Published in final edited form as:
Steroids. 2014 December ; 91: 20–31. doi:10.1016/j.steroids.2014.08.014.

Brain mineralocorticoid receptors in cognition and cardiovascular homeostasis

Elise Gomez-Sanchez
Departments of Medicine, Pharmacology & Toxicology & Neurobiology & Anatomical Science University of Mississippi Medical Center & G.V.(Sonny) Montgomery VA Medical Center, Jackson, MS 39216

Abstract

Mineralocorticoid receptors (MR) mediate diverse functions supporting osmotic and hemodynamic homeostasis, response to injury and inflammation, and neuronal changes required for learning and memory. Inappropriate MR activation in kidneys, heart, vessels, and brain hemodynamic control centers results in cardiovascular and renal pathology and hypertension. MR binds aldosterone, cortisol and corticosterone with similar affinity, while the glucocorticoid receptor (GR) has less affinity for cortisol and corticosterone. As glucocorticoids are more abundant than aldosterone, aldosterone activates MR in cells co-expressing enzymes with 11β-hydroxydehydrogenase activity to inactivate them. MR and GR co-expressed in the same cell interact at the molecular and functional level and these functions may be complementary or opposing depending on the cell type. Thus the balance between MR and GR expression and activation is crucial for normal function. Where 11β-hydroxydehydrogenase 2 (11β-HSD2) that inactivates cortisol and corticosterone in aldosterone target cells of the kidney and nucleus tractus solitarius (NTS) is not expressed, as in most neurons, MR are activated at basal glucocorticoid concentrations, GR at stress concentrations. An exception may be pre-autonomic neurons of the PVN which express MR and 11β-HSD1 in the absence of hexose-6-phosphate dehydrogenase required to generate the requisite cofactor for reductase activity, thus acts as a dehydrogenase. MR antagonists, valuable adjuncts to the treatment of cardiovascular disease, also inhibit MR in the brain that are crucial for memory formation and exacerbate detrimental effects of excessive GR activation on cognition and mood. 11β-HSD1 inhibitors combat metabolic and cognitive diseases related to glucocorticoid excess, but may exacerbate MR action where 11β-HSD1 acts as a dehydrogenase, while non-selective 11β-HSD1&2 inhibitors cause injurious disruption of MR hemodynamic control. MR functions in the brain are multifaceted and optimal MR:GR activity is crucial. Therefore selectively targeting down-stream effectors of MR specific actions may be a better therapeutic goal.

Corresponding author: Elise Gomez-Sanchez, G.V. (Sonny) Montgomery VA Medical Center, Jackson, MS, 39216, Tel: 601-368-3844, egomez-sanchez@umc.edu.

Keywords

aldosterone; mineralocorticoid receptor; 11β-hydroxysteroid dehydrogenase; cognition; depression; hypertension; cardiovascular disease

Introduction

Because of their complexity, understanding the functions of the mineralocorticoid receptor (MR) lagged that of the other receptors. Like other steroid hormone receptors, MR are ligand-activated nuclear transcription factors for protein effectors of MR action that also initiate rapid non-genomic effects through cell signaling pathways presumably through MR associated with the plasma membrane. A full discussion of the rapid non-transcriptional signaling by the MR is not attempted herein[1–9]. MR and glucocorticoid receptors (GR) are expressed in many tissues types, often in the same cells, where they interact at molecular and functional levels, at times in synergy, others in opposition. Ligand activated MR and GR in the cytosol enter the cell nucleus, form dimers that bind to hormone response elements on the DNA as a complex with co-transcription factors[10–13]. These transcription factors can be repressors or activators and are cell-type and context specific. MR and GR form homodimers and heterodimers with different transcriptional efficacy depending on the cell type both *in vitro* and *in vivo*[14–18], thus the appropriate balance of MR and GR activation is crucial for homeostasis and a discussion of one is often not adequate without consideration of the other, especially in the CNS. This is especially important in analyzing the function of neurons expressing both MR and GR where MR activation tends to be excitatory and GR mediated events tend to mitigate excitation[19–21].

Also unlike the other steroid receptors with relatively narrow ligand specificities, the MR has similar intrinsic affinity for aldosterone, the major glucocorticoids cortisol and corticosterone, deoxycorticosterone, and progesterone. Progesterone is a competitive MR antagonist that is inactivated by several enzymes in aldosterone target renal epithelial cells [22], but attains sufficient concentrations during pregnancy and the luteal phase of the estrus cycle in species with distinct luteal and follicular phases to inhibit MR, leading to renin-angiotensin-aldosterone system (RAAS) activation and doubling of aldosterone levels in women during the luteal phase[23–26]. The presence of MR in ovaries, testes, uterus and placenta[27–29] has led to the proposal that progesterone binding to the MR may serve a reproductive function[30]. Despite higher levels of aldosterone, premenopausal women have a reduced risk of cardiovascular disease due to as yet unclear interactions with the estrogen receptor and estrogen mediated events, in part through yet incompletely-defined, MR-independent effects of aldosterone[6, 31–35].

Concentrations of endogenous glucocorticoids exceed those of aldosterone by 2–3 orders of magnitude, thus they are the physiological ligand for MR as well as for GR, except in aldosterone target cells in which pre-receptor inactivation of glucocorticoids by enzymes with 11β-steroid dehydrogenase (11β-HSD) activity occurs. Description of the 11β-steroid dehydrogenase enzymes, 11β-HSD types 1 & 2 will be addressed below. As a gross generalization, activation of MR in the higher centers of the brain by glucocorticoids is

crucial for neuronal plasticity, learning and memory, while activation of MR in the hypothalamus and brain stem modulates electrolyte and hemodynamic homeostasis[8, 9]. At a time in which the use of MR antagonists is being resurrected to protect from the ravages of heart failure and the development and therapeutic use of MR agonists and 11β–HSD1 antagonists are being considered to stop the progression of cardiometabolic disorders and age-related cognitive decline, there is a pressing need to widen the focus of studies of MR activities in the CNS.

Mineralocorticoid receptors function is crucial in epithelial and non-epithelial cells

Several decades after the adrenal gland was reported to be critically important for life by Thomas Addison in the mid-1800s, it was recognized that the adrenal cortex produced different factors classified by their functions. Mineralocorticoids increased vectorial transport of Na^+, K^+ and H^+, followed by water, across epithelia of the nephron, colon and amphibian urinary bladder; glucocorticoids had gluconeogenesis/glycogen depletion and anti-inflammatory properties [36–43]. The first mineralocorticoid to be isolated, deoxycorticosterone (deoxycorticosterone; DOC)[36] was life-saving for patients in adrenal failure, however excessive amounts were soon found to cause hypertension and pathological remodeling of the heart and kidneys [44, 45] (reviewed in [8]. The selective effect of aldosterone on fluid and electrolyte homeostasis is reflected in its first name upon its isolation, ‘electrocortin’[46, 47]. Subsequent studies over the last 50 years have demonstrated that MR regulates fluid and electrolyte homeostasis by multiple complex events far beyond the scope of this review [48, 49]. Three years later, Jerome Conn described Primary Aldosteronism in patients with persistent hypertension and hypokalemia [50]. Primary Aldosteronism is now recognized as a major cause of secondary hypertension associated with more severe cardiovascular and renal complications than essential hypertension of similar severity and duration[51–55]. Primary aldosteronism is also associated with depression and cognitive decline[56–59].

Mineralocorticoids exert extra-renal effects on blood pressure in addition to increasing Na^+ and water retention by kidneys[44, 47], as discovered in early studies showing that they increased vascular tone directly by increasing ion, particularly calcium, within vascular smooth muscle cells, effects that occurred before an increase in blood pressure was evident, as well as indirectly through activation of the sympathetic nervous system (SNS)[60–66]. The massive literature addressing MR-mediated regulation of ion channel function of vascular endothelial and smooth muscle cells, as well as vessel remodeling is beyond the scope of this review [5, 67–72]. Similarly, MR-mediated changes in ion transport in neurons increases their excitability[19–21]. Inappropriate MR activation in cerebral vessels impacts neurological function, thus must be considered in discussions of the clinical effects of altered MR actions in the brain[73, 74].

The role of the brain in mineralocorticoid hypertension was first shown by ablation studies. The paraventricular nucleus (PVN) of the hypothalamus, circumventricular organs, brain stem, central sympathetic neurons, and interconnecting tracts were shown to also contribute to or be essential for mineralocorticoid-salt excess and renovascular hypertension [75–79], reviewed in[8]. The PVN comprises many types of neurons that receive and integrate

information from diverse areas of the brain, including neuroendocrine neurons that secrete peptides that control pituitary function, pre-sympathetic neurons projecting to the medulla and spinal cord, parasympathetic neurons projecting to the dorsal motor nucleus of the vagus, and interneurons[80–82]. The r o le of brain MR in mineralocorticoid-salt hypertension was confirmed by the lateral intracerebroventricular (icv) infusion of MR agonists and antagonists at doses too small to cause an effect when diluted by the blood volume upon peripheral infusion[83–87], reviewed in [8]. Similar studies in several labs confirmed that MR-regulated increases in ion channel activity previously documented in the kidney and vessels were also instrumental in centrally mediated mineralocorticoid-salt hypertension, [88–93] and that activation of the SNS was a primary effector of mineralocorticoid hypertension [85, 94, 95]. The selectivity of the MR antagonists in these studies was confirmed by the demonstration that the intracerebroventricular infusion of siRNA for MR abrogated the increased SNS activation and hypertension induced by either aldosterone-salt or AngII-salt excess [96]. More recently MR were visualized within pre-sympathetic neurons of the rat PVN projecting to the spinal cord by a combination of retrograde tracer and fluoroimmunohistochemistry[82]. Chronically increasing or decreasing endogenous plasma aldosterone concentrations with a low or high sodium diet, respectively, significantly increased total MR expression and translocation of MR from the cytoplasm to the nuclei of pre-sympathetic neurons in rats adapted to the low, compared to high salt diet[82]. This is consistent with the activation of the SNS to support the circulation during sodium, thus water and volume, depletion [97, 98]. This adaptive mechanism for terrestrial animals, most of which do not have ready access to large amounts of sodium, is quite different from the experimental model of mineralocorticoid-salt excess hypertension in which mineralocorticoids are elevated in the context of a high sodium intake.

Aldosterone increases sodium appetite, also an adaptive mechanism shaped by evolution, that is centrally regulated[99–101]. Inappropriate mineralocorticoid excess increases sodium appetite even when in the sodium replete state[102, 103]. While MR that mediate the increases in blood pressure appear to reside primarily in the hypothalamus and circumventricular organs of the third ventricle, those initiating sodium appetite are primarily in the medulla and amygdala [99, 104–107]. Small concentrations and volumes of aldosterone infused into the lateral cerebroventricles produce hypertension without altering sodium appetite[108], similar infusions into the fourth ventricle increase sodium appetite with no effect on the blood pressure[109], presumably by activating aldosterone sensitive neurons of the NTS[107, 110]. The capacity for common laboratory animals to regulation their sodium intake has often been underappreciated and over-ridden by the excessive amounts of sodium in standard maintenance chows. The voluntary sodium intake between Sprague-Dawley rats weaned to a sodium deficient diet and an *al libitum* choice between saline and water to drink was shown to be about 15% of the sodium consumed by cohorts provided a commonly used rodent chow containing 0.5% Na. At 10 weeks of age body weights were no different between groups, however blood pressures were significantly higher in those receiving the standard chow than those consuming sodium by free choice[111].

Pathological cardiac remodeling produced by inappropriate systemic MR activation is not entirely dependent upon hypertension as demonstrated by a combination of systemic and intracerebroventricular (icv) infusions of MR agonists and antagonists in rats, emphasizing the importance of local MR action in peripheral non-epithelial tissues [84, 112]. The extensive literature on the mechanisms of injury mediated by MR in the heart, vessels, and kidneys led to the first clinical trials, RALES and EPHESUS, that demonstrated that addition of mineralocorticoid antagonists to standard therapy for chronic heart failure at low doses that do not further lower the blood pressure, significantly benefited cardiovascular function, as well as prolonged and increased the quality of life[113, 114]. Benefits of MR antagonists occurred even in patients who did not have elevated aldosterone levels. Successful outcomes of similar subsequent trials have led to increased use of MR antagonists in treatment regimens for renal and cardiac failure, as well as milder dysfunction [113, 115–118].

Inappropriate MR activation leads to inflammation that precedes the cell death and fibrosis in the heart, vessels and kidneys in several experimental models including the L-NAME, Angiotensin II-salt excess, mineralocorticoid-salt excess, and several genetic models of hypertension [119–126] and involves classic mediators of inflammation, including NADPH oxidase, ROS and inflammatory cytokines[73, 127–130]. Activation of NADPH oxidase and production of ROS are among the rapid non-transcriptional actions of MR critical for its rapid signaling in the heart[131] and in neurons[132–135] required for normal function, but that become pathological when inappropriate[136–144, 145, 146]. Excessive neuronal NADPH oxidase expression and activity in the NTS, RVLM and PVN are found in animal models of hypertension including those produced by myocardial infarction and by the chronic administration of phenylephrine, AngII, mineralocorticoids, or lipopolysaccharides [96, 133, 147–149]. Excessive neuronal NADPH oxidase activation in the hippocampus correlates with chronic stress and depression[145, 146]. The physiological ligand for the rapid non-genomic actions mediated by MR associated with the plasma membrane, is not certain. Studies in peripheral cells assume that aldosterone is the ligand, however 11β-HSD1&2 enzymes are microsomal. In hippocampal neurons the affinity of the membrane associated MR for glucocorticoids was less than that of the MR mediating transcriptional effects[150]. A high salt diet, oxidative and nitrosative stresses may induce post-translational modifications and alter MR intracellular trafficking, including to the membrane[1, 2], that might alter its ligand affinity, as well as its activity. There is evidence that increased ROS activates Rac1 GTP in neurons, as well as the kidney and heart, to produce ligand-independent activation of the transcriptional MR [134, 151]. Ligand-independent activation of the transcriptional MR has been used to explain why MR antagonists are effective treatments for heart failure even when circulating aldosterone levels are normal[134, 151].

Circulating inflammatory cytokines due to peripheral injury and inflammation increase SNS drive through an MR-mediated mechanism and may also explain some of the therapeutic effects MR antagonists in heart failure patients who have no significant aldosterone elevation. Pioneering studies from Robert Felder’s lab in rats, confirmed and extended by others, demonstrate that cardiac injury produced by a myocardial infarction activates neural afferents to the brain and increases circulating inflammatory cytokines that activate MR in

the PVN, thus increase SNS drive to the periphery, exacerbating cardiac injury[92, 144, 149, 152–155]. Inflammatory cytokines do not normally cross the blood brain barrier to directly influence neurons in the PVN, however they increase cyclooxygenase 2 (COX-2) activity in perivascular macrophages, resulting in increased prostaglandin E2, which does diffuse across the blood brain barrier, and activation of NADPH oxidase through MR. These events lead to inflammatory cytokine production within the brain and sympathetic nervous system excitation[156]. Antagonists of cytokines, COX-2, NADPH oxidase, and ROS scavengers, as well as of the MR, inhibit this cascade of events and decrease the maladaptive persistent increase in SNS drive that prevents healing and exacerbates damage and dysfunction of the infarcted heart[96, 149, 154]. Similarly, inhibitors of inflammation also prevent the excessive sustained sympathetic nervous system activation and hypertension in aldo-salt and AII-salt excess models[96].

Activation of the sympathetic nervous and RAAS systems is an adaptive response to a decrease in blood pressure, however the sustained inappropriate increase in sympathetic activity is maladaptive and associated with hypertension and chronic heart failure[157]. The standard practice of using thiazide and thiazide-like diuretics as first line treatment for hypertension lowers the blood pressure, but may cause a compensatory increase in SNS activation, resulting in unintended and too often unmeasured and underappreciated effects of sympathoexcitation, including increased blood glucose and insulin resistance[158, 159]. Untoward effects related to inappropriate SNS activation were avoided with the use of low doses of MR antagonists with or instead of the diuretic[158, 159]. These findings further support the increased use of MR antagonists for the treatment of cardiovascular and cardiometabolic disease[160–162], but ignore other crucial functions of MR, particularly those in the cerebral cortex and hippocampus.

The mineralocorticoid receptor is highly expressed in the whole brain in areas that do not have direct influence over the cardiovascular system, but are involved in memory, learning, affect, and the regulation of the HPA axis [6, 9, 150, 163, 164]. MR function is essential for long term potentiation (LTP) formation, the basis for memory and learning[132, 165–167]. Diabetes in the rat causes a reduction in *in vitro* LTP formation and levels of brain derived neurotrophic factor that is reversed by an MR *agonist* [168]. In contrast to magnocellular neurons and pre-sympathetic neurons of the PVN, that express MR, but not GR[169], most, if not all MR in neurons in the hippocampus and cortex are co-expressed with GR and, as explained more fully below, are occupied by endogenous glucocorticoids, with MR occupied at normal diurnal peak levels and GR activated during higher stress levels[164, 170, 171]. The MR and GR in these neurons interact functionally to ensure the appropriate level of vigilance and reaction to stress[6, 150, 163, 164]. In addition to transcriptional effects, rapid non-nuclear effects involving presynaptic ERK1/2 and/or NADPH oxidase are essential for MR-mediated learning and memory formation[21, 134, 163, 172–177].

Confusion over the natural ligand for the mineralocorticoid receptor (MR)

Binding and activity studies demonstrated that natural glucocorticoids, albeit at significantly higher concentrations than those required for DOCA or aldosterone, also produced mineralocorticoid effects on epithelial ion transport *in vitro* in toad bladder-Ussing chamber

studies used to define mineralocorticoid action [178, 179]. Similarly, early studies showed that aldosterone and DOCA activate the glucocorticoid receptor (GR)[180], but at higher concentrations than those attained even in Primary Aldosteronism, a fact to be considered when interpreting experimental results involving supra-physiological amounts of mineralocorticoids, especially DOCA[181]. Intravenous infusion of tritiated aldosterone and corticosterone in adrenalectomized rats pretreated with unlabeled GR-specific ligands produced distinct overlapping autoradiograph patterns in the brain[182–185]. Binding of both steroids was highest in the hippocampus, followed by the choroid plexus, and select nuclei of the brain stem. Binding in the cortex, thalamus and hypothalamus was significantly greater for aldosterone than for corticosterone [183–185]. By this time it was recognized that aldosterone binding to its receptor caused it to move into the cell nucleus and initiate transcription [186]. To avoid the bias of using large amounts of a single steroid in adrenalectomized rats as required for autoradiography, Yongue and Roy measured endogenous aldosterone and corticosterone within cell nuclei isolated from different parts of the brains of intact rats under basal and stressed conditions that increased corticosterone levels, and after a chronically low salt diet to stimulate or high salt diet to suppress endogenous aldosterone production[187]. Under these conditions of physiological concentrations of both aldosterone and corticosterone, the highest concentrations of aldosterone were found in cell nuclei from the hypothalamus, not from the hippocampus where autoradiography indicated the highest concentrations of MR would be found. The highest concentrations of corticosterone were measured in the hippocampus even at basal corticosterone levels[187]. Aldosterone retention in the brain was not as greatly influenced by circulating endogenous levels of steroid as was that of corticosterone[187].

In addition to his pioneering work with the role of mineralocorticoid excess in hypertension and its pathological effects in the heart and kidneys in the 1940’s, Hans Selye recognized the importance of steroid activity in the brain and that glucocorticoids acted both in the brain and periphery to produce the “general adaptation syndrome”, now known as the stress response [188, 189]. Demonstration of the selective retention of corticosterone in the hippocampus prompted studies on the role of glucocorticoids in cognition, learning, memory, and mood, as well as the response to stress by many labs[163, 190]. It became apparent that corticosterone was bound by two receptors in the hippocampus, a higher affinity, Type I corticosteroid receptor occupied at basal levels of corticosterone at the peak of its circadian rhythm, and Type II corticosteroid receptor that was occupied at stress levels [191] and that the balance of Type I and Type II corticosteroid receptor activation and function was crucial for normal adaptation to environmental stressors[189, 191]. Acute activation of the lower affinity Type II receptors dampened the responses to stress; severe or chronic over-activation of these was shown to be detrimental to neurons, reducing dendrites and synapses and neuronal death. Use of sophisticated methods for the time demonstrated that the hippocampal Type I and Type II corticosteroid receptors were the same as the MR and GR identified in peripheral tissues[192, 193]. Cloning of the human MR conclusively demonstrated that the MR and Type I corticosteroid receptor were the same[194]. The cloned MR was also shown to have similar affinities for aldosterone, cortisol, corticosterone, DOC, and progesterone *in vitro*[194], though it clearly had tissue-specific ligand preference *in vivo* described years before.

The glucocorticoids cortisol and corticosterone circulate at 1000 times the concentration of aldosterone in rats and humans with about 80–90% bound to corticosteroid binding globulin (CBG; transcortin) and albumin, providing concentrations of free glucocorticoids that are 100 times those of aldosterone. Stanley Ulick had demonstrated that patients with Apparent Mineralocorticoid Excess, a pseudohyperaldosteronism characterized by hypertension and hypokalemia, low aldosterone and normal cortisol levels, had impaired conversion of cortisol to its inactive metabolite cortisone due to a deficiency in 11β-hydroxysteroid dehydrogenase (11β-HSD) activity [195–197]. Paul Stewart showed that licorice inhibited 11β-HSD dehydrogenase activity and induced a similar syndrome[198]. Very soon thereafter the role of 11β-HSD dehydrogenase activity in providing pre-receptor ligand selectivity to the MR for aldosterone in aldosterone target cells was demonstrated[199–206].

There are at least two 11β-hydroxysteroid dehydrogenases, 11β-HSD1 and 11β-HSD2[204, 207–209];Gomez-Sanchez, 1997 #3110;Gomez-Sanchez, 1997 #2519;Krozowski, 1999 #7650}, located primarily in endoplasmic reticulum (ER) [210–212]. The existence of other 11β-HSDs has been postulated[213–215] and an 11β-HSD3 has been described in porcine testes[216]. Cloning and characterization of 11β-HSD2 [217, 218], clarified the confusion caused by experiments using tissue homogenates that tore the ER and juxtaposed enzymes and co-factors that normally reside in separate cellular compartments. 11β-HSD1 is bi-directional, but in the liver where it is most abundant it is responsible for the oxido-reduction of inactive cortisone and 11-dehydrocorticosterone, converting them to cortisol and corticosterone, thus increasing the intracellular availability of activating ligand for both the GR and MR, particularly in the liver, adipose tissue and hippocampus, where the MR is normally bound by glucocorticoids[219, 220]. The obligate cofactor for 11β-HSD1 reductase activity is NADPH which is regenerated from $NADP^+$ within microsomes by hexose-6-phosphate dehydrogenase (H6PDH). (NADPH formed by glucose-6-phosphate dehydrogenase in the cytosol does not readily cross the ER membrane). Pre-adipocytes, do not express H6PD, thus 11β-HSD1 functions primarily as a dehydrogenase using $NADP^+$ as cofactor in these cells. Upon adipocyte maturation and expression of H6PD, 11β-HSD1 becomes a reductase[221–223].

11β-HSD2 is a unidirectional NAD^+-dependent dehydrogenase that converts cortisol and corticosterone to the inactive cortisone and 11-dehydrocorticosterone[210, 215, 224]. Aldosterone is not a substrate. In the absence of ligand, MR in aldosterone target cells are thought to associate with 11β-HSD2 within the endoplasmic reticulum creating a micro-environment in which aldosterone can attain sufficient concentrations compared to those of cortisol or corticosterone to bind and activate the MR[210, 211, 225]. An alternative hypothesis is that the change in redox potential produced by the dehydrogenase activity alters the structure, thus activity, of the MR bound by the more abundant glucocorticoid[226]. The metabolite of 11β-HSD2, 11-dehydrocorticosterone, was found to dampen MR-mediated increase in sodium transport, presumably acting as a check on aldosterone stimulated activity[227, 228]. Estrogens were found to significantly increase 11β-HSD2 expression in the rat kidney, however the formation of inactive dimers was also increased and the increase in 11β-HSD2 expression was not associated with an increase dehydrogenase activity[229, 230]. The mechanism for control of 11β-HSD2 dimerization has not been clarified.

11β-HSD2 is highly expressed in the normal placenta and the fetal brain where it mitigates exposure of the fetus to high glucocorticoid levels required for the mother's metabolism during gestation[231–233]. Inhibition of 11β-HSD1 & 2 by relatively non-selective antagonists results intrauterine growth retardation and alterations of the HPA axis, increased anxiety, impaired ability to learn under stressful conditions, as well as hypertension[234–240]. The effects of 11β-HSD2 inhibition during gestation on the adult progeny are similar to those produced by fetal malnutrition, relatively benign perinatal stress, and iatrogenic glucocorticoid treatment during ontogeny, especially with synthetic steroids that are not inactivated by 11β-HSD2 that are also associated with low for term birth weight or intrauterine growth restriction (IUGR). IUGR is associated with epigenetic changes in the corticoid receptors that alter functional MR:GR ratios in tissue-specific ways and have significant negative implications on the HPA axis, energy metabolism, cardiovascular health, as well as the ability to cope with psychological stress as an adult[165, 234, 241–243].

As a reductase of cortisone/11-dehydrocorticosterone, 11β-HSD1 augments glucocorticoid action by increasing intracellular concentrations of active steroid, thus activation of either the MR or GR or both, depending on the cell type[220, 234, 243–246]. 11β-HSD1&2 may be found in different cell types in the same tissue. 11β-HSD1 in proximal cells and 11β-HSD2 in collecting duct cells of the kidney where both appear to function as a dehydrogenase[247]. Both are expressed and tightly regulated throughout gestation in the placenta, 11 beta-HSD1 in decidualized stromal cells on the maternal side of the placenta, 11 beta-HSD2 in villous cytotrophoblast, syncytiotrophoblasts and trophoblast cells from the fetus that invade the placental bed and maternal vasculature[248]. While most have found 11β-HSD1 expression in smooth muscle cells and 11β-HSD2 in endothelial cells of vessels[249], both enzymes were reported to be expressed in human aortic vascular and bronchial smooth muscle cells[250] 11β-HSD1, but not 11β-HSD2, in these smooth muscle cells was increased in by inflammatory cytokines, resulting in an increased net conversion of ^{3}H-cortisone to ^{3}H-cortisol [250]. Both 11β-HSD1 & 2, along with GR, and MR mRNAs, were reported to be expressed in isolated rat and bovine granulosa cells. Net glucocorticoid inactivation by 11 beta HSD2 in immature cells changed to activation by 11β-HSD1 in granulosa cells stimulated by gonadotropins [251–254]. Imunohistochemistry of the rat ovary detected strong 11β-HSD2, but no 11β-HSD1 in granulosa cells of immature follicles and both in the granulosa cells of the corpora luteum [27]. An increase in conversion of the inactive 11-dehydro metabolites to active cortisol and corticosterone after ovulation would mitigate local inflammation in acute injury, including rupture of the ovarian follicle or injured vessel[250, 253, 254], however chronically it could lead to inappropriate MR and GR activation. Another example of 11β-HSD dehydrogenase/reductase activity switching during differentiation is the adipocyte[221–223]. The requirement for pre-receptor modulation of glucocorticoid concentrations is clearly dynamic.

DNA methylation and epigenetic repression of 11β-HSD2 transcription was shown to cause of the increase in the ratio of tissue 11β-HSD1:11β-HSD2, thus glucocorticoid action, and to be implicated in the cardiometabolic syndrome[255]. 11beta-HSD2-deficiency or inhibition causes hypertension, while 11beta-HSD1 deficiency or inhibition is atheroprotective, improves glycemic control and reduces the ravages of aging on vessels, memory and

cognition in animals [220, 249, 256–260] and humans[261]. Therefore 11β-HSD1 has become a target for the development of selective antagonists to mitigate diseases associated with excessive glucocorticoid action, including obesity, type II diabetes, cardiometabolic syndrome, and age-associated dementia in which excessive cortisol action on the GR is thought to have a role[257, 258, 262–267]. Selective 11β-HSD1 antagonists have been synthesized and tested [263, 264, 268–271], though not much information on their clinical efficacy is found in the literature as yet. They have shown promise in accelerating wound healing in stressed patients[272] and in ameliorating glycemic control in obese, but not simply overweight, type II diabetic humans[264].

Potentially significant environmental 11β-HSD enzyme inhibitors have been identified as disruptors of the balance of MR:GR action with implications for human health[273]. Endogenous antagonists of the 11β-HSDs, glycyrrhetininc acid like factors (GALFs) were proposed as modulators of MR action in experimental models and humans and a cause of hypertension[274–276]. GALFs are thought to be produced from endogenous glucocorticoids and their metabolites excreted in the bile, converted by microbial action in the gut to 21-dehydroxylated products, 11β-OH-progesterone, or 11β-OH-(allo)-5a-preganolones, then reabsorbed, later to be excreted in the urine from whence they have been isolated[274–276]. While the significance of these compounds has been questioned [277, 278], recent recognition of the importance of intestinal microbial action in metabolism and risk for a surprising variety of diseases may make this issue worth revisiting.

The possibility that 11β-HSD1 can function as a dehydrogenase is often overlooked; as both reductase and dehydrogenase functions are blocked by 11β-HSD1 inhibitors and may cause unexpected results in clinical trials of selective 11β-HSD1 inhibitors. Non-selective11β-HSD inhibitors increase blood pressure and SNS activity through MR activation in the PVN [279–281], but where 11β-HSD2 is not found [82, 107, 110]. This does not occur in adrenalectomized rats, confirming the requirement for endogenous adrenal steroids including corticosterone[281]. H6PD is required in the microsome to generate NADPH, the obligatory cofactor for 11β-HSD1 reductase activity. Pre-sympathetic neurons of the PVN were found to co-express MR and 11β-HSD1, but not H6PD or GR, suggesting that 11β-HSD1 acts as a dehydrogenase, providing extrinsic selectivity for aldosterone[82] and explain how the non-selective 11β-HSD inhibitors increase SNS and blood pressure[281]. In addition to cardiovascular and renal effects, SNS activation also increases gluconeogenesis, thus exacerbating metabolic problems associated with obesity and cardiometabolic syndrome[159]. Unfortunately, selective 11β-HSD1 inhibitors may not be the panacea for aging and obesity.

Expression of 11β-HSD2 is very limited in the adult brain

It has been detected in epithelia cells of the subcommissural organ and a few neurons of the ventromediolateral hypothalamus, vestibular nucleus, and NTS [82, 282–287]. Sodium depletion increases endogenous aldosterone levels and activity of aldosterone target neurons that co-express MR and 11β-HSD2 in the NTS, resulting in an increase in sodium appetite[286, 288]. These neurons become quiescent and sodium appetite decreases upon oral sodium repletion[286, 288]. Despite the absence of 11β-HSD2, ample evidence accrued

over several decades by many labs indicates that aldosterone activates MR in autonomic neurons of the PVN. In addition the hypertension produced by the oral, subcutaneous or icv administration of non-selective 11β-HSD1&2 inhibitors glycyrrhizic and glycyrrhetinic acid and carbenoxolone, and the more 11β-HSD2 selective 11α-hydroxyprogesterone [289] produce hypertension that is prevented by the concomitant icv infusion of MR antagonists[279, 280]. Moreover, treatment or rats with glycyrrhizic acid and carbenoxolone produced sympathoexcitation that was inhibited by an MR antagonist and adrenalectomy prevented the effect, suggesting that a pre-receptor dehydrogenase mechanism protecting the MR from endogenous glucocorticoid activation exists in the PVN[281]. Both 11β-HSD1 and H6PD mRNA and protein were reported in the hypothalamus and other areas of the rat brain, however these studies were of relatively large blocks of tissue; they did not address individual cells[290]. More recently MR and 11β-HSD1, but neither GR nor H6PD, were detected by immunofluorescence within pre-autonomic neurons in the PVN identified by a retrograde tracer from the intermediolateral cell column of the spinal cord. Plasma aldosterone, MR expression and translocation to the nucleus, and c-fos activity were increased in pre-sympathetic neurons in the PVN of rats adapted to a low, compared to high salt diet, while the plasma corticosterone levels were not different [82]. These data suggest that 11β-HSD1 acts as a dehydrogenase and provide aldosterone selectivity to the MR in these pre-sympathetic neurons[82] and that the physiological role for MR in these neurons is to activate the SNS and maintain normal blood pressure during sodium depletion.

The balance between MR and GR mediated functions in the brain is crucial, differs for each cell type and is dynamic[6, 164, 291–293]. In the hippocampus, where GR activation is crucial for the modulation of MR-mediated excitation during stress[164], epigenetic repression of GR is associated with increased anxiety and response to stress[241, 242, 294]. Imbalance between MR and GR expression and/or activation also contributes significantly to depression and the loss of cognitive function during depression [163, 164, 173, 292, 293, 295, 296]. Decreases in absolute MR and relative levels of MR:GR message in the prefrontal and anterior cingulate cortex and, conversely, the increase in the MR:GR ratio in the PVN were documented in patients with depression compared to controls with no history of depression[297].

Transgenic mice with MR deleted only in the forebrain neurons have uncontrolled arousal and anxiety that impedes learning[173, 176], while over-expression of MR in the forebrain neurons reduces anxiety, and increases resilience to ischemia [298]. GR deletion decreases anxiety, but also impairs hippocampal-dependent explicit memory and increases HPA activity [296]. MR and GR neurotrophic effects are quite specific. Granule cells of the dentate gyrus of the hippocampus are lost in mice with targeted MR deletion in forebrain neurons; the morphology and function of hippocampal CA1 neurons are abnormal in those with GR deleted in forebrain neurons[296].

Similarly over-expression of the MR in the dentate gyrus granule cell layer in rats enhances the consolidation of non-spatial memory, augments short term memory, and protects against the effects of glucocorticoid excess in rats[174, 299], while selective over-expression of the MR in the basolateral amygdala of adult rats is anxiolytic and dampens to the response to acute stress [300]. Activation of GR decreases the excitability of neurons produced by a

stressful event, thereby restoring normal function[171], however severe stress early or chronic stress later in life leads to epigenetic changes increasing GR expression and chronic suppression of neuronal excitation producing animal behaviors analogous to depression in humans[165, 301].

The chronic infusion of corticosterone into the lateral ventricle at the same or double the molar dose of aldosterone that produces hypertension by itself had no effect on blood pressure, however its co-infusion in equimolar amounts of aldosterone blocked the hypertension produced by the icv infusion of aldo alone [302]. Similarly, a series of experiments in which MR and GR agonists and antagonists were infused intracerebroventricularly confirmed that activation of central MR increases, and of GR decreases, the blood pressure[303]. While we detected no GR in the pre-synaptic neurons of the PVN, GR and MR are abundantly expressed in adjacent parvocellular neurons, some of which are interneurons that modulate the pre-sympathetic neurons[304]. The infused corticosterone in these experiments may have acted through GR or MR in neurons that moderate the activity of the pre-sympathetic neurons of the PVN. If this is so, while selective inhibitors of GR or 11β-HSD1 curb excessive GR activation within the hippocampus and slow the progression of the ravages of obesity and age experimentally, it may be at the cost of losing dampening effect on excessive sympathoexcitation. Similarly, though the benefits of MR antagonists in heart failure are indisputable, there is persuasive evidence based on animal and human studies that decreasing the functional balance between MR and GR in the cerebral cortex and hippocampus by inhibiting MR and/or increasing GR activities leads to deleterious changes in the HPA axis, depression, memory deficits and lower cognition[8, 163].

Fludrocortisone, an MR agonist, was shown to be an asset to the standard treatment for depression[305], however it would seem contraindicated for those at risk for hypertension or in heart failure. Depression, hypertension and cardiovascular disease are frequent co-morbidities and independent risk factors for each other[155, 306, 307], as are primary Aldosteronism and depression[59, 308]. All involve an imbalance of MR:GR activation in the brain.

In summary, as was shown for the stress response, memory, cognition, and mood[163, 188, 309, 310], the MR and GR work in concert in the brain to mediate essential and complementary actions for cardiovascular and osmotic homeostasis. In seeking to correct an imbalance between MR and GR, and aldosterone- and glucocorticoid-mediated actions in one target system, it is essential to consider the effects on others.

Acknowledgments

This work was supported by Award Number 1018X007080 from the Biomedical Laboratory Research & Development Service of the VA Office of Research and Development and the National Institutes of Health grants RO1HL105383, RO1HL27255 and MH67996

References

1. Gekle M, Bretschneider M, Meinel S, Ruhs S, Grossmann C. Rapid mineralocorticoid receptor trafficking. Steroids. 2014; 81:103–8. [PubMed: 24252381]

2. Meinel S, Gekle M, Grossmann C. Mineralocorticoid receptor signaling: Crosstalk with membrane receptors and other modulators. Steroids. 2014

3. Harvey BJ, Alzamora R, Stubbs AK, Irnaten M, McEneaney V, Thomas W. Rapid responses to aldosterone in the kidney and colon. J Steroid Biochem Mol Biol. 2007

4. Losel R, Schultz A, Wehling M. A quick glance at rapid aldosterone action. Mol Cell Endocrinol. 2004; 217:137–41. [PubMed: 15134812]

5. Quinn S, Harvey BJ, Thomas W. Rapid aldosterone actions on epithelial sodium channel trafficking and cell proliferation. Steroids. 2014; 81:43–8. [PubMed: 24269741]

6. Groeneweg FL, Karst H, de Kloet ER, Joels M. Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. Mol Cell Endocrinol. 2012; 350:299–309. [PubMed: 21736918]

7. Krug AW, Pojoga LH, Williams GH, Adler GK. Cell membrane-associated mineralocorticoid receptors? New evidence. Hypertension. 2011; 57:1019–25. [PubMed: 21482958]

8. Gomez-Sanchez EP, Gomez-Sanchez CE. Central regulation of blood pressure by the mineralocorticoid receptor. Mol Cell Endocrinol. 2012; 350:289–98. [PubMed: 21664417]

9. Gomez-Sanchez E, Gomez-Sanchez CE. The multifaceted mineralocorticoid receptor. Comprehensive Physiology. 2014; 4:965–94. [PubMed: 24944027]

10. Grossmann C, Ruhs S, Langenbruch L, Mildenberger S, Stratz N, Schumann K, et al. Nuclear shuttling precedes dimerization in mineralocorticoid receptor signaling. Chemistry & biology. 2012; 19:742–51. [PubMed: 22726688]

11. Martinerie L, Munier M, Le Menuet D, Meduri G, Viengchareun S, Lombes M. The mineralocorticoid signaling pathway throughout development: expression, regulation and pathophysiological implications. Biochimie. 2013; 95:148–57. [PubMed: 23026756]

12. Viengchareun S, Le Menuet D, Martinerie L, Munier M, Pascual-Le Tallec L, Lombes M. The mineralocorticoid receptor: insights into its molecular and (patho)physiological biology. Nucl Recept Signal. 2007; 5:e012. [PubMed: 18174920]

13. Pascual-Le Tallec L, Lombes M. The mineralocorticoid receptor: a journey exploring its diversity and specificity of action. Mol Endocrinol. 2005; 19:2211–21. [PubMed: 15802372]

14. Kuroda K, Venkatakrishnan R, Salker MS, Lucas ES, Shaheen F, Kuroda M, et al. Induction of 11beta-HSD 1 and activation of distinct mineralocorticoid receptor- and glucocorticoid receptor-dependent gene networks in decidualizing human endometrial stromal cells. Mol Endocrinol. 2013; 27:192–202. [PubMed: 23275455]

15. Ackermann D, Gresko N, Carrel M, Loffing-Cueni D, Habermehl D, Gomez-Sanchez C, et al. In vivo nuclear translocation of mineralocorticoid and glucocorticoid receptors in rat kidney: differential effect of corticosteroids along the distal tubule. Am J Physiol Renal Physiol. 2010; 299:F1473–85. [PubMed: 20861076]

16. Yang J, Young MJ. The mineralocorticoid receptor and its coregulators. J Mol Endocrinol. 2009; 43:53–64. [PubMed: 19617444]

17. Yokota K, Shibata H, Kurihara I, Kobayashi S, Suda N, Murai-Takeda A, et al. Coactivation of the N-terminal transactivation of mineralocorticoid receptor by Ubc9. J Biol Chem. 2007; 282:1998–2010. [PubMed: 17105732]

18. Farman N, Rafestin-Oblin ME. Multiple aspects of mineralocorticoid selectivity. Am J Physiol Renal Physiol. 2001; 280:F181–92. [PubMed: 11208593]

19. Datson NA, van der Perk J, de Kloet ER, Vreugdenhil E. Identification of corticosteroid-responsive genes in rat hippocampus using serial analysis of gene expression. Eur J Neurosci. 2001; 14:675–89. [PubMed: 11556892]

20. De Kloet ER, Van Acker SA, Sibug RM, Oitzl MS, Meijer OC, Rahmouni K, et al. Brain mineralocorticoid receptors and centrally regulated functions. Kidney International. 2000; 57:1329–36. [PubMed: 10760063]

21. Olijslagers JE, de Kloet ER, Elgersma Y, van Woerden GM, Joels M, Karst H. Rapid changes in hippocampal CA1 pyramidal cell function via pre- as well as postsynaptic membrane mineralocorticoid receptors. Eur J Neurosci. 2008; 27:2542–50. [PubMed: 18547242]

22. Quinkler M, Johanssen S, Bumke-Vogt C, Oelkers W, Bahr V, Diederich S. Enzyme-mediated protection of the mineralocorticoid receptor against progesterone in the human kidney. Mol Cell Endocrinol. 2001; 171:21–4. [PubMed: 11165007]
23. Gray MJ, Strausfeld KS, Watanabe M, Sims EA, Solomon S. Aldosterone secretory rates in the normal menstrual cycle. J Clin Endocrinol Metab. 1968; 28:1269–75. [PubMed: 5679990]
24. Clark BA, Elahi D, Epstein FH. The influence of gender, age, and the menstrual cycle on plasma atrial natriuretic peptide. J Clin Endocrinol Metab. 1990; 70:349–52. [PubMed: 2137132]
25. Boschitsch E, Mayerhofer S, Magometschnigg D. Hypertension in women: the role of progesterone and aldosterone. Climacteric. 2010; 13:307–13. [PubMed: 20443718]
26. Ahmed AH, Gordon RD, Taylor PJ, Ward G, Pimenta E, Stowasser M. Are women more at risk of false-positive primary aldosteronism screening and unnecessary suppression testing than men? J Clin Endocrinol Metab. 2011; 96:E340–6. [PubMed: 20962019]
27. Gomez-Sanchez EP, Gomez-Sanchez MT, de Rodriguez AF, Romero DG, Warden MP, Plonczynski MW, et al. Immunohistochemical Demonstration of the Mineralocorticoid Receptor, 11{beta}-Hydroxysteroid Dehydrogenase-1 and -2, and Hexose-6-phosphate Dehydrogenase in Rat Ovary. J Histochem Cytochem. 2009; 57:633–41. [PubMed: 19255253]
28. Gomez-Sanchez CE, de Rodriguez AF, Romero DG, Estess J, Warden MP, Gomez-Sanchez MT, et al. Development of a panel of monoclonal antibodies against the mineralocorticoid receptor. Endocrinology. 2006; 147:1343–8. [PubMed: 16293659]
29. Driver PM, Rauz S, Walker EA, Hewison M, Kilby MD, Stewart PM. Characterization of human trophoblast as a mineralocorticoid target tissue. Mol Hum Reprod. 2003; 9:793–8. [PubMed: 14614041]
30. Funder JW. Why are mineralocorticoid receptors so nonselective? Curr Hypertens Rep. 2007; 9:112–6. [PubMed: 17442221]
31. Gros R, Ding Q, Liu B, Chorazyczewski J, Feldman RD. Aldosterone mediates its rapid effects in vascular endothelial cells through GPER activation. Am J Physiol Cell Physiol. 2013; 304:C532–40. [PubMed: 23283935]
32. Pojoga LH, Coutinho P, Rivera A, Yao TM, Maldonado ER, Youte R, et al. Activation of the mineralocorticoid receptor increases striatin levels. Am J Hypertens. 2012; 25:243–9. [PubMed: 22089104]
33. Batenburg WW, Jansen PM, van den Bogaerdt AJ, AH JD. Angiotensin II-aldosterone interaction in human coronary microarteries involves GPR30, EGFR, and endothelial NO synthase. Cardiovasc Res. 2012; 94:136–43. [PubMed: 22260839]
34. Gros R, Ding Q, Sklar LA, Prossnitz EE, Arterburn JB, Chorazyczewski J, et al. GPR30 expression is required for the mineralocorticoid receptor-independent rapid vascular effects of aldosterone. Hypertension. 2011; 57:442–51. [PubMed: 21242460]
35. Gros R, Ding Q, Davis M, Shaikh R, Liu B, Chorazyczewski J, et al. Delineating the receptor mechanisms underlying the rapid vascular contractile effects of aldosterone and estradiol. Can J Physiol Pharmacol. 2011; 89:655–63. [PubMed: 21854125]
36. Steiger M, Reichstein T. Desoxy-corticosterone (21-oxy-progesterone). Aus d-3-oxo-etiocholensäure. Helv Chim Acta. 1937; 20:1164.
37. Swingle WW, Maxwell R, Ben M, Baker C, Lebrie SJ, Eisler M. A comparative study of aldosterone and other adrenal steroids in adrenalectomized dogs. Endocrinology. 1954; 65:813–21. [PubMed: 13210328]
38. Ingle DJ. The relationship of the adrenal cortex to homeostasis. Journal - Michigan State Medical Society. 1950; 49:943. [PubMed: 15437172]
39. Ingle DJ, Prestrud MC, Li CH. A further study of the essentiality of the adrenal cortex in mediating the metabolic effects of adrenocorticotrophic hormone. Endocrinology. 1948; 43:202–7. [PubMed: 18890096]
40. Simpson SA, Tait JF. Recent progress in methods of isolation, chemistry, and physiology of aldosterone. Recent Prog Horm Res. 1955; 11:183–219.
41. Kendall EC. Hormones of the adrenal cortex in clinical medicine. Edinburgh medical journal. 1952; 59:1–12. [PubMed: 14906260]

42. Bush IE. Chemical and biological factors in the activity of adrenocortical steroids. Pharmacol Rev. 1962; 14:317–445. [PubMed: 14017298]
43. Tait SA, Tait JF. The correspondence of S.A.S. Simpson and J.F. Tait with T. Reichstein during their collaborative work on the isolation and elucidation of the structure of electrocortin (later aldosterone). Steroids. 1998; 63:440–53. [PubMed: 9727090]
44. Kuhlman D, Ragan C, Ferrebee JW, Atchley DW, Loeb RF. Toxic effects of deoxycorticosterone esters in dogs. Science. 1939; 90:496–7. [PubMed: 17769062]
45. Rodbard S, Freed SC. The effect of desoxycorticosterone acetate on the blood pressure of the dog. Endocrinology. 1942; 30:365–8.
46. Grundy HM, Simpson SA, Tait JF. Isolation of a highly active mineralocorticoid from beef adrenal extract. Nature. 1952; 169:795–6. [PubMed: 14941045]
47. Sala G, Luetscher JA Jr. The effect of sodium-retaining corticoid, electrocortin, desoxycorticosterone, and cortisone on renal function and excretion of sodium and water in adrenalectomized rats. Endocrinology. 1954; 55:516–8. [PubMed: 13200463]
48. Pearce D, Kleyman TR. Salt, sodium channels, and SGK1. J Clin Invest. 2007; 117:592–5. [PubMed: 17332888]
49. Soundararajan R, Lu M, Pearce D. Organization of the ENaC-regulatory machinery. Critical reviews in biochemistry and molecular biology. 2012; 47:349–59. [PubMed: 22506713]
50. Conn JW. Primary aldosteronism, a new clinical syndrome. The Journal of laboratory and clinical medicine. 1955; 45:3–7. [PubMed: 13233623]
51. Ferriss JB, Beevers DG, Brown JJ, Davies DL, Fraser R, Lever AF, et al. Clinical, biochemical and pathological features of low-renin (“primary”) hyperaldosteronism. Am HeartJ. 1978; 95:375–88. [PubMed: 622981]
52. Tanabe A, Naruse M, Naruse K, Hase M, Yoshimoto T, Tanaka M, et al. Left ventricular hypertrophy is more prominent in patients with primary aldosteronism than in patients with other types of secondary hypertension. Hypertension Res. 1997; 20:85–90.
53. Rossi GP, Sacchetto A, Pavan E, Palatini P, Graniero GR, Canali C, et al. Remodeling of the left ventricle in primary aldosteronism due to Conn’s adenoma. Circulation. 1997; 95:1471–8. [PubMed: 9118515]
54. Hawkins UA, Gomez-Sanchez EP, Gomez-Sanchez CM, Gomez-Sanchez CE. The Ubiquitous Mineralocorticoid Receptor: Clinical Implications. Curr Hypertens Rep. 2012; 14:573–80. [PubMed: 22843494]
55. Calhoun DA. Hyperaldosteronism as a common cause of resistant hypertension. Annual review of medicine. 2013; 64:233–47.
56. Sonino N, Tomba E, Genesia ML, Bertello C, Mulatero P, Veglio F, et al. Psychological Assessment of Primary Aldosteronism: A Controlled Study. J Clin Endocrinol Metab. 2011; 96:E878–83. [PubMed: 21389142]
57. Sonino N, Fallo F, Fava GA. Psychological aspects of primary aldosteronism. Psychother Psychosom. 2006; 75:327–30. [PubMed: 16899970]
58. Kunzel HE, Apostolopoulou K, Pallauf A, Gerum S, Merkle K, Schulz S, et al. Quality of life in patients with primary aldosteronism: gender differences in untreated and long-term treated patients and associations with treatment and aldosterone. J Psychiatr Res. 2012; 46:1650–4. [PubMed: 23017810]
59. Kunzel HE. Psychopathological symptoms in patients with primary hyperaldosteronism–possible pathways. Horm Metab Res. 2012; 44:202–7. [PubMed: 22351473]
60. Raab W, Humphreys RJ, Lepeschkin E. Potentiation of pressor effects of nor-epinephrine and epinephrine in man by desoxycorticosterone acetate. J Clin Invest. 1950; 29:1397–404. [PubMed: 14778903]
61. Mattox VR, Mason HL, Albert A, Code CF. Properties of a sodium-retaining principle from beef adrenal extract. Journal of the American Chemical Society. 1953; 75:4869–70.
62. Vanatta JC, Cottle KE. Effect of desoxycorticosterone acetate on the peripheral vascular reactivity of dogs. Am J Physiol. 1955; 151:119–22. [PubMed: 14376581]
63. Jones AW, Hart RG. Altered ion transport in aortic smooth muscle during deoxycorticosterone acetate hypertension in rats. Circ Res. 1975; 37:333–41. [PubMed: 1157222]

64. Berecek KH, Bohr DF. Structural and functional changes in vascular resistance and reactivity in the deoxycorticosterne acetate (DOCA)-hypertensive pig. Circ Res. 1977; 40(5):1146–52.
65. Berecek KH, Stocker M, Gross F. Changes in renal vascular reactivity at variuos stages of deoxycorticosterone hypertension in rats. Circ Res. 1980; 46:H619–H203.
66. Garwitz ET, Jones AW. Altered arterial ion transport and its reversal in aldosterone hypertensive rat. Am J Physiol. 1982; 243:H927–H33. [PubMed: 7149045]
67. DuPont JJ, Hill MA, Bender SB, Jaisser F, Jaffe IZ. Aldosterone and vascular mineralocorticoid receptors: regulators of ion channels beyond the kidney. Hypertension. 2014; 63:632–7. [PubMed: 24379184]
68. Messaoudi S, Azibani F, Delcayre C, Jaisser F. Aldosterone, mineralocorticoid receptor, and heart failure. Mol Cell Endocrinol. 2012; 350:266–72. [PubMed: 21784127]
69. McCurley A, Jaffe IZ. Mineralocorticoid receptors in vascular function and disease. Mol Cell Endocrinol. 2012; 350:256–65. [PubMed: 21723914]
70. Briet M, Schiffrin EL. Vascular actions of aldosterone. Journal of vascular research. 2013; 50:89–99. [PubMed: 23172373]
71. Schiffrin EL. The many targets of aldosterone. Hypertension. 2004; 43:938–40. [PubMed: 15007036]
72. Schiffrin EL. Effects of aldosterone on the vasculature. Hypertension. 2006; 47:312–8. [PubMed: 16432039]
73. Rigsby CS, Ergul A, Portik Dobos V, Pollock DM, Dorrance AM. Effects of spironolactone on cerebral vessel structure in rats with sustained hypertension. Am J Hypertens. 2011; 24:708–15. [PubMed: 21350432]
74. Dorrance AM, Osborn HL, Grekin R, Webb RC. Spironolactone reduces cerebral infarct size and EGF-receptor mRNA in stroke-prone rats. Am J Physiol Regul Integr Comp Physiol. 2001; 281:R944–50. [PubMed: 11507012]
75. Brody MJ, Fink GD, Buggy J, Haywood JR, Gordon FJ, Johnson AK. The role of the anteroventral third ventrical (AV3V) region in experimental hypertension. Circ Res. 1978; 43:2–13.
76. Brody MJ, Varner KJ, Vasquez EC, Lewis SJ. Central nervous system and the pathogenesis of hypertension. Sites and mechanisms. Hypertension. 1991; 18:III7–12. [PubMed: 1937689]
77. Bealer SL. Anteroventral third ventricle periventricular tissue contributes to cardiac baroreflex responses. Clin Exp Pharmacol Physiol. 2000; 27:460–4. [PubMed: 10831253]
78. Kubo T, Hashimoto M. Effects of intraventricular and intraspinal 6-hyroxydopamine and blood pressure of DOCA-saline hypertensive rats. Arch Int Pharmacodyn. 1979; 238:50–9. [PubMed: 485704]
79. Takeshita A, Mark AL, Brody MJ. Prevention of salt-induced hypertension in Dahl strain by 6-hyrdoxydopamine. Am J Physiol. 1979; 236:H48–H52. [PubMed: 434173]
80. Pyner S. Neurochemistry of the paraventricular nucleus of the hypothalamus: implications for cardiovascular regulation. Journal of chemical neuroanatomy. 2009; 38:197–208. [PubMed: 19778682]
81. Ferguson AV, Latchford KJ, Samson WK. The paraventricular nucleus of the hypothalamus - a potential target for integrative treatment of autonomic dysfunction. Expert Opin Ther Targets. 2008; 12:717–27. [PubMed: 18479218]
82. Chen J, Gomez-Sanchez CE, Penman A, May PJ, Gomez-Sanchez EP. Expression of Mineralocorticoid and Glucocorticoid Receptors In Pre-autonomic Neurons of the Rat Paraventricular Nucleus. Am J Physiol Regul Integr Comp Physiol. 2013
83. Gomez-Sanchez EP. Intracerebroventricular infusion of aldosterone induces hypertension in rats. Endocrinology. 1986; 118:819–23. [PubMed: 3943493]
84. Young MJ, Funder JW. Mineralocorticoids, salt, hypertension: effects on the heart. Steroids. 1996; 61:233–5. [PubMed: 8733007]
85. Janiak PC, Lewis SJ, Brody MJ. Role of central mineralocorticoid binding sites in development of hypertension. Am J Physiol. 1990; 259:R1025–34. [PubMed: 2240262]

86. Rahmouni K, Barthelmebs M, Grima M, Imbs JL, De Jong W. Involvement of brain mineralocorticoid receptor in salt-enhanced hypertension in spontaneously hypertensive rats. Hypertension. 2001; 38:902–6. [PubMed: 11641306]

87. Huang BS, White RA, Jeng AY, Leenen FH. Role of central nervous system aldosterone synthase and mineralocorticoid receptors in salt-induced hypertension in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol. 2009; 296:R994–R1000. [PubMed: 19118098]

88. Gomez-Sanchez EP, Gomez-Sanchez CE. The effect of the central infusion of benzamil on Dahl S rat hypertension. Am J Physiol. 1995; 269:H1044–H7. [PubMed: 7573500]

89. Gomez-Sanchez EP, Gomez-Sanchez CE. Effect of central amiloride infusion on mineralocorticoid hypertension. Am J Physiol. 1994; 267:E754–E8. [PubMed: 7977727]

90. Keep RF, Si X, Shakui P, Ennis SR, Betz AL. Effect of amiloride analogs on DOCA-salt-induced hypertension in rats. Am J Physiol. 1999; 276:H2215–20. [PubMed: 10362706]

91. Abrams JM, Engeland WC, Osborn JW. Effect of intracerebroventricular benzamil on cardiovascular and central autonomic responses to DOCA-salt treatment. Am J Physiol Regul Integr Comp Physiol. 2010; 299:R1500–10. [PubMed: 20926762]

92. Huang BS, Leenen FH. Blockade of brain mineralocorticoid receptors or Na+ channels prevents sympathetic hyperactivity and improves cardiac function in rats post-MI. Am J Physiol Heart Circ Physiol. 2005; 288:H2491–7. [PubMed: 15615845]

93. Huang BS, Leenen FH. Brain amiloride-sensitive Phe-Met-Arg-Phe-NH(2)–gated Na(+) channels and Na(+)-induced sympathoexcitation and hypertension. Hypertension. 2002; 39:557–61. [PubMed: 11882607]

94. Rahmouni K, Barthelmebs M, Grima M, Imbs JL, Wybren DeJ. Brain mineralocorticoid receptor control of blood pressure and kidney function in normotensive rats. Hypertension. 1999; 33:1201–6. [PubMed: 10334812]

95. Huang BS, Wang H, Leenen FH. Enhanced sympathoexcitatory and pressor responses to central Na+ in Dahl saltsensitive vs. -resistant rats. Am J Physiol Heart Circ Physiol. 2001; 281:H1881–9. [PubMed: 11668047]

96. Xue B, Beltz TG, Yu Y, Guo F, Gomez-Sanchez CE, Hay M, et al. Central interactions of aldosterone and angiotensin II in aldosterone- and angiotensin II-induced hypertension. Am J Physiol Heart Circ Physiol. 2011; 300:H555–64. [PubMed: 21112947]

97. Kaufman LJ, Vollmer RR. Low sodium diet augments plasma and tissue catecholamine levels in pithed rats. Clinical and experimental hypertension Part A, Theory and practice. 1984; 6:1543–58.

98. Vitiello MV, Prinz PN, Halter JB. Sodium-restricted diet increases nighttime plasma norepinephrine and impairs sleep patterns in man. J Clin Endocrinol Metab. 1983; 56:553–6. [PubMed: 6822653]

99. Johnson AK, Thunhorst RL. The neuroendocrinology of thirst and salt appetite: visceral sensory signals and mechanisms of central integration. Front Neuroendocrinol. 1997; 18:292–353. [PubMed: 9237080]

100. Geerling JC, Loewy AD. Central regulation of sodium appetite. Exp Physiol. 2008; 93:177–209. [PubMed: 17981930]

101. Lu B, Yang XJ, Chen K, Yang DJ, Yan JQ. Dietary sodium deprivation evokes activation of brain regional neurons and down-regulation of angiotensin II type 1 receptor and angiotensin-convertion enzyme mRNA expression. Neuroscience. 2009; 164:1303–11. [PubMed: 19733634]

102. Relman AJ, Schwartz WB. The effect of DOCA on electrolyte balance in normal man and its relation to sodium intake. Yale J Biol Med. 1952; 24:540–56. [PubMed: 14951401]

103. Hall CE, Hall O. Interaction between deoxycorticosterone treatment, fluid intake, sodium consumption, blood pressure, and organ changes in rats during drinking water, saline, or sucrose solution. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 1969; 47:81–6.

104. Sakai RR, Nicolaidis S, Epstein AN. Salt appetite is suppressed by interference with angiotensin II and aldosterone. Am J Physiol. 1986; 251:R762–R8. [PubMed: 3532826]

105. Sakai RR, McEwen BS, Fluharty SJ, Ma LY. The amygdala: site of genomic and nongenomic arousal of aldosterone-induced sodium intake. Kidney International. 2000; 57:1337–45. [PubMed: 10760064]

106. Geerling JC, Engeland WC, Kawata M, Loewy AD. Aldosterone target neurons in the nucleus tractus solitarius drive sodium appetite. J Neurosci. 2006; 26:411–7. [PubMed: 16407537]

107. Shin JW, Geerling JC, Loewy AD. Inputs to the ventrolateral bed nucleus of the stria terminalis. J Comp Neurol. 2008; 511:628–57. [PubMed: 18853414]

108. Gomez-Sanchez EP. Dose-response studies of intracerebroventricular infusion of aldosterone in sensitized and nonsensitized rats. J Hypertension. 1988; 6:437–42.

109. Formenti S, Bassi M, Nakamura NB, Schoorlemmer GH, Menani JV, Colombari E. Hindbrain mineralocorticoid mechanisms on sodium appetite. Am J Physiol Regul Integr Comp Physiol. 2013; 304:R252–9. [PubMed: 23193117]

110. Geerling JC, Loewy AD. Aldosterone-sensitive neurons in the nucleus of the solitary tract: bidirectional connections with the central nucleus of the amygdala. J Comp Neurol. 2006; 497:646–57. [PubMed: 16739197]

111. Martus W, Kim D, Garvin JL, Beierwaltes WH. Commercial rodent diets contain more sodium than rats need. Am J Physiol Renal Physiol. 2005; 288:F428–31. [PubMed: 15637348]

112. Gomez-Sanchez EP, Zhou MY, Gomez-Sanchez CE. Mineralocorticoids, salt and high blood pressure: causes. Steroids. 1996; 61:184–8. [PubMed: 8732997]

113. Young MJ, Rickard AJ. Mechanisms of mineralocorticoid salt-induced hypertension and cardiac fibrosis. Mol Cell Endocrinol. 2012; 350:248–55. [PubMed: 21930186]

114. Pitt B. Effect of aldosterone blockade in patients with systolic left ventricular dysfunction: implications of the RALES and EPHESUS studies. Mol Cell Endocrinol. 2004; 217:53–8. [PubMed: 15134801]

115. Pitt B, Zannad F, Cody R, Castaigne APA, Palensky J, Wittes J. The effect of spironolactone on mobidity and mortality in patients with severe heart failure. Randomized Aldactone evaluation study investigators. New Engl J Med. 1999; 341:709–17. [PubMed: 10471456]

116. Pfeffer MA. New treasures from old? EPHESUS. Eplerenome Post-AHI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther. 2001; 15:11–3. [PubMed: 11504157]

117. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. J Am Coll Cardiol. 2011; 58:1958–66. [PubMed: 22032706]

118. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364:11–21. [PubMed: 21073363]

119. Bene NC, Alcaide P, Wortis HH, Jaffe IZ. Mineralocorticoid receptors in immune cells: Emerging role in cardiovascular disease. Steroids. 2014

120. Jaffe IZ, Jaisser F. Endothelial cell mineralocorticoid receptors: turning cardiovascular risk factors into cardiovascular dysfunction. Hypertension. 2014; 63:915–7. [PubMed: 24566083]

121. Koenig JB, Jaffe IZ. Direct role for smooth muscle cell mineralocorticoid receptors in vascular remodeling: novel mechanisms and clinical implications. Curr Hypertens Rep. 2014; 16:427. [PubMed: 24633842]

122. Pruthi D, McCurley A, Aronovitz M, Galayda C, Karumanchi SA, Jaffe IZ. Aldosterone promotes vascular remodeling by direct effects on smooth muscle cell mineralocorticoid receptors. Arterioscler Thromb Vasc Biol. 2014; 34:355–64. [PubMed: 24311380]

123. Williams GH. Cardiovascular benefits of aldosterone receptor antagonists. Climacteric. 2003; 6(Suppl 3):29–35. [PubMed: 15018246]

124. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. Kidney Int. 2003; 63:1791–800. [PubMed: 12675855]

125. Rocha R, Rudolph AE, Frierdich GE, Nachowiak DA, Kekec BK, Blomme EA, et al. Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol. 2002; 283:H1802–10. [PubMed: 12384457]

126. Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. Ann N Y Acad Sci. 2002; 970:89–100. [PubMed: 12381544]

127. Luther JM, Gainer JV, Murphey LJ, Yu C, Vaughan DE, Morrow JD, et al. Angiotensin II induces interleukin-6 in humans through a mineralocorticoid receptor-dependent mechanism. Hypertension. 2006; 48:1050–7. [PubMed: 17043157]

128. Queisser N, Schupp N. Aldosterone, oxidative stress, and NF-kappaB activation in hypertension-related cardiovascular and renal diseases. Free radical biology & medicine. 2012; 53:314–27. [PubMed: 22609249]

129. Queisser N, Fazeli G, Schupp N. Superoxide anion and hydrogen peroxide-induced signaling and damage in angiotensin II and aldosterone action. Biological chemistry. 2010; 391:1265–79. [PubMed: 20868230]

130. Rude MK, Duhaney TA, Kuster GM, Judge S, Heo J, Colucci WS, et al. Aldosterone stimulates matrix metalloproteinases and reactive oxygen species in adult rat ventricular cardiomyocytes. Hypertension. 2005; 46:555–61. [PubMed: 16043662]

131. Caldiz CI, Diaz RG, Nolly MB, Chiappe de Cingolani GE, Ennis IL, Cingolani HE, et al. Mineralocorticoid receptor activation is crucial in the signalling pathway leading to the Anrep effect. J Physiol. 2011; 589:6051–61. [PubMed: 22174146]

132. Maggio N, Segal M. Cellular basis of a rapid effect of mineralocorticosteroid receptors activation on LTP in ventral hippocampal slices. Hippocampus. 2012; 22:267–75. [PubMed: 21080413]

133. Glass MJ, Chan J, Frys KA, Oselkin M, Tarsitano MJ, Iadecola C, et al. Changes in the subcellular distribution of NADPH oxidase subunit p47phox in dendrites of rat dorsomedial nucleus tractus solitarius neurons in response to chronic administration of hypertensive agents. Exp Neurol. 2007; 205:383–95. [PubMed: 17418121]

134. Kawakami-Mori F, Shimosawa T, Mu S, Wang H, Ogura S, Yatomi Y, et al. NADPH oxidase-mediated Rac1 GTP activity is necessary for nongenomic actions of the mineralocorticoid receptor in the CA1 region of the rat hippocampus. Am J Physiol Endocrinol Metab. 2012; 302:E425–32. [PubMed: 22114025]

135. Kang YM, Ma Y, Zheng JP, Elks C, Sriramula S, Yang ZM, et al. Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. Cardiovasc Res. 2009; 82:503–12. [PubMed: 19246475]

136. Moura A-M, Worcel M. Direct action of aldosterone on transmembrane 22Na efflux from arterial smooth muscle: rapid and delayed effects. Hypertension. 1984; 6:425–30. [PubMed: 6329952]

137. Fiebeler A, Luft FC. The mineralocorticoid receptor and oxidative stress. Heart Fail Rev. 2005; 10:47–52. [PubMed: 15947891]

138. Marney AM, Brown NJ. Aldosterone and end-organ damage. Clin Sci (Lond). 2007; 113:267–78. [PubMed: 17683282]

139. Grossmann C, Gekle M. New aspects of rapid aldosterone signaling. Mol Cell Endocrinol. 2009; 308:53–62. [PubMed: 19549592]

140. Callera GE, Yogi A, Briones AM, Montezano AC, He Y, Tostes RC, et al. Vascular proinflammatory responses by aldosterone are mediated via c-Src trafficking to cholesterol-rich microdomains: role of PDGFR. Cardiovasc Res. 2011; 91:720–31. [PubMed: 21576132]

141. Whaley-Connell AT, Habibi J, Nistala R, DeMarco VG, Pulakat L, Hayden MR, et al. Mineralocorticoid receptor-dependent proximal tubule injury is mediated by a redox-sensitive mTOR/S6K1 pathway. American journal of nephrology. 2012; 35:90–100. [PubMed: 22205374]

142. Wendler A, Albrecht C, Wehling M. Nongenomic actions of aldosterone and progesterone revisited. Steroids. 2012; 77:1002–6. [PubMed: 22285849]

143. Zhu X, Manning RD Jr, Lu D, Gomez-Sanchez CE, Fu Y, Juncos LA, et al. Aldosterone stimulates superoxide production in macula densa cells. Am J Physiol Renal Physiol. 2011; 301:F529–35. [PubMed: 21270097]

144. Kang YM, Zhang ZH, Johnson RF, Yu Y, Beltz T, Johnson AK, et al. Novel effect of mineralocorticoid receptor antagonism to reduce proinflammatory cytokines and hypothalamic activation in rats with ischemia-induced heart failure. Circ Res. 2006; 99:758–66. [PubMed: 16960100]

145. Schiavone S, Jaquet V, Sorce S, Dubois-Dauphin M, Hultqvist M, Backdahl L, et al. NADPH oxidase elevations in pyramidal neurons drive psychosocial stress-induced neuropathology. Translational psychiatry. 2012; 2:e111. [PubMed: 22832955]

146. Seo JS, Park JY, Choi J, Kim TK, Shin JH, Lee JK, et al. NADPH oxidase mediates depressive behavior induced by chronic stress in mice. J Neurosci. 2012; 32:9690–9. [PubMed: 22787054]

147. Zhang ZH, Yu Y, Wei SG, Felder RB. Centrally administered lipopolysaccharide elicits sympathetic excitation via NAD(P)H oxidase-dependent mitogen-activated protein kinase signaling. J Hypertens. 2010; 28:806–16. [PubMed: 20027123]

148. Gabor A, Leenen FH. Central neuromodulatory pathways regulating sympathetic activity in hypertension. J Appl Physiol. 2012; 113:1294–303. [PubMed: 22773773]

149. Felder RB. Mineralocorticoid receptors, inflammation and sympathetic drive in a rat model of systolic heart failure. Exp Physiol. 2010; 95:19–25. [PubMed: 19648480]

150. de Kloet ER, Karst H, Joels M. Corticosteroid hormones in the central stress response: quick-and-slow. Front Neuroendocrinol. 2008; 29:268–72. [PubMed: 18067954]

151. Nagase M, Fujita T. Role of Rac1-mineralocorticoid-receptor signalling in renal and cardiac disease. Nature reviews Nephrology. 2013; 9:86–98.

152. Francis J, Beltz T, Johnson AK, Felder RB. Mineralocorticoids act centrally to regulate blood-borne tumor necrosis factor-alpha in normal rats. Am J Physiol Regul Integr Comp Physiol. 2003; 285:R1402–9. [PubMed: 14615404]

153. Zhang ZH, Francis J, Weiss RM, Felder RB. The renin-angiotensin-aldosterone system excites hypothalamic paraventricular nucleus neurons in heart failure. Am J Physiol Heart Circ Physiol. 2002; 283:H423–33. [PubMed: 12063317]

154. Yu Y, Zhang ZH, Wei SG, Serrats J, Weiss RM, Felder RB. Brain perivascular macrophages and the sympathetic response to inflammation in rats after myocardial infarction. Hypertension. 2010; 55:652–9. [PubMed: 20142564]

155. Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T. Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 2010; 61:509–21. [PubMed: 21081794]

156. Kang YM, Zhang ZH, Xue B, Weiss RM, Felder RB. Inhibition of brain proinflammatory cytokine synthesis reduces hypothalamic excitation in rats with ischemia-induced heart failure. Am J Physiol Heart Circ Physiol. 2008; 295:H227–36. [PubMed: 18487441]

157. Brooks VL, Osborn JW. Hormonal-sympathetic interactions in long-term regulation of arterial pressure: an hypothesis. Am J Physiol. 1995; 268:R1343–58. [PubMed: 7611509]

158. Menon DV, Arbique D, Wang Z, Adams-Huet B, Auchus RJ, Vongpatanasin W. Differential effects of chlorthalidone versus spironolactone on muscle sympathetic nerve activity in hypertensive patients. J Clin Endocrinol Metab. 2009; 94:1361–6. [PubMed: 19158191]

159. Raheja P, Price A, Wang Z, Arbique D, Adams-Huet B, Auchus RJ, et al. Spironolactone Prevents Chlorthalidone-Induced Sympathetic Activation and Insulin Resistance in Hypertensive Patients. Hypertension. 2012

160. Rossi GP, Seccia TM. Changes in aldosterone and obesity-related cardiometabolic risk factors with a 1-year weight loss intervention in normotensive overweight and obese young adults. Hypertens Res. 2013

161. Whaley-Connell A, Johnson MS, Sowers JR. Aldosterone: role in the cardiometabolic syndrome and resistant hypertension. Prog Cardiovasc Dis. 2010; 52:401–9. [PubMed: 20226958]

162. Lastra-Gonzalez G, Manrique-Acevedo C, Sowers JR. The role of aldosterone in cardiovascular disease in people with diabetes and hypertension: an update. Curr Diab Rep. 2008; 8:203–7. [PubMed: 18625117]

163. Harris AP, Holmes MC, de Kloet ER, Chapman KE, Seckl JR. Mineralocorticoid and glucocorticoid receptor balance in control of HPA axis and behaviour. Psychoneuroendocrinology. 2013; 38:648–58. [PubMed: 22980941]

164. Joels M, Sarabdjitsingh RA, Karst H. Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. Pharmacol Rev. 2012; 64:901–38. [PubMed: 23023031]

165. Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, et al. Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered

synaptic functioning, and differential responsiveness to glucocorticoids and stress. J Neurosci. 2008; 28:6037–45. [PubMed: 18524909]

166. Maggio N, Segal M. Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. J Neurosci. 2007; 27:5757–65. [PubMed: 17522319]
167. Pavlides C, McEwen BS. Effects of mineralocorticoid and glucocorticoid receptors on long-term potentiation in the CA3 hippocampal field. Brain Research. 1999; 851:204–14. [PubMed: 10642845]
168. Stranahan AM, Arumugam TV, Lee K, Mattson MP. Mineralocorticoid receptor activation restores medial perforant path LTP in diabetic rats. Synapse. 2010; 64:528–32. [PubMed: 20196138]
169. Chen J, Gomez-Sanchez CE, Penman A, May PJ, Gomez-Sanchez E. Expression of mineralocorticoid and glucocorticoid receptors in preautonomic neurons of the rat paraventricular nucleus. Am J Physiol Regul Integr Comp Physiol. 2014; 306:R328–40. [PubMed: 24381176]
170. de Kloet ER, Oitzl MS, Joels M. Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci. 1999; 22:422–6. [PubMed: 10481183]
171. Sarabdjitsingh RA, Joels M, de Kloet ER. Glucocorticoid pulsatility and rapid corticosteroid actions in the central stress response. Physiology & behavior. 2012; 106:73–80. [PubMed: 21971364]
172. Schwabe L, Tegenthoff M, Hoffken O, Wolf OT. Mineralocorticoid receptor blockade prevents stress-induced modulation of multiple memory systems in the human brain. Biological psychiatry. 2013; 74:801–8. [PubMed: 23871473]
173. Brinks V, Berger S, Gass P, de Kloet ER, Oitzl MS. Mineralocorticoid receptors in control of emotional arousal and fear memory. Horm Behav. 2009; 56:232–8. [PubMed: 19447109]
174. Ferguson D, Sapolsky R. Overexpression of mineralocorticoid and transdominant glucocorticoid receptor blocks the impairing effects of glucocorticoids on memory. Hippocampus. 2008; 18:1103–11. [PubMed: 18651616]
175. Hodgson ZG, Meddle SL, Roberts ML, Buchanan KL, Evans MR, Metzdorf R, et al. Spatial ability is impaired and hippocampal mineralocorticoid receptor mRNA expression reduced in zebra finches (Taeniopygia guttata) selected for acute high corticosterone response to stress. Proc Biol Sci. 2007; 274:239–45. [PubMed: 17148253]
176. Berger S, Wolfer DP, Selbach O, Alter H, Erdmann G, Reichardt HM, et al. Loss of the limbic mineralocorticoid receptor impairs behavioral plasticity. Proc Natl Acad Sci U S A. 2006; 103:195–200. [PubMed: 16368758]
177. Schaaf MJ, De Kloet ER, Vreugdenhil E. Corticosterone effects on BDNF expression in the hippocampus. Implications for memory formation. Stress. 2000; 3:201–8. [PubMed: 10938581]
178. Alberti KG, Sharp GW. Four classes of steroid identified by their interaction with mineralocorticoid receptors in the toad bladder. Biochem J. 1969; 115:45P.
179. Funder JW, Feldman D, Edelman I. Specific Aldosterone binding in rat kidney and parotid. J Steroid Biochem. 1972; 3:209–18. [PubMed: 4651322]
180. Rousseau G, Baxter JD, Funder JW, Edelman IS, Tomkins GM. Glucocorticoid and mineralocorticoid receptors for aldosterone. J Steroid Biochem. 1972; 3:219–27. [PubMed: 4346760]
181. Vinson GP. The mislabelling of deoxycorticosterone: making sense of corticosteroid structure and function. J Endocrinol. 2011; 211:3–16. [PubMed: 21715433]
182. Gerlach JL, McEwen BS. Rat brain binds adrenal steroid hormone: radioautography of hippocampus with corticosterone. Science. 1972; 175:1133–6. [PubMed: 5060047]
183. Stumpf, WE.; Sar, M. Within the Brain–Pituitary–Adrenocortical System. Academic Press; 1979. Glucocorticosteroids and mineralocorticosteroid hormone target sites in the brain Autoradiographic studies with corticosterone, aldosterone, deoxycorticosterone: in interaction within the brain-pituitary-adrenocortical system; p. 137-47.
184. Birmingham MK, Sar M, Stumpf WE. Localization of aldosterone and corticosterone in the central nervous system, assessed by quantitative autoradiography. Neurochem Res. 1984; 9:333–50. [PubMed: 6377108]

185. De Kloet ER. Brain corticosteroid receptor balance and homeostatic control. Frontiers in Neuroendocrinology. 1991; 12:95–164.

186. Marver D, Stewart J, Funder JW, Feldman D, Edelman IS. Renal aldosterone receptors: studies with (3H)aldosterone and the anti-mineralocorticoid (3H)spirolactone (SC-26304). Proc Natl Acad Sci U S A. 1974; 71:1431–5. [PubMed: 4364539]

187. Yongue BG, Roy EJ. Endogenous aldosterone and corticosterone in brain cell nuclei of adrenal-intact rats: regional distribution and effects of physiological variations in serum steroids. Brain Res. 1987; 436:49–61. [PubMed: 3690353]

188. Selye H. The general adaptation syndrome and the diseases of adaptation. J Clin Endocrinol Metab. 1946; 6:117–230. [PubMed: 21025115]

189. de Kloet ER, de Jong IE, Oitzl MS. Neuropharmacology of glucocorticoids: focus on emotion, cognition and cocaine. Eur J Pharmacol. 2008; 585:473–82. [PubMed: 18417120]

190. McEwen BS, Weiss JM, Schwartz LS. Selective retention of corticosterone by limbic structures in rat brain. Nature. 1968; 220:911–2. [PubMed: 4301849]

191. Reul JMH, De Kloet ER. Two receptor systems for coticosterone in rat brain: microdistribution and differential occupation. Endocrinology. 1985; 117:2505–11. [PubMed: 2998738]

192. Coirini H, Marusic ET, De Nicola AF, Rianbow TC, McEwen BS. Identification of mineralocorticoid binding sites in rat brain by competition studies and density gradient centrifugation. Neuroendocrinology. 1983; 37:354–60. [PubMed: 6316188]

193. Krozowski ZS, Funder JW. Renal mineralocorticoid receptors and hippocampal corticosterone-binding species have identical intrinsic steroid specificity. Proc Natl Acad Sci U S A. 1983; 80:6056–60. [PubMed: 6310613]

194. Arriza JL, Simerly RB, Swanson LW, Evans RM. The neuronal mineralocorticoid receptor as a mediator of glucocorticoid response. Neuron. 1988; 1:887–900. [PubMed: 2856104]

195. Ulick S, Levine LS, Gunczler P. A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. J Clin Endocrinol Metab. 1979; 49:757–64. [PubMed: 226561]

196. Shackleton CHL, Arteaga JRE, Lopez JM, Winter JSD. Congenital 11β-hydroxysteroid dehydrogenase deficiency associated with juvenile hypertension: corticosteroid metabolite profiles of four patients and their families. Clin Endocrinol. 1985; 22:701–12.

197. Monder C, Shackleton CH, Bradlow HL, New MI, Stoner E, Iohan F, et al. The syndrome of apparent mineralocorticoid excess: its association with 11 beta-dehydrogenase and 5 beta-reductase deficiency and some consequences for corticosteroid metabolism. J Clin Endocrinol Metab. 1986; 63:550–7. [PubMed: 3460996]

198. Stewart PM, Wallace MA, Valentino R, Burt D, Shackleton CH, Edwards CRW. Mineralocorticoid activity of liquorice: 11-Beta-hydroxysteroid dehydrogenase deficiency comes of age. The Lancet. 1987:821–4.

199. Stewart PM, Corrie JET, Shackleton CHL, Edwards CRW. Syndrome of apparent mineralocorticoid excess. A defect in the cortisol-cortisone shuttle. J Clin Invest. 1988; 82:340–9. [PubMed: 3164727]

200. Edwards CRW, Burt D, McIntyre MA, De Kloet ER, Stewart PM, Brett L, et al. Localisation of 11β-hydroxysteroid dehydrogenase-tissue specific protector of the mineralocorticoid receptor. Lancet. 1988; ii:986–9. [PubMed: 2902493]

201. Funder JW, Pearce PT, Smith R, Smith AI. Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. Science. 1988; 242:583–5. [PubMed: 2845584]

202. Brem AS, Matheson KL, Conca T, Morris DJ. Effect of carbenoxolone on glucocorticoid metabolism and Na transport in toad bladder. Am J Physiol. 1989; 257:F700–4. [PubMed: 2508491]

203. Castelle R, Schwarting R, Miuller C, Hierhelzer K. Immunohistochemical localization of 11-hydroxysteroid dehydrogenase in rat kidney with moncolonal antibody. Renal Phys Biochem. 1989; 12(5–6):320–7.

204. Krozowski Z, Stuchberry S, White PC, Monder C, Funder JW. Characterization of 11β-hydroxysteroid dehydrogenase gene expression: Identification of multiple unique forms of

messenger ribonucleic acid in the rat kidney. Endocrinology. 1990; 127:3009–13. [PubMed: 2249639]

205. Naray-Fejes-Toth A, Watlington CO, Fejes-Toth G. 11β-Hydroxysteroid dehydrogenase activity in the renal target cells of aldosterone. Endocrinology. 1991; 129:17–21. [PubMed: 2055180]
206. Brem AS, Morris DJ. Interactions between glucocorticoids and mineralocorticoids in the regulation of renal electrolyte transport. Mol Cell Endocrinol. 1993; 97:C1–5. [PubMed: 8143889]
207. Monder C. The forms and functions of 11β-hydroxysteroid dehydrogenase. J Steroid Biochem Mol Biol. 1993; 45:161–5. [PubMed: 8481341]
208. Brem AS, Bina RB, Klinger JR, King T, Werner JC. Glucocorticoid metabolism in the newborn rat heart. Proc Soc Expt Biol Med. 1995; 209:146–51.
209. Brem AS, Bina RB, King T, Morris DJ. Bidirectional activity of 11β-hydroxysteroid dehydrogenase in vascular smooth muscle cells. Steroids. 1995; 60:406–10. [PubMed: 7570714]
210. Naray-Fejes-Toth A, Fejes-Toth G. Subcellular localization of the type 2 11beta-hydroxysteroid dehydrogenase. A green fluorescent protein study. J Biol Chem. 1996; 271:15436–42. [PubMed: 8663122]
211. Odermatt A, Arnold P, Frey FJ. The intracellular localization of the mineralocorticoid receptor is regulated by 11beta-hydroxysteroid dehydrogenase type 2. J Biol Chem. 2001; 276:28484–92. [PubMed: 11350956]
212. Morris DJ, Brem AS, Ge R, Jellinck PH, Sakai RR, Hardy MP. The functional roles of 11beta-HSD1: vascular tissue, testis and brain. Mol Cell Endocrinol. 2003; 203:1–12. [PubMed: 12782398]
213. Gomez-Sanchez EP, Gomez-Sanchez CE. First there was one, then two…why more 11beta-hydroxysteroid dehydrogenases? Endocrinology. 1997; 138:5087–8. [PubMed: 9389486]
214. Gomez-Sanchez EP, Ganjam V, Chen YJ, Cox DL, Zhou MY, Thanigaraj S, et al. The sheep kidney contains a novel unidirectional, high affinity $NADP^+$-dependent 11β-hydroxysteroid dehydrogenase (11-HSD3). Steroids. 1997; 62:444–50. [PubMed: 9178432]
215. Slight SH, Ganjam VK, Gomez-Sanchez CE, Weber KT. High affinity NAD^+-dependent 11β-hydroxysteroid dehydrogenase in the human heart. J Mol Cell Cardiol. 1996; 28:781–7. [PubMed: 8732505]
216. Ohno S, Nakagawara S, Honda Y, Nakajin S. Evidence for expression of 11beta-hydroxysteroid dehydrogenase type3 (HSD11B3/HSD11B1L) in neonatal pig testis. Molecular and cellular biochemistry. 2013; 381:145–56. [PubMed: 23881245]
217. Stewart PM, Murry BA, Mason JI. Human kidney 11β-hydroxysteroid dehydrogenase is a high affinity nicotinamide adenine dinucleotide dependent enzyme and differs from the cloned type I isoform. J Clin Endocrinol Metab. 1994; 79:480–4. [PubMed: 8045966]
218. Agarwal AK, Rogerson FM, Mune T, White PC. Gene structure and chromosomal localization of the human HSD11K gene encoding the kidney (type 2) isozyme of 11 beta-hydroxysteroid dehydrogenase. Genomics. 1995; 29:195–9. [PubMed: 8530071]
219. Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1- a tissue-specific amplifier of glucocorticoid action. Endocrinology. 2001; 142:1371–6. [PubMed: 11250914]
220. Chapman K, Holmes M, Seckl J. 11beta-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev. 2013; 93:1139–206. [PubMed: 23899562]
221. Bujalska IJ, Walker EA, Hewison M, Stewart PM. A switch in dehydrogenase to reductase activity of 11 beta-hydroxysteroid dehydrogenase type 1 upon differentiation of human omental adipose stromal cells. J Clin Endocrinol Metab. 2002; 87:1205–10. [PubMed: 11889189]
222. Bujalska IJ, Draper N, Michailidou Z, Tomlinson JW, White PC, Chapman KE, et al. Hexose-6-phosphate dehydrogenase confers oxo-reductase activity upon 11 beta-hydroxysteroid dehydrogenase type 1. J Mol Endocrinol. 2005; 34:675–84. [PubMed: 15956339]
223. Atanasov AG, Nashev LG, Schweizer RA, Frick C, Odermatt A. Hexose-6-phosphate dehydrogenase determines the reaction direction of 11beta-hydroxysteroid dehydrogenase type 1 as an oxoreductase. FEBS Lett. 2004; 571:129–33. [PubMed: 15280030]

224. Zhou MY, Gomez-Sanchez EP, Cox DL, Cosby D, Gomez-Sanchez CE. Cloning, expression and tissue distribution of the rat NAD+-dependent 11β-hydroxysteroid dehydrogenase. Endocrinology. 1995; 136:3729–34. [PubMed: 7649078]

225. Naray-Fejes-Toth A, Fejes-Toth G. Extranuclear localization of endogenous 11beta-hydroxysteroid dehydrogenase-2 in aldosterone target cells. Endocrinology. 1998; 139:2955–9. [PubMed: 9607806]

226. Funder JW. Mineralocorticoid receptor activation and oxidative stress. Hypertension. 2007; 50:840–1. [PubMed: 17923584]

227. Brem AS, Matheson KL, Latif S, Morris DJ. Activity of 11 beta-hydroxysteroid dehydrogenase in toad bladder: effects of 11-dehydrocorticosterone. Am J Physiol. 1993; 264:F854–8. [PubMed: 8498539]

228. Brem AS, Matheson KL, Barnes JL, Morris DJ. 11-Dehydrocorticosterone, a glucocorticoid metabolite, inhibits aldosterone action in toad bladder. Am J Physiol. 1991; 261:F873–9. [PubMed: 1951719]

229. Gomez-Sanchez EP, Ganjam V, Chen YJ, Liu Y, Clark SA, Gomez-Sanchez CE. The 11beta hydroxysteroid dehydrogenase 2 exists as an inactive dimer. Steroids. 2001; 66:845–8. [PubMed: 11576624]

230. Gomez-Sanchez EP, Ganjam V, Chen YJ, Liu Y, Zhou MY, Toroslu C, et al. Regulation of 11 beta-hydroxysteroid dehydrogenase enzymes in the rat kidney by estradiol. Am J Physiol Endocrinol Metab. 2003; 285:E272–9. [PubMed: 12700160]

231. Seckl JR, Chapman KE. Medical and physiological aspects of the 11beta-hydroxysteroid dehydrogenase system. European Journal of Biochemistry. 1997; 249:361–4. [PubMed: 9370341]

232. Diaz R, Brown RW, Seckl JR. Distinct ontogeny of glucocorticoid and mineralocorticoid receptor and 11beta-hydroxysteroid dehydrogenase types I and II mRNAs in the fetal rat brain suggest a complex control of glucocorticoid actions. Journal of Neuroscience. 1998; 18:2570–80. [PubMed: 9502816]

233. Welberg LA, Seckl JR, Holmes MC. Inhibition of 11beta-hydroxysteroid dehydrogenase, the foeto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring. European Journal of Neuroscience. 2000; 12:1047–54. [PubMed: 10762336]

234. Cottrell EC, Holmes MC, Livingstone DE, Kenyon CJ, Seckl JR. Reconciling the nutritional and glucocorticoid hypotheses of fetal programming. FASEB J. 2012; 26:1866–74. [PubMed: 22321728]

235. Speirs HJ, Seckl JR, Brown RW. Ontogeny of glucocorticoid receptor and 11beta-hydroxysteroid dehydrogenase type-1 gene expression identifies potential critical periods of glucocorticoid susceptibility during development. J Endocrinol. 2004; 181:105–16. [PubMed: 15072571]

236. Hirasawa G, Takeyama J, Sasano H, Fukushima K, Suzuki T, Muramatu Y, et al. 11Beta-hydroxysteroid dehydrogenase type II and mineralocorticoid receptor in human placenta. Journal of Clinical Endocrinology & Metabolism. 2000; 85:1306–9. [PubMed: 10720080]

237. Hirasawa G, Sasano H, Suzuki T, Takeyama J, Muramatu Y, Fukushima K, et al. 11Beta-hydroxysteroid dehydrogenase type 2 and mineralocorticoid receptor in human fetal development. Journal of Clinical Endocrinology & Metabolism. 1999; 84:1453–8. [PubMed: 10199794]

238. Condon J, Gosden C, Gardener D, Nickson P, Hewison M, Howie AJ, et al. Expression of type 2 11beta-hydroxysteroid dehydrogenase and corticosteroid hormone receptors in early human fetal life. Journal of Clinical Endocrinology & Metabolism. 1998; 83:4490–7. [PubMed: 9851798]

239. Condon J, Ricketts ML, Whorwood CB, Stewart PM. Ontogeny and sexual dimorphic expression of mouse type 2 11beta-hydroxysteroid dehydrogenase. Mol Cell Endocrinol. 1997; 127:121–8. [PubMed: 9099907]

240. Burton PJ, Smith RE, Krozowski ZS, Waddell BJ. Zonal distribution of 11 beta-hydroxysteroid dehydrogenase types 1 and 2 messenger ribonucleic acid expression in the rat placenta and decidua during late pregnancy. Biol Reprod. 1996; 55:1023–8. [PubMed: 8902213]

241. Zhang TY, Labonte B, Wen XL, Turecki G, Meaney MJ. Epigenetic mechanisms for the early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. Neuropsychopharmacology. 2013; 38:111–23. [PubMed: 22968814]

242. Hunter RG. Epigenetic effects of stress and corticosteroids in the brain. Frontiers in cellular neuroscience. 2012; 6:18. [PubMed: 22529779]

243. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. Horm Behav. 2011; 59:279–89. [PubMed: 20591431]

244. Wyrwoll CS, Holmes MC, Seckl JR. 11beta-Hydroxysteroid dehydrogenases and the brain: From zero to hero, a decade of progress. Front Neuroendocrinol. 2010

245. Reynolds RM, Walker BR, Phillips DI, Dennison EM, Fraser R, Mackenzie SM, et al. Programming of hypertension: associations of plasma aldosterone in adult men and women with birthweight, cortisol, and blood pressure. Hypertension. 2009; 53:932–6. [PubMed: 19380612]

246. Krozowski Z, Li KX, Koyama K, Smith RE, Obeyesekere VR, Stein-Oakley A, et al. The type I and type II 11beta-hydroxysteroid dehydrogenase enzymes. [Review] [71 refs]. Journal of Steroid Biochemistry & Molecular Biology. 1999; 69:391–401. [PubMed: 10419017]

247. Gong R, Morris DJ, Brem AS. Human renal 11beta-hydroxysteroid dehydrogenase 1 functions and co-localizes with COX-2. Life sciences. 2008; 82:631–7. [PubMed: 18261751]

248. Driver PM, Kilby MD, Bujalska I, Walker EA, Hewison M, Stewart PM. Expression of 11 beta-hydroxysteroid dehydrogenase isozymes and corticosteroid hormone receptors in primary cultures of human trophoblast and placental bed biopsies. Mol Hum Reprod. 2001; 7:357–63. [PubMed: 11279298]

249. Hadoke PW, Kipari T, Seckl JR, Chapman KE. Modulation of 11beta-hydroxysteroid dehydrogenase as a strategy to reduce vascular inflammation. Current atherosclerosis reports. 2013; 15:320. [PubMed: 23512604]

250. Cai TQ, Wong B, Mundt SS, Thieringer R, Wright SD, Hermanowski-Vosatka A. Induction of 11beta-hydroxysteroid dehydrogenase type 1 but not -2 in human aortic smooth muscle cells by inflammatory stimuli. J Steroid Biochem Mol Biol. 2001; 77:117–22. [PubMed: 11377976]

251. Acosta TJ, Tetsuka M, Matsui M, Shimizu T, Berisha B, Schams D, et al. In vivo evidence that local cortisol production increases in the preovulatory follicle of the cow. J Reprod Dev. 2005; 51:483–9. [PubMed: 15947453]

252. Tetsuka M, Yamamoto S, Hayashida N, Hayashi KG, Hayashi M, Acosta TJ, et al. Expression of 11beta-hydroxysteroid dehydrogenases in bovine follicle and corpus luteum. J Endocrinol. 2003; 177:445–52. [PubMed: 12773125]

253. Tetsuka M, Milne M, Simpson GE, Hillier SG. Expression of 11 beta-hydroxysteroid dehydrogenase, glucocorticoid receptor, and mineralocorticoid receptor genes in rat ovary. Biol Reprod. 1999; 60:330–5. [PubMed: 9915998]

254. Tetsuka M, Haines LC, Milne M, Simpson GE, Hillier SG. Regulation of 11beta-hydroxysteroid dehydrogenase type 1 gene expression by LH and interleukin-1beta in cultured rat granulosa cells. J Endocrinol. 1999; 163:417–23. [PubMed: 10588815]

255. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. J Clin Invest. 2004; 114:1146–57. [PubMed: 15489962]

256. Kipari T, Hadoke PW, Iqbal J, Man TY, Miller E, Coutinho AE, et al. 11beta-hydroxysteroid dehydrogenase type 1 deficiency in bone marrow-derived cells reduces atherosclerosis. Faseb J. 2013; 27:1519–31. [PubMed: 23303209]

257. Tiganescu A, Tahrani AA, Morgan SA, Otranto M, Desmouliere A, Abrahams L, et al. 11beta-Hydroxysteroid dehydrogenase blockade prevents age-induced skin structure and function defects. J Clin Invest. 2013; 123:3051–60. [PubMed: 23722901]

258. Holmes MC, Carter RN, Noble J, Chitnis S, Dutia A, Paterson JM, et al. 11beta-hydroxysteroid dehydrogenase type 1 expression is increased in the aged mouse hippocampus and parietal cortex and causes memory impairments. J Neurosci. 2010; 30:6916–20. [PubMed: 20484633]

259. Holmes MC, Seckl JR. The role of 11beta-hydroxysteroid dehydrogenases in the brain. Mol Cell Endocrinol. 2006; 248:9–14. [PubMed: 16413106]

260. Seckl JR, Yau J, Holmes M. 11Beta-hydroxysteroid dehydrogenases: a novel control of glucocorticoid action in the brain. Endocr Res. 2002; 28:701–7. [PubMed: 12530686]

261. Sandeep TC, Yau JL, MacLullich AM, Noble J, Deary IJ, Walker BR, et al. 11Beta-hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. Proc Natl Acad Sci U S A. 2004; 101:6734–9. [PubMed: 15071189]

262. Walker BR, Seckl JR. 11beta-Hydroxysteroid dehydrogenase Type 1 as a novel therapeutic target in metabolic and neurodegenerative disease. Expert Opin Ther Targets. 2003; 7:771–83. [PubMed: 14640912]

263. Wan ZK, Chenail E, Li HQ, Kendall C, Wang Y, Gingras S, et al. Synthesis of potent and orally efficacious 11beta-hydroxysteroid dehydrogenase type 1 inhibitor HSD-016. The Journal of organic chemistry. 2011; 76:7048–55. [PubMed: 21736359]

264. Hollis G, Huber R. 11beta-Hydroxysteroid dehydrogenase type 1 inhibition in type 2 diabetes mellitus. Diabetes, obesity & metabolism. 2011; 13:1–6.

265. Atanasov AG, Odermatt A. Readjusting the glucocorticoid balance: an opportunity for modulators of 11beta-hydroxysteroid dehydrogenase type 1 activity? Endocr Metab Immune Disord Drug Targets. 2007; 7:125–40. [PubMed: 17584152]

266. Draper N, Stewart PM. 11beta-hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. J Endocrinol. 2005; 186:251–71. [PubMed: 16079253]

267. Nair S, Lee YH, Lindsay RS, Walker BR, Tataranni PA, Bogardus C, et al. 11beta-Hydroxysteroid dehydrogenase Type 1: genetic polymorphisms are associated with Type 2 diabetes in Pima Indians independently of obesity and expression in adipocyte and muscle. Diabetologia. 2004; 47:1088–95. [PubMed: 15156315]

268. Feig PU, Shah S, Hermanowski-Vosatka A, Plotkin D, Springer MS, Donahue S, et al. Effects of an 11beta-hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome. Diabetes, obesity & metabolism. 2011; 13:498–504.

269. Harno E, White A. Will treating diabetes with 11beta-HSD1 inhibitors affect the HPA axis? Trends Endocrinol Metab. 2010; 21:619–27. [PubMed: 20594868]

270. Scott JS, Bowker SS, Deschoolmeester J, Gerhardt S, Hargreaves D, Kilgour E, et al. Discovery of a potent, selective, and orally bioavailable acidic 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) inhibitor: discovery of 2-[(3S)-1-[5-(cyclohexylcarbamoyl)-6-propylsulfanylpyridin-2-yl]-3-piperidyl]acet ic acid (AZD4017). J Med Chem. 2012; 55:5951–64. [PubMed: 22691057]

271. Vicker N, Su X, Ganeshapillai D, Smith A, Purohit A, Reed MJ, et al. Novel non-steroidal inhibitors of human 11beta-hydroxysteroid dehydrogenase type 1. J Steroid Biochem Mol Biol. 2007; 104:123–9. [PubMed: 17482805]

272. Youm JK, Park K, Uchida Y, Chan A, Mauro TM, Holleran WM, et al. Local blockade of glucocorticoid activation reverses stress- and glucocorticoid-induced delays in cutaneous wound healing. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2013; 21:715–22.

273. Ma X, Lian QQ, Dong Q, Ge RS. Environmental inhibitors of 11beta-hydroxysteroid dehydrogenase type 2. Toxicology. 2011; 285:83–9. [PubMed: 21515335]

274. Souness GW, Morris DJ. 11α- and 11β-Hydroxyprogesterone, potent inhibitors of 11β-hydroxysteroid dehydrogenase, possess hypertensinogenic activity in the rat. Hypertension. 1996; 27:421–5. [PubMed: 8698448]

275. Semafuko WEB, Sheff MF, Grimes CA, Latif SA, Sadaniantz A, Levinson P, et al. Inhibition of 11β-hydroxysteroid dehydrogenase and 5β-steroid reductase in urine from patients with congestive heart failure. Ann Clin Lab Sci. 1993; 23:456–61. [PubMed: 8291900]

276. Morris DJ, Semafuko WEB, Latif SA, Vogel B, Grimes CA, Sheff MF. Detection of glycyrrhetinic acid-like factors (GALFs) in human urine. Hypertension. 1992; 20:356–60. [PubMed: 1516955]

277. Walker BR, Aggarwal I, Stewart PM, Padfield PL, Edwards CR. Endogenous inhibitors of 11 beta-hydroxysteroid dehydrogenase in hypertension. J Clin Endocrinol Metab. 1995; 80:529–33. [PubMed: 7852515]

278. Walker BR, Campbell JC, Fraser R, Stewart PM, Edwards CRW. Mineralocorticoid excess and inhibition of 11β-hydroxysteroid dehydrogenase in patients with ectopic ACTH syndrome. Clin Endocrinol. 1992; 37:483–92.

279. Gomez-Sanchez EP, Gomez-Sanchez CE. Central Hypertensinogenic effects of glycyrrhizic acid and carbenoxolone. Am J Physiol. 1992; 263:E1125–E30. [PubMed: 1476186]

280. Gomez-Sanchez EP, Gomez-Sanchez CE. Maternal hypertension and progeny blood pressure: role of aldosterone and 11β-HSD. Hypertension. 1999; 33:1369–73. [PubMed: 10373218]

281. Zhang ZH, Kang YM, Yu Y, Wei SG, Schmidt TJ, Johnson AK, et al. 11beta-hydroxysteroid dehydrogenase type 2 activity in hypothalamic paraventricular nucleus modulates sympathetic excitation. Hypertension. 2006; 48:127–33. [PubMed: 16717146]

282. Moisan M-P, Seckl JR, Edwards CRW. 11β-Hydroxysteroid dehydrogenase bioactivity and messenger RNA expression in rat forebrain: localization in hypothalamus, hippocampus, and cortex. Endocrinology. 1990; 127:1450–5. [PubMed: 2387261]

283. Seckl JR, Brown RW, Rajan V, Low SC, Edwards CRW. 11β-Hydroxysteroid dehydrogenase and corticosteroid actions in the brain. J Endocrinol. 1993; 137:S9.

284. Brown RW, Diaz R, Robson AC, Kotelevtsev YV, Mullins JJ, Kaufman MHS. The ontogeny of 11 beta-hydroxysteroid dehydrogenase type 2 and mineralocorticoid receptor gene expression reveal intricate control of glucocorticoid action in development. Endocrinology. 1996; 137:794–7. [PubMed: 8593833]

285. Roland BL, Li KX, Funder JW. Hybridization histochemical localization of 11 beta-hydroxysteroid dehydrogenase type 2 in rat brain. Endocrinology. 1995; 136:4697–700. [PubMed: 7664691]

286. Geerling JC, Kawata M, Loewy AD. Aldosterone-sensitive neurons in the rat central nervous system. J Comp Neurol. 2006; 494:515–27. [PubMed: 16320254]

287. Geerling JC, Loewy AD. Aldosterone in the brain. Am J Physiol Renal Physiol. 2009; 297:F559–76. [PubMed: 19261742]

288. Geerling JC, Loewy AD. Sodium deprivation and salt intake activate separate neuronal subpopulations in the nucleus of the solitary tract and the parabrachial complex. J Comp Neurol. 2007; 504:379–403. [PubMed: 17663450]

289. Bujalska I, Shimojo M, Howie A, Stewart PM. Human 11 beta-hydroxysteroid dehydrogenase: studies on the stably transfected isoforms and localization of the type 2 isozyme within renal tissue. Steroids. 1997; 62:77–82. [PubMed: 9029719]

290. Gomez-Sanchez EP, Romero DG, de Rodriguez AF, Warden MP, Krozowski Z, Gomez-Sanchez CE. Hexose-6-Phosphate Dehydrogenase and 11{beta}-Hydroxysteroid Dehydrogenase-1 Tissue Distribution in the Rat. Endocrinology. 2008; 149:525–33. [PubMed: 18039793]

291. Groeneweg FL, Karst H, de Kloet ER, Joels M. Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. Mol Cell Endocrinol. 2011

292. Pasricha N, Joels M, Karst H. Rapid effects of corticosterone in the mouse dentate gyrus via a nongenomic pathway. J Neuroendocrinol. 2011; 23:143–7. [PubMed: 21092068]

293. Zhou M, Kindt M, Joels M, Krugers HJ. Blocking mineralocorticoid receptors prior to retrieval reduces contextual fear memory in mice. PLoS One. 2011; 6:e26220. [PubMed: 22022574]

294. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nature neuroscience. 2004; 7:847–54.

295. Karst H, Berger S, Turiault M, Tronche F, Schutz G, Joels M. Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. Proc Natl Acad Sci U S A. 2005; 102:19204–7. [PubMed: 16361444]

296. Kellendonk C, Gass P, Kretz O, Schutz G, Tronche F. Corticosteroid receptors in the brain: gene targeting studies. Brain Res Bull. 2002; 57:73–83. [PubMed: 11827739]

297. Qi XR, Kamphuis W, Wang S, Wang Q, Lucassen PJ, Zhou JN, et al. Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients. Psychoneuroendocrinology. 2012; 38:863–70. [PubMed: 23137715]

298. Lai M, Horsburgh K, Bae SE, Carter RN, Stenvers DJ, Fowler JH, et al. Forebrain mineralocorticoid receptor overexpression enhances memory, reduces anxiety and attenuates neuronal loss in cerebral ischaemia. Eur J Neurosci. 2007; 25:1832–42. [PubMed: 17432969]

299. Ferguson D, Sapolsky R. Mineralocorticoid receptor overexpression differentially modulates specific phases of spatial and nonspatial memory. J Neurosci. 2007; 27:8046–52. [PubMed: 17652595]

300. Mitra R, Ferguson D, Sapolsky RM. Mineralocorticoid receptor overexpression in basolateral amygdala reduces corticosterone secretion and anxiety. Biological psychiatry. 2009; 66:686–90. [PubMed: 19500777]

301. Datson NA, van den Oever JM, Korobko OB, Magarinos AM, de Kloet ER, McEwen BS. Previous history of chronic stress changes the transcriptional response to glucocorticoid challenge in the dentate gyrus region of the male rat hippocampus. Endocrinology. 2013; 154:3261–72. [PubMed: 23633533]

302. Gomez-Sanchez EP, Venkataraman MT, Thwaites D, Fort C. ICV infusion of corticosterone antagonizes ICV-aldosterone hypertension. Am J Physiol. 1990; 258:E649–53. [PubMed: 2333961]

303. van den Berg DTWM, De Kloet ER, van Dijken HH, de Jong W. Differential Central Effects of Mineralocorticoid and Glucocorticoid Agonists and Antagonists on Blood Pressure. Endocrinology. 1990; 126:118–24. [PubMed: 2293978]

304. Pyner S, Coote JH. Identification of branching paraventricular neurons of the hypothalamus that project to the rostroventrolateral medulla and spinal cord. Neuroscience. 2000; 100:549–56. [PubMed: 11098118]

305. Otte C, Hinkelmann K, Moritz S, Yassouridis A, Jahn H, Wiedemann K, et al. Modulation of the mineralocorticoid receptor as add-on treatment in depression: a randomized, double-blind, placebo-controlled proof-of-concept study. J Psychiatr Res. 2010; 44:339–46. [PubMed: 19909979]

306. Grippo AJ, Moffitt JA, Sgoifo A, Jepson AJ, Bates SL, Chandler DL, et al. The integration of depressive behaviors and cardiac dysfunction during an operational measure of depression: investigating the role of negative social experiences in an animal model. Psychosom Med. 2012; 74:612–9. [PubMed: 22753634]

307. Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress. 2009; 12:1–21. [PubMed: 19116888]

308. Emanuele E, Geroldi D, Minoretti P, Coen E, Politi P. Increased plasma aldosterone in patients with clinical depression. Arch Med Res. 2005; 36:544–8. [PubMed: 16099336]

309. Selye H, Stone H. Pathogenesis of the cardiovascular and renal changes which usually accompany malignant hypertension. J Urol. 1946; 56:399–419. [PubMed: 21000062]

310. de Kloet ER, Derijk RH, Meijer OC. Therapy Insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? Nat Clin Pract Endocrinol Metab. 2007; 3:168–79. [PubMed: 17237843]

Highlights

- Brain MR mediate diverse events including memory, learning & hemodynamic regulation
- The ratio of MR:GR is crucial for normal cell function and whole body homeostasis.
- Glucocorticoids occupy most neuron MR and GR at basal & stress levels, respectively.
- 11β-HSD1 dehydrogenase activity may confer aldosterone selectivity to MR in some neurons.
- MR & 11β-HSD1 antagonists may have good & bad consequences on brain MR function.

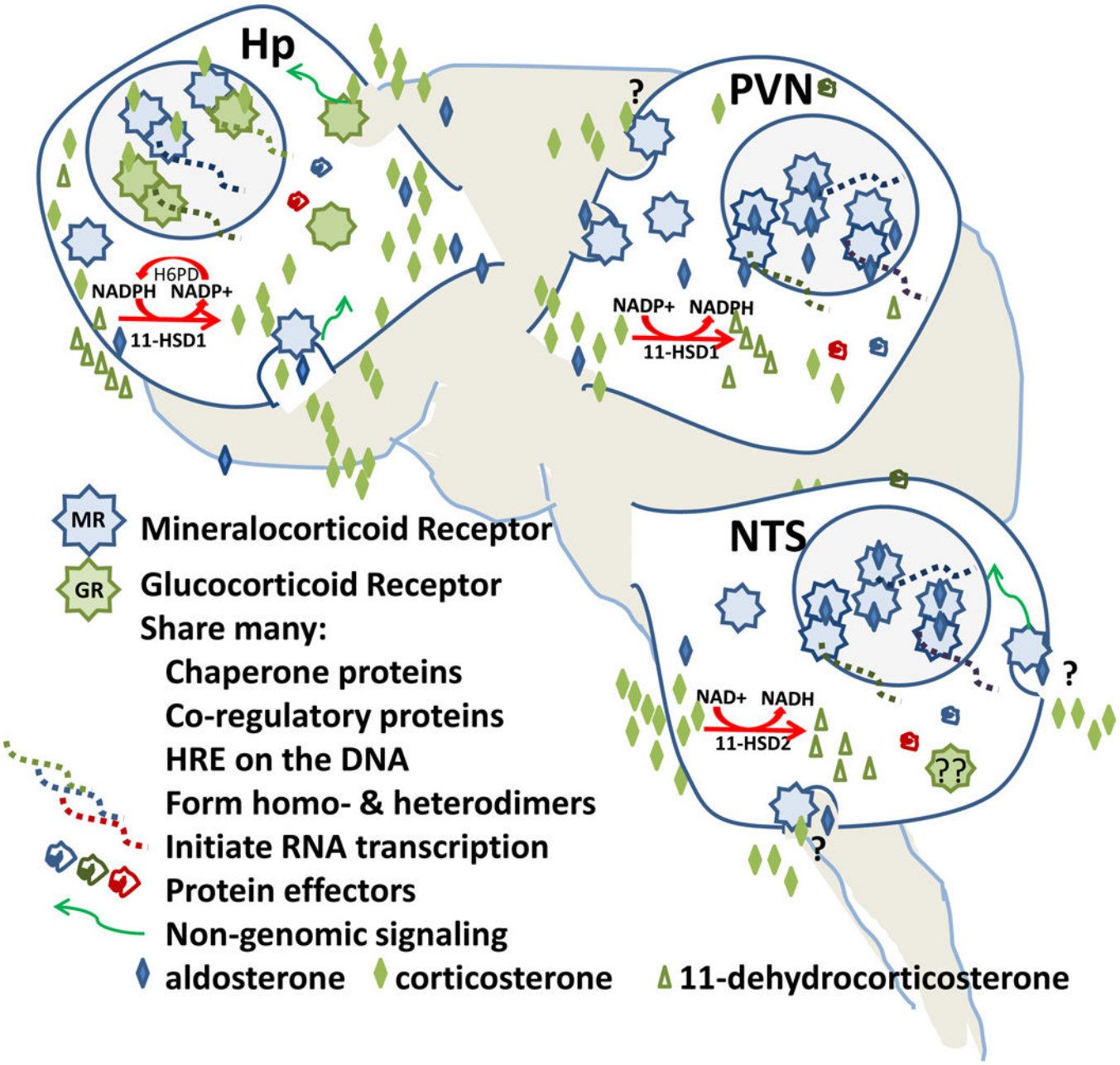

Figure.

Schematic of 3 types of MR ligand selectivity in neurons. Hp: Hippocampal neurons express both MR and GR; endogenous glucocorticoids are the physiological ligand for the MR and 11β-HSD1 is thought to act as a reductase. PVN: Pre-sympathetic neurons of the PVN express only MR, no GR; aldosterone appears to be the physiological ligand for the MR due to dehydrogenase activity of 11β-HSD1 in the absence of H6PD. NTS: Aldosterone target cells of the NTS express MR and 11β-HSD2, an obligate dehydrogenase. ?: preferred ligand for the membrane-associated MR is not certain. ??: whether GR is Expressed GR in aldo-target cells is not certain.