertension produced by aldosterone/salt excess through a reduction in sympathetic drive, but did not alter sodium appetite in this model [48]. A similar central nervous system (CNS) mechanism might occur in human patients with heart failure. Addition of spironolactone to a standardized treatment for heart failure, which included a loop diuretic and angiotensin II receptor antagonist, significantly decreased cardiac sympathetic drive and benefited left ventricular function [76].

Inflammatory reactions are an adaptive immediate response to injury [77], and augmentation of sympathetic drive to the heart is an essential homeostatic function. Treatment with MR antagonists a day or more after coronary ligation significantly benefited the outcome in experimental MI; by contrast, initiating peripheral or central MR antagonist treatment before or at the time of coronary ligation decreased the survival of rats [78]. Thus, although MR antagonists have had clear benefits in patients with established disease, aggressive pre-emptive treatment might limit adaptive responses to injury.

How well does aldosterone access brain Parenchyma?

Despite being lipophilic, steroid accumulation in the brain is influenced by multiple drug resistance proteins, or p-glycoproteins, which actively pump specific compounds out of cells and might alter the intracellular aldosterone and glucocorticoid concentration ratio. P-glycoproteins are expressed in select neurons, as well as in brain microvascular endothelial cells and podocytes of astrocytes where they contact microvessels [79]. Transport (and thus exclusion) by the human p-glycoprotein is significantly lower for aldosterone than for cortisol, whereas corticosterone extrusion is minimal, suggesting that corticosterone, which circulates at 5–10% the level of cortisol in humans, is an important ligand for the MR and GR in the human brain [80]. Levels of corticosterone in the brain would still be expected to greatly exceed those of aldosterone. Expression of p-glycoproteins in neurons is variable and specific to the type of neuron; for example, they are relatively abundant in granule cells of the dentate gyrus [79], thus p-glycoproteins might provide a degree of ligand specificity for certain neurons. Although p-glycoproteins have been cited as a major impediment for aldosterone binding of MR in the brain [5], aldosterone concentrations in the normal rat brain after extensive perfusion with heparinized saline are only slightly lower than those in plasma, although still two orders of magnitude lower than levels of corticosterone [81]. The consistent finding of aldosterone in brain-cell nuclei from all parts of the brain studied [26] suggests that aldosterone is able to access MR in throughout the brain, not only in circumventricular areas unprotected by the blood–brain barrier.

Two other mechanisms can be postulated to increase local concentrations of aldosterone in or near aldosterone target cells: the synthesis of aldosterone within the brain, which would have paracrine or autocrine function; and the formation of an aldosterone derivative that efficiently activates MR, but is not a substrate for the p-glycoprotein. All of the components required for *de novo* aldosterone synthesis from cholesterol are expressed in rat and human brains, specifically in the neurons [82–84]. Minced brain tissue from adrenalectomized and intact rats synthesized aldosterone from both endogenous and tritiated, substrates when incubated *in vitro* [85,86]. However, because most of the aldosterone in the brain is derived from the circulation and local synthesis is so limited, synthesis of aldosterone in the brain has only been reliably measured after adrenalectomy, thus the physiologic regulation and relevance of extra-adrenal aldosterone synthesis has been difficult to ascertain [83,87,88].

Inappropriate aldosterone production within the brain appears to be involved in the pathogenesis of hypertension in the Dahl salt-sensitive (SS) rat. The salt-sensitive hypertension in the SS rat is caused by multiple genetic factors and problems with sodium

and hemodynamic regulation. Despite suppressed circulating aldosterone, salt-induced hypertension in SS rats is prevented by the same measures that prevent mineralocorticoid/salt hypertension, including central infusion of MR and epithelial sodium channel antagonists, AV3 V area ablation, and chemical sympathectomy 84]. Expression of mRNA for the *Cyp11b2* gene encoding for aldosterone synthase, the last and unique enzyme in the synthesis of aldosterone, is higher in the brain and lower in the adrenal glands of SS rats compared with Sprague-Dawley (SD) rats. In addition, SS rats have higher aldosterone concentrations in their brains than do SD and Dahl salt-resistant (SR) rats, but they have lower or similar total circulating aldosterone compared with SD and SR rats [84]. Salt-sensitive hypertension in the SS rat is mitigated by the central infusion of several inhibitors of steroid synthesis, including one specific for aldosterone synthase [30,89,98]. This suggests that the dysregulation of aldosterone synthesis in or near aldosterone target neurons that are important for blood pressure regulation is a factor in the hypertension of the SS rats.

There is substantial evidence for an endogenous ouabain-like factor with an important role in the central control of the blood pressure [90–94]. Endogenous ouabain is similar to therapeutic cardenolides in that it inhibits the Na/K ATPase pump, but differs from the cardenolides in that it increases the activity of other ion channels in vascular smooth muscle and other excitable cells [94]. Endogenous ouabain activity has been found to increase with sodium overload, and cause hypertension and vascular pathology that are prevented by MR antagonists. Despite more than 30 years of concerted effort, the exact structure or mechanism for the synthesis of ouabain in a mammal has not been elucidated or any intermediates isolated [95,96]. Ouabain is thought to be synthesized in the adrenal gland and share with other adrenal steroids, including aldosterone, cortisol and corticosterone, the same synthetic pathway from cholesterol up through the step requiring 3-β-hydroxysteroid dehydrogenase activity. Ouabain is implicated in the hypertension of the Dahl SS rat [91,97]. ICV infusion of partially inhibitory doses of trilostane, an inhibitor of 3-β-hydroxysteroid dehydrogenase, inhibited salt-induced hypertension in the Dahl SS rat [98]. Interpretation of this model awaits precise measurement of ouabain, corticosterone and aldosterone, as the synthesis of all three are dependent upon 3-β-hydroxysteroid dehydrogenase activity. The role of inhibition of the action of endogenous ouabain as a mechanism of action of MR antagonists in human heart failure is yet to be definitively resolved [99].

Steroids, including aldosterone, circulate in significant amounts as fatty acid esters that are hydrophobic and are concentrated in tissues, particularly in brain and fat [100,101]. Unlike those of corticosterone, aldosterone esters have greater biologic activity than the parent compound [102–104]. As aldosterone esters are rapidly and completely hydrolyzed to aldosterone in blood, plasma and serum at room temperature, they are not distinguished from aldosterone by commonly used procedures [104]. Significant amounts of an aldosterone ester have been measured in the normal rat brain, whereas aldosterone-18-monoacetate, aldosterone-21-monoacetate and aldosterone-21-mono-oleate were significantly more potent than aldosterone itself in increasing the blood pressure when infused ICV [104]. The increase in potency would not surmount the problem of the greater amount of glucocorticoid competing for the MR unless the regulation of aldosterone ester formation is a mechanism to concentrate aldosterone in aldosterone target neurons, a possibility that is being explored.

Concluding remarks

Understanding of the role of brain MR in cardiovascular regulation and disease has been accelerated in the past 10 years by the development of powerful techniques and reagents in molecular biology, biochemistry, immunohistochemistry and cell imaging, and by the

interest engendered by clinical trials demonstrating clear benefits in survival and quality of life of MR antagonist treatment of patients in chronic heart failure. Although a great deal is known about what the MR does in healthy transport epithelia, such as that of kidney tubules and the colon, much of what is known about its function in non-epithelial cells, including the heart, vessels and brain, is based on patho-physiology, Figure 1. An exception is the recent refinement of our understanding of the role that MR plays in the circuitry involved in determining sodium status and regulating sodium appetite. Among the more compelling findings is the role of circulating inflammatory cytokines in signaling to the PVN, thereby increasing sympathetic drive to the periphery and exacerbating heart failure. Because the majority of MR in the brain have functions unrelated to cardiovascular homeostasis or inflammation, it is crucial to learn more about the basic biology and function of the MR to guide the development of targeted therapeutic agents. A short list of potential target areas for study is shown in Box 2

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Box 1

Possible mechanisms conferring aldosterone selectivity on MR

Intrinsic

- Alternative translation initiation site
- Alternative splice variant

Receptor activation and transcription

- Cell-specific expression of chaperone proteins promoting MR conformations with different ligand binding efficiencies
- Different homo- and heterodimerization efficiencies between the MR and GR depending on ligand
- Cell-specific expression of co-repressors and co-activators with different affinities for the MR depending on the constituents of the receptor dimer
- Cell-specific expression of co-repressors and co-activators that determine to which HRE the receptor complex will bind and its transcription affinity
- Different binding efficiency of the receptor complex to HRE depending on its constituents.

Extrinsic

- 11β-hydroxysteroid Dehydrogenase inactivation of glucocorticoid
- Local extra-adrenal aldosterone synthesis

Box 2

Outstanding questions

- How does aldosterone exert an effect in non-epithelial tissues that do not express the 11β-HSD2 in the midst of far larger concentrations of glucocorticoids?
- How does corticosterone inhibit the MR response to aldosterone in some contexts, yet activates it in others?
- How does the pattern of gene transcription that is modulated by MR differ for aldosterone and cortisol or corticosterone in different cell-types *in vivo*?
- How does excessive salt alter MR signaling in non-epithelial cells?
- What are the relative contributions of MR activation in the CNS and kidney to sodium and hemodynamic homeostasis?
- What is the contribution of non-genomic signaling of aldosterone to hypertension and cardiovascular disease?
- What is the role and ligand for the MR in normal hemodynamic regulation by the brain?
- What are the mechanisms of MR antagonist effects on affect and cognition?

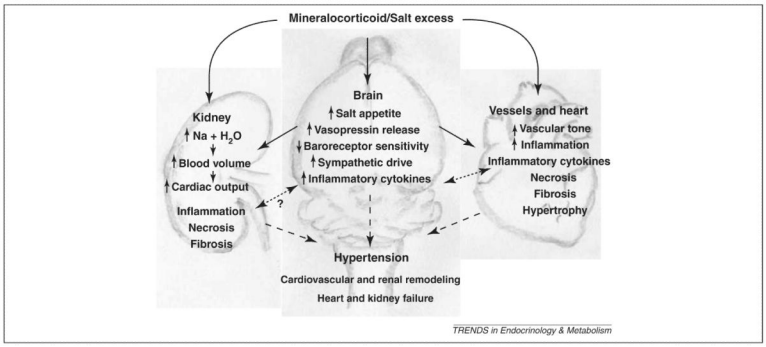

Figure 1.

Excessive mineralocorticoid/salt: proposed mechanisms for hypertension and end-organ pathology. Excessive mineralocorticoid/salt acts in the kidney directly and through CNS effects, also indirectly, to increase sodium and water retention, blood volume and cardiac output in the heart, in the vessels to increase tone, and in both to cause inflammation and fibrosis. CNS effects include increased sodium appetite, vasopressin release and sympathetic drive, and decreased baroreceptor sensitivity, resulting in hypertension, necrosis, fibrosis, and eventual organ failure. Circulating inflammatory cytokines increase neural excitation and sympathetic drive.