HHS Public Access

Author manuscript

Compr Physiol. Author manuscript; available in PMC 2015 July 31.

Published in final edited form as:

Compr Physiol. 2014 July ; 4(3): 965–994. doi:10.1002/cphy.c130044.

The Multifaceted Mineralocorticoid Receptor

Elise Gomez-Sanchez[*,1] and **Celso E. Gomez-Sanchez**[1]

[1]G.V.(Sonny) Montgomery V.A. Medical Center and Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi

Abstract

The primary adrenal cortical steroid hormones, aldosterone, and the glucocorticoids cortisol and corticosterone, act through the structurally similar mineralocorticoid (MR) and glucocorticoid receptors (GRs). Aldosterone is crucial for fluid, electrolyte, and hemodynamic homeostasis and tissue repair; the significantly more abundant glucocorticoids are indispensable for energy homeostasis, appropriate responses to stress, and limiting inflammation. Steroid receptors initiate gene transcription for proteins that effect their actions as well as rapid non-genomic effects through classical cell signaling pathways. GR and MR 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. Thus the appropriate balance of MR and GR activation is crucial for homeostasis. MR has the same binding affinity for aldosterone, cortisol, and corticosterone. Glucocorticoids activate MR in most tissues at basal levels and GR at stress levels. Inactivation of cortisol and corticosterone by 11β-HSD2 allows aldosterone to activate MR within aldosterone target cells and limits activation of the GR. Under most conditions, 11β-HSD1 acts as a reductase and activates cortisol/corticosterone, amplifying circulating levels. 11β-HSD1 and MR antagonists mitigate inappropriate activation of MR under conditions of oxidative stress that contributes to the pathophysiology of the cardiometabolic syndrome; however, MR antagonists decrease normal MR/GR functional interactions, a particular concern for neurons mediating cognition, memory, and affect.

Introduction

The mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) are highly homologous members of the Steroid Receptor Family of ligand activated transcription factors that initiate or suppress the transcription of effector proteins, as well as initiate rapid non-genomic, or extra-nuclear, events through several cell signaling pathways. As transcription factors, MR and GR compete for the same ligands, form homodimers and heterodimers with each other, bind many of the same hormone response elements on the DNA, and share many co-regulatory proteins required for the efficient initiation of gene transcription. Yet clearly there are separate mineralocorticoid and glucocorticoid effects and their primary ligands, aldosterone and cortisol (corticosterone in some species including the rat and mouse), serve diverse purposes and are regulated very differently. Rapid non-genomic effects of membrane-associated MR and GR also may alter gene transcription

[*]Correspondence to egomez-sanchez@umc.edu.

indirectly as the culmination of cell signaling pathways (107, 206). Thus the MR and GR do not fit the simple lock and key concept for receptor and ligand (nor do the other steroid hormone receptors). Aldosterone and cortisol/corticosterone also mediate rapid effects independent of either the MR or GR that are only recently being clarified, probably through G-coupled proteins (190,191,474,476). Figure 1 simplifies the actions of the MR and aldosterone. GR actions are slightly simpler to study because the only relevant endogenous ligands are the glucocorticoids, however GR do bind and are activated by pharmacological levels aldosterone and deoxycorticosterone, which has introduced confusion in the literature.

Bruce McEwen, a pioneer in the area of adrenal steroid receptors and their function, demonstrated that tritiated corticosterone rapidly crossed the blood brain barrier and was retained in higher concentrations and for longer in the hippocampus and septal areas of the brain than in the blood of adrenalectomized rats (292). Separate mineralocorticoid and glucocorticoid binding sites for corticosterone in the hippocampus were confirmed by competition and density gradient centrifugation studies (76) and the high affinity site was shown to have the same intrinsic binding affinities for corticocosterone and aldosterone in the kidney and hippocampus (252), laying the foundation for studies of pre-receptor mechanisms providing extrinsic ligand specificity to the MR.

The concept that the ratio of MR:GR function is crucial for normal adaptation to the ever-changing environment was developed from studies of the physiological and behavioral adaptation to stress (88, 92, 95 2005, 209, 372) and is important for understanding other processes in which MR and GR participate, including those in the kidney and colon, quintessential mineralocorticoid target organs (2, 129, 130).

MRs and GRs are expressed in many cell types, often in the same cell, where they interact at both the molecular and functional levels to mediate and modulate diverse functions. Prominent MR functions include modulation of ion and fluid transport crucial for osmotic and hemodynamic homeostasis, as well as membrane excitability in neurons and muscle cells, trophic and adaptive responses to injury, and neuronal responses critical for learning, memory, and early response to stress. GR are essential for energy homeostasis, including gluconeogenesis, and the response to stress and inflammation. In the latter role, GR often dampen MR functions. Inappropriate activation of MR in the heart, vessels, kidneys, and brain hemodynamic control centers results in increased reactive oxygen species, inflammation and cardiovascular and renal disease (175). Use of MR antagonists has increased considerably in the last decade since clinical studies demonstrated their significant benefit as additions to standard therapy for chronic heart failure despite normal to low plasma aldosterone (aldo) levels in these patients (175, 386, 499). Addition of MR antagonists to hypertension treatment reduces diuretic-induced sympathetic nervous system activation resulting in insulin resistance (366), as well as the insulin resistance of the metabolic syndrome (440, 478).

The effects of MR antagonists on cognitive functions have been contradictory and appear to depend upon the health of the individual and the ratio of MR:GR function. MR antagonists increase cognition in heart failure patients, sometimes despite lack of significant effect on cardiac function (32, 84, 488). In contrast, short term use of MR antagonists in healthy

normotensive human subjects has adverse effects on attention, memory, and cognition, results that parallel those in animal models (80, 342, 492, 511). Decreases in MR or the ratio of MR:GR expression in other brain areas are implicated in depression and cognitive decline in humans (89, 100, 359) and intact MR function is crucial to the ability to learn under stress and the ability to form memories (401-403). Studies in humans with adrenal failure in which glucocorticoids are replaced at graded levels such that only MR or MR and GR are occupied, concur with those in adrenalectomized animals demonstrating that balanced activation of MR and GR provides optimal cognitive performance (448). In the long term, appropriate activation of the MR is essential for normal neuronal differentiation, migration, and function, an important consideration for the adult human, as well as the developing brain (47, 146, 315, 460).

This article summarizes mechanisms of MR actions in diverse tissues and their importance to hemodynamic homeostasis, thus basis for pathology when deranged. These are inextricably joined to glucocorticoid receptor activities and the activity of enzymes responsible for prereceptor modulation of ligands, as well as levels of aldosterone, cortisol, and corticosterone.

Mammalian Adrenocorticosteroids and Their Receptors

The main steroids of the adrenal cortex are the mineralocorticoid aldosterone, the glucocorticoids cortisol and corticosterone, and the adrenal androgens androstenedione, 11β-hydroxyandrostenedione, and dehydroepiandrosterone sulfate, synthesized in the zonas glomerulosa, fasciculata, and reticularis, respectively. Cortisol synthesis requires the action of 17α-hydroxylase on pregnenolone within the adrenal zona fasciculata; androgens also require the presence of the 17α-hydroxylase and its associated activity 17-lyase to split the side chain for the generation of C19 steroids. Corticosterone is the primary glucocorticoid in species, including the rat and mouse, in which 17α-hydroxylase is not expressed in the zona fasciculata. Reflecting their class names, mineralocorticoids mediate electrolyte and fluid homeostasis and glucocorticoids control immediate energy requirements and dampen inflammatory responses as part of the stress response, as well as the longer term regulation of bone, carbohydrate, and lipid metabolism. Synthesis of adrenal androgens is generally low; however, it is important for females and significantly increased by ACTH (369, 371, 486).

Adrenal steroids act through the MRs, GRs, and androgen receptors (ARs) which are members of the steroid hormone receptor family, along with the estrogen and progesterone receptors (ERs and PRs), within the superfamily of ligand-regulated transcription factors that comprises, in addition to steroid and thyroid hormone receptors, the retinoic acid, vitamin-D, peroxisome proliferator-activated, and retinoid-X receptors. Based on the phylogeny of their structures and those of their ligands and enzymes required for ligand synthesis and metabolism, several schemas for the evolution of the steroid hormone receptors have been proposed, with ER being the oldest. Whether MR or GR and PR are closer to the primordial receptor is a matter of continuing discussion (3, 21, 45, 224, 243). In one schema, the MR, which differs the most from the other adrenal steroid receptors, is

closest to the ancestral receptor, while GR and PR share a common more immediate ancestor (224, 243).

Dehydroepiandrosterone and its metabolites are thought to have been the ligands for the ancestral ER. Evolution of the 17β-hydroxysteroid dehydrogenases providing for the synthesis of estrogens and androgens occurred at about the same time as the ligand binding domain (LBD) of the AR evolved to accommodate C19 rather than C21 steroids (21). The requirement for a separate system to regulate energy and electrolyte homeostasis occurred relatively recently. The consensus is that 11-deoxycorticosterone (DOC), corticosterone, and cortisol were the ligands for MR before the CYP11B2 enzyme required to make aldosterone from DOC evolved from a gene duplication of the DNA of the primordial CYP11B1, the last enzyme in corticosterone and cortisol synthesis, following the divergence of the two receptors (3,21,45,54,134,224,243,345). Some mammals, do not have a separate CYP11B2 gene, among these are cattle from whence aldosterone was first isolated (198). Nonetheless, only aldosterone is synthesized from DOC in the zona glomerulosa of these adrenals, as 17β-hydroxysteroid dehydrogenase (HSD) is not expressed in the zona glomerulosa (330, 335, 339).

Glucocorticoid synthesis is under the control of the hypothalamic-pituitary-adrenal axis and has a distinct circadian rhythm with peak production just before awakening. Hypothalamic corticotropin releasing hormone (CRH) neurons release CRH in response to vasopressinergic stimulation from the suprachiasmic “clock” neurons (22, 432), as well as to stimulation from other brain centers perceiving stress, including hypoglycemia (422). Activation of MR and GR on CRH neurons by cortisol or corticosterone provide feedback control (204). Both MR and GR are important for the long-term adaptation of the hippocampus to stress and its modulation of the HPA (89). Studies using selective antagonists demonstrate that MR, not GR, are crucial for the habituation response to repeated stress on the release of corticosterone through negative feedback on the release of CRH from hypothalamic CRH neurons (77, 154). Signals from the hippocampus also modulate CRH neuron activity. Among many functions, CRH stimulates the release of adrenocortical trophic hormone (ACTH) from pituitary corticotrophs (204). ACTH acutely stimulates the mobilization of cholesterol into the mitochondria of adrenocortical cells by steroidogenic acute regulatory protein where the first step in steroidogenesis, side chain cleavage by Cytochrome P450scc, occurs. ACTH increases aldosterone and adrenal androgen synthesis, as well as glucocorticoid synthesis. ACTH also increases the expression of Cytochrome P450scc and in particular CYP11B1, 11β-hydroxylase, the last step in the synthesis of cortisol and corticosterone within the zona fasciculata.

Aldosterone synthesis is regulated primarily at the level of CYP11B2, aldosterone synthase, the last and unique enzyme for aldosterone synthesis, which is increased by Angiotensin II (AII) through its type 1 receptor (AT1R) and low sodium and suppressed by low potassium (175, 215, 216, 382). DOC is the substrate for CYP11B2 as well as CYP11B1 in those species without adrenal 17β-hydroxysteroid dehydrogenase including the rat and mouse.

Progesterone is a competitive MR antagonist with a similar affinity for the MR as aldosterone. It circulates in low concentrations in comparison to aldosterone, cortisol, and

corticosterone in males and nonpregnant females and is inactivated by several enzymes in aldosterone target epithelia of the kidney (363). Progesterone levels reach significant levels in pregnancy and the luteal phase of the estrus cycle in species with a distinct luteal and follicular phase, including women. Inhibition of the MR by progesterone in aldosterone target cells activates the RAAS during the second half of the estrus cycle, resulting in the doubling of aldosterone levels in women during the luteal phase (41, 75, 183). Over 45 years ago, it was suggested that premenopausal women be screened for aldosterone producing adenomas only during the follicular phase of the cycle to avoid spurious diagnoses of hyperaldosteronism during the luteal phase (183), a suggestion that was reiterated recently along with a call for new reference ranges for the Aldosterone:Renin ratio used to screen patients for Primary Aldosteronism (PA) in premenopausal women (8). During normal pregnancy, there is a progressive and tightly controlled increase in aldosterone along with progesterone, essential to maintain fluid and electrolyte homeostasis during the volume expansion required for normal placental growth and function (152,153). While elevated aldosterone levels and inappropriate activation of the MR are associated with hypertension and cardiovascular disease, healthy premenopausal women, have a lower risk for these diseases, despite higher aldosterone levels, demonstrating the complexity of steroid interactions (41).

The number of cells within the zona fasciculata greatly exceeds that of the zona glomerulosa which comprises a narrow rim of only a few cells deep under the outer capsule of the adrenal. Thus, the mass of cortisol or corticosterone synthesized vastly exceeds that of aldosterone. To further regulate ligand availability, individual target cells evolved the ability to inactivate or reactivate cortisol and corticosterone before it reached the MR or GR.

Prereceptor regulation of steroid ligands is an essential mechanism for regulating receptor activation and ligand specificity. HSDs evolved concomitantly with the receptors and ligands and regulate the availability of steroid ligands (inactivating or activating) within the target cell and provide cell type-specific “prereceptor regulation” of ligand binding (352). The steroid dehydrogenases 17β-HSD and 11β-HSD inactivate or activate C17β steroids, estrogens and androgens, and C11β steroids, cortisol and corticosterone, respectively. 11β-HSD2 also converts 11β-hydroxy-testosterone to 11-keto-testosterone, the active androgen in fish. As MR and GR took on separate functions, inactivation of glucocorticoids by 11β-HSD2 in aldosterone target cells provided extrinsic selectivity of the MR for aldosterone in tissues involved in fluid and electrolyte homeostasis or transport, including the renal tubular, colon and salivary gland epithelium, subcommissural organ, and a small number of aldo sensitive neurons of the nucleus tractus solitarius (NTS) (21,147,164). Placental 11β-HSD2 is also crucial for the maintenance of optimal glucocorticoid levels in the fetus despite elevated levels required for the high energy requirements of the dam (69, 81, 484). Discovery of this prereceptor regulation mechanism partially solved a vexing problem of ligand specificity for the MR in different tissues.

Cloning of the MR gene confirmed that there is only one MR that has similar affinity for cortisol, corticosterone, progesterone, DOC, and aldosterone *in vitro*, but nonetheless exhibits different ligand “preference” depending on the tissues: aldosterone in the kidney and colon epithelia, and cortisol and corticosterone in most of the brain. In older literature

the MR has been called the Type 1 corticosteroid receptor due to its higher affinity, as opposed to the lower affinity Type 2 corticosteroid receptor, the GR (17, 94, 133, 373). The affinity of the GR for cortisol and corticosterone is approximately one tenth that of the MR for these glucocorticoids; the affinity of GR for aldosterone is about one tenth that of cortisol and corticosterone. In mammals, the glucocorticoids cortisol and corticosterone circulate at 100-fold (free) to 1000-fold (total) the concentration of aldosterone, so even though binding to corticosteroid binding globulin (CBG; transcortin) and albumin reduces free glucocorticoids by about 80% to 90%, that which remains still is far greater than plasma levels of aldosterone. Consequently, under physiological conditions most MR, including those of the myocardium and brain, are occupied by nonstress levels of glucocorticoids (17, 89, 114, 132). GR are thought to be occupied by cortisol or corticosterone primarily at the zenith of the circadian cycle and during stress. CBG does not simply limit free steroids in the plasma; it protects glucocorticoid from degradation and maintains a dynamic equilibrium of free and bound plasma glucocorticoid levels for tissue needs (101, 287). CBG-null transgenic mice have a significantly dampened corticosterone surge and display altered behavior in response to stress partially remediated by intrahippocampal infusion of corticosterone (308). DOC is also bound to CBG, however under normal circumstances, due to its lower total concentrations, relatively little free DOC is available receptor binding in comparison to cortisol, corticosterone or aldosterone (252).

11β-hydroxysteroid dehydrogenases: prereceptor regulators of MR and GR ligands, Figure 2. The syndrome of apparent mineralocorticoid excess (AME) provided a clinical model to discover the role of 11β-HSD2 in aldosterone selectivity for MR (110, 139). AME is characterized by hypertension and frank or easily provoked hypokalemia and alkalosis, as expected for PA, except that, while plasma cortisol levels are normal, renin, and aldosterone are very low. Measurement of urinary cortisol metabolites demonstrated a decrease in total cortisol production and impaired conversion to cortisone (110,311,428,429,450,480). It is now known that inactivating mutations of the 11β-HSD2 gene and pharmacological inhibition of the enzyme by the excessive ingestion of licorice and its synthetic analog carbenoxolone allow cortisol or corticosterone to activate MR in aldosterone target cells, producing AME (34, 110, 139, 428, 464, 479). High levels of cortisol in ectopic ACTH syndrome are presumed to saturate the 11β-HSD2 in aldosterone target cells, allowing cortisol to activate MR and produce an AME-like syndrome (451). While the consequences of activation of the MR by aldosterone or glucocorticoids are the same for some functions (138, 450), they are different for others (93, 94, 180, 338, 373, 452, 453, 482). Recognition of these differences and their underlying mechanisms will allow more specific targeting with therapeutic agents.

Discovery of the mechanisms of prereceptor regulation of cortisol and cortisone may have been delayed by discrepant data from whole cell and *in vivo* studies compared to enzyme kinetic studies done with tissue homogenates in which cells and organelles were broken, mixing enzymes, cofactors, and substrates that normally are in separate subcellular compartments (169, 170). We now know that there are two, perhaps more, 11β-hydroxysteroid dehydrogenases, 11β-HSD1, and 11β-HSD2 (164, 168, 173, 251, 310). 11β-

HSD1 and 11β-HSD2 are products of distinct genes that are located primarily in endoplasmic reticulum (ER) where they are associated with the inner membranes (323, 334).

11β-HSD1 is a reversible dehydrogenase that in most tissues 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 to both the GR and MR (409). In homogenized cells 11β-HSD1 functions as a dehydrogenase. The obligate cofactor for 11β-HSD1 reductase activity is NADPH. NADPH does not readily cross the ER membrane, thus NADPH formed outside by glucose-6-phosphate dehydrogenase cannot reach the 11β-HSD1. Without the microsomal hexose-6-phosphate dehydrogenase (H6PDH), to reduce $NADP^+$ and generate NADPH, 11β-HSD1 is a dehydrogenase (19, 52). For example, 11β-HSD1 functions primarily as a dehydrogenase in preadipocytes, as these do not express H6PD. Upon differentiation and expression of H6PD, 11β-HSD1 becomes a reductase (53). The expression of 11β-HSD1, but not H6PD, in preautonomic nerves of the PVN suggests that MR in these neurons may normally be regulated by endogenous aldosterone (71).

11β-HSD2 is a unidirectional NAD^+-dependent dehydrogenase of the ER that converts cortisol and corticosterone to the inactive cortisone and 11-dehydrocorticosterone (173, 323, 418, 512). It is coexpressed with the MR in aldosterone target cells where a majority of MR may be tethered to the enzyme within the ER in the absence of aldosterone (322,323,334). Quantification of 11β-HSD2 protein does not always predict function. Under nondenaturing conditions a significant proportion of the 11β-HSD2 exists as an inactive dimer. Addition of reducing agents β-mercaptoethanol or dithioerythritol allows the detection of the expected ~40 kDa band in Western blot analysis and significantly increases NAD^+-dependent conversion of ^{3}H-corticosterone by kidney microsomal protein with a K(m) of ~15 nmol/L, similar to that of the cloned and expressed enzyme (169). Prereceptor regulation of the relative concentrations of aldosterone and glucocorticoids by 11β-HSD2 may have its own braking system, as the product cortisone was found to directly inhibit aldosterone-induced MR activation in an *in vitro* system (334). Estrogens significantly increased the expression of 11β-HSD2 message and protein, primarily as dimers, in the rat kidney, while decreasing that of 11β-HSD1. However, the increase was not associated with an increase in *in vivo* conversion of corticosterone to 11-dehydrocorticosterone as measured by urine metabolites. *In vitro* activity was also unaffected by the increase unless the 11β-HSD2 dimers were reduced to monomers, suggesting that enzyme dimerization rapidly regulates 11beta-HSD2, thus MR, activity (170). The functional significance of this increase in 11beta-HSD2 upon conversion of 11β-hydroxy-testosterone to active 11-ketotestosterone in the kidney has not been reported, but it does appear to have a function in the ovary (301).

Expression of 11β-HSD2 protein is limited in most parts of the adult brain (147, 171, 307, 405) where most MR are occupied by glucocorticoids. A noted exception are a few neurons of the NTS which expresses both MR and 11β-HSD2. These neurons are activated by a low sodium intake associated with high aldo levels and mediate an increase in sodium appetite (147, 148). The sympathetic nervous system is overactive in PA (216, 248); however, despite experimental evidence that aldosterone acts within the paraventricular nucleus of the hypothalamus (PVN) and amygdala to mediate hemodynamic and renal effects through

modulation of the sympathetic nervous system and salt appetite (28, 49, 118, 175, 367, 368, 389, 487), abundant MR, but no 11β-HSD2 has been detected in these areas (147). Notwithstanding, the efficiency with which tritiated corticosterone is converted to 11-dehydrocorticosterone by minces of rat brain tissue suggests dehydrogenase activity by 11β-HSD1, which is highly expressed in the brain. The existence of another 11β-HSD has been postulated from kinetic studies (158, 160, 168, 173, 418), including a unidirectional $NADP^+$-dependent cortisol dehydrogenase that appears to be specifically expressed in the brain (336). H6PD message and protein were found in general areas of the brain along with 11β-HSD1 (178); however, these studies did not address individual cells. MR, but not GR, are expressed in preautonomic neurons in the PVN identified by a retrograde tracer injected in the intermediolateral cell column of the spinal cord. 11β-HSD2 was not detected in the PVN, confirming several earlier reports. 11β-HSD1, but not H6PD, was coexpressed with MR in tracer-identified neurons, suggesting that aldosterone selectivity of MR in these neurons may be conferred by dehydrogenase activity of 11β-HSD1 (71).

Because 11β-HSD1 participates in normal physiology as a reductase and an amplifier of glucocorticoid action in specific cells by regeneration of active steroid from circulating cortisone and 11-dehydrocorticosterone, it has recently become a target for the development of specific treatments of the metabolic syndrome, type II diabetes, obesity, and the dementia associated with aging in which excessive cortisol action has a role (15, 20, 105, 221, 321, 408, 441, 465). 11β-HSD1 also participates in the metabolism of 7-ketocholesterol, which has potential implication in the development of atherosclerosis and dyslipidemia (404). In addition, an 11β-HSD1 polymorphism has also been identified as a risk factor for depression (96).

While generally either 11β-HSD1 or 11β-HSD2 are found in a cell, both enzymes may be expressed in the same cell (106, 438). In the case of the granulosa cell, the predominance of one 11β-HSD over depends on the gonadotropin concentrations (437). In summary, the regulation of intracellular glucocorticoid concentrations by 11β-HSD1 and 11β-HSD2 is crucial for the regulation of both MR and GR activation in a variety of tissues and attention to the availability of cofactors must be considered when analyzing their activities (71, 127, 221, 304, 312, 425, 427, 439).

Prereceptor inactivation of DOC and progesterone also provides aldosterone selectivity to the MR (55, 363, 411). DOC is a potent mineralocorticoid *in vitro* that has similar affinity for the MR as aldosterone (18, 411). In the adrenal zona glomerulosa 21-hydroxylation of progesterone yields DOC which is then converted to aldosterone by aldosterone synthase under the control of the Renin-angiotensin-aldosterone system. DOC is also synthesized by 21-hydroxylation of circulating progesterone in many tissues (160, 381, 436, 500) independently of the RAAS. DOC circulates in concentrations approximating those of aldosterone, particularly during pregnancy, though most of it is bound to CBG (252). 17β-Hydroxysteroid dehydrogenase type 5 (17β-HSD5), also called AKR1C3 in the human, is a member of the aldo-keto reductase family and has multiple functions (411). In addition to converting androstenedione to testosterone in androgen target cells, it is a 20α-hydroxysteroid dehydrogenase that converts DOC to the inactive 20α-hydroxy-DOC, thus providing prereceptor ligand regulation for the MR in aldosterone target cells of renal

tubular and colon epithelial cells (411). Progesterone also has high affinity for the MR and circulates in relevant concentrations to compete with aldosterone in pregnancy and the luteal phase (364). There are several enzymes in kidney tubular epithelial cells including 17β-HSD5 that render progesterone inactive at the MR (363).

Extra-adrenal steroid synthesis as prereceptor ligand modulation has been proposed for GR and MR as a way to augment local steroid concentrations that would act in an autocrine or paracrine fashion. Several labs have documented the existence of all of the enzymes required for adrenal steroid synthesis from cholesterol within the brain of rats and humans (86, 160, 161, 166, 174, 274, 275, 300, 500); however, the relevance of the very small amounts synthesized to normal physiology has not been clearly demonstrated. Several tissues have local RAS that may regulate extra-adrenal aldosterone synthesis (276) and mRNA for CYP11B2 in the hippocampus and cerebellum, but not hypothalamus and brain stem were found to be increased by a chronic low salt diet (493). The relevance of this finding if it is confirmed is uncertain, as there is no evidence that MR in these areas of the brain are normally activated by aldosterone. However, as will be discussed below, aldosterone appears to act through GPER, formerly called GPR30, which does not bind cortisol or corticosterone at physiological concentrations (119,124,188,190) and which is expressed in the brain.

It has been shown that inhibitors of the late pathways of corticosterone and aldosterone synthesis in the brain inhibit the hypertension of the sodium challenged Dahl Salt-Sensitive rat, suggesting the participation of relevant amounts their synthesis in the CNS for autocrine or paracrine function in this model (177, 179, 227).

Extra-adrenal synthesis of cortisol, corticosterone or aldosterone in the heart, particularly the failing heart, has been an area of great controversy (97, 165, 415, 416, 435, 446, 473, 496), however the consensus at this time is that aldosterone synthesis in the heart does not occur in relevant amounts (6, 86, 165, 446, 447). Reports of extra-adrenal synthesis of aldosterone in other organs await replication (48).

Steroid hormone receptors share common structural domains that reflect function: an amino-, or N-terminal region (NTD), DNA binding domain (DBD), hinge, and the LBD at the carboxy-terminus (18, 113, 279, 344, 461). The structures of the MR and GR are more similar to each other than to other steroid hormone receptors, with homologies of about 57% in the LBD, 94% in the DBD, and 15% in the NTD (345, 461).

The homology between the LBDs results in similar affinity of the MR for cortisol, corticosterone, and aldosterone which is 10-fold that of GR for cortisol and corticosterone. The importance of physiological concentrations and proportions of ligands when studying MR and GR mediated functions cannot be overemphasized. Similarities in the LBDs of GR and MR also means that aldosterone at high pharmacological concentrations activate GR. This does not occur *in vivo* because aldo production is so low in comparison to that of cortisol, even in PA. However, GR activation by high levels of mineralocorticoids may become an artifact of experimental design leading to misinterpretation. Similarly, pharmacological doses of glucocorticoids overwhelm protection by 11β-HSD2 and activate

aldosterone-target MR and nonphysiologically high levels of mineralocorticoids can activate MR that do not express 11β-HSD2 and are normally occupied by glucocorticoids.

Use of **deoxycorticosterone (DOC) or its acetate (DOCA)** to study mineralocorticoid action presents another important concern for interpretation (462). DOC was discovered and synthesized several years before the more potent mineralocorticoid aldosterone was isolated and synthesized (424). Because of its significantly lower cost, DOCA, is often used as a mineralocorticoid and mistakenly equated to aldosterone. However DOCA is inactive; its conversion to DOC by as yet unidentified esterases occurs with variable efficiently and is slow in some organs, particularly in skeletal muscle (462). DOC is inactivated in the renal tubule and colon epithelia by 20-ketosteroid reductase, an isozyme of the human AKR1C3 gene (411). Therefore, though DOC has an *in vitro* affinity for the MR similar to aldo, cortisol, and corticosterone, the activity of DOC in vivo in these transport epithelia is approximately 2% that of aldo. DOC and DOCA have a renal mineralocorticoid effect when used at high enough doses to saturate the AKR1C3 isozyme, however, these high concentrations of DOC are far beyond its physiological range, so in other organs, most of which do not express AKR1C3, commonly used DOC and DOCA doses may have antagonistic effects on GR, in addition to activating the MR (462). In an early clinical study, it was found that DOCA treatment exacerbated symptoms of rheumatoid arthritis and that these signs improved with the concomitant administration of cortisone (112). With our present knowledge of the importance of MR:GR interactions, it is important to reinterpret the literature that assumed that DOC and DOCA act as pure mineralocorticoids, especially in the area of nonepithelial tissue hypertrophy and fibrosis, where they may have also been inhibiting GR (462).

Steroid hormone receptors are ligand activated nuclear transcription factors, Figure 3. While some members of the steroid receptor family are found primarily in the nucleus, in the absence of ligand most MR, GR, and AR are located primarily in the cytoplasm and are shuttled to the nucleus when activated by a ligand and back to the cytoplasm when unbound and transcriptionally inactive (184, 197). In the cytosol, the receptors are bound to receptor- and cell-specific chaperone and scaffolding proteins that facilitate posttranslational modification of the receptors [phosphorylation is particularly important for MR activation (345)], ligand binding, and attachment to the motor mechanism that shuttles the receptors between the cytoplasm and nucleus (42, 142, 143, 329, 351, 353). Ligand binding to the LBD of the MR and GR unmasks a nuclear localization signal sequence that aids translocation of the receptors to the nucleus. The conformational change produced by ligand binding also uncovers a highly conserved activation function site, AF2, essential for the binding of coregulatory factors of the DNA transcription assembly. The LBD of the MR and GR also have similar dimerization sites exposed after nuclear translocation that allow them to form homo- and heterodimers with each other (345). Due to the close homology of their DBD, MR, and GR share hormone response elements (HREs) or glucocorticoid response elements (GREs).

Among the best understood chaperone proteins for the MR and GR are heat shock proteins 90 and 70 (hsp90 and hsp70) and immunophylins (83, 142, 143, 345). Regulation of chaperone proteins alter ligand binding probability; however, these proteins are not specific

for the MR and GR; they have other functions, including as chaperones for other steroid hormone receptors. Measurement of MR in subcellular fractions of mouse ventricular cardiomyocytes in which hsp90 expression is limited and in several cultured cell models in which hsp90 expression was manipulated, suggest that hsp90 shields the nuclear localization signal sequences, keeping the unbound MR in the cytoplasm (217). In the absence of sufficient hsp90 expression, MR were located primarily in the nucleus where they remained inactive until bound by ligands, as do several other steroid hormone receptors, including the ER (217). Hsp90-bound MR have been reported in the nucleus, suggesting that shedding of the hsp90 may not be essential for nuclear localization of MR (141); however, the consensus is that hsp90 is lost upon MR or GR binding to a ligand.

Upon binding to an agonist and divestment of chaperone proteins, the hinge portion of the receptor molecule flexes, allowing the N- and carboxy termini to approximate each other and uncovering the nuclear localization signal 2 (NLS2) in the LBD, and NLS1 in the hinge region (345). The receptors are then transported into the nucleus, within 10 to 20 min for the MR activated by aldosterone *in vitro*, where they form dimers and recruit cotranscription factors that stabilize their binding to the promoters of specific genes at HRE (GRE) (117, 141, 328, 345, 351, 353, 379). A nuclear export signal located between the NSL1 on the hinge and the DBD is important for subsequent movement of the MR out of the nucleus and in to the cytosol (345).

Dimer formation is determined by the conformation of the DBD and parts of the LBD which are defined in part by the activating ligands (125, 443, 461). The homology of their DBD and LBD allow GR and MR to form heterodimers in addition to homodimers before binding to the same HRE (329,397,423,443,445,461). Homodimers of MR and GR have different transcriptional efficiencies than their heterodimers depending on the HRE (reporter gene) *in vitro* (461) and are probably important regulators of MR transcriptional activity *in vivo* (2). The intermittent secretion of glucocorticoids to maintain glycemic control and respond to stress, superimposed upon their prominent circadian secretion, controls the activation of GR, thus the formation of MR:GR heterodimers. MR homodimers predominate at low circadian levels of glucocorticoids; heterodimer and GR homodimer formation would be highest during stress. This may be particularly relevant in the brain, where glucocorticoids are the ligand for most neurons and the relative expression of MRs and GRs differ between neuron types, including neurons in different areas of the hippocampus (89).

The relative amounts of MR and GR expression and that of 11β-HSD2 differ in the epithelial cells of each segment of the kidney nephron. Results from *in vivo* studies using physiological concentrations of ligands, suggest that MR:GR heterodimers, rather than MR:MR homodimers, are most efficient in initiating the transcription of genes associated with ion channel activation, the primary mineralocorticoid activity in this prototypical aldosterone target tissue (2). Similarly, MR expressed by itself in cultured neuronal and colon epithelial cells was found to be unable or inefficient in initiating transcription at several HREs including that of epithelial sodium channels (ENaC); transfection with GR markedly enhanced transcription (445). Conversely, in a different *in vitro* study using, Na/K-ATPaseβ1, another gene classically associated with mineralocorticoid function, as the reporter gene, either MR or GR could initiate transcription, but coexpression of MR and GR

repressed transcription. When the MR NTD, which is significantly larger than that of the GR, was mutated to that of the GR (98), transcription efficiency of the heterodimer was like that of either homodimer, suggesting that the promoter site on the ATPaseβ1 gene requires symmetry for dimer binding or recruitment of transcription coactivators. Clarifying the role of MR and GR homodimer and heterodimer transcriptional efficiency for different genes may lead to a strategy for targeted therapeutics (489).

Coregulatory proteins, the coactivators, and corepressors, interact at activation function regions, AF1 in the NTD and AF2 in the LBD, to modulate transcription efficiency of the receptor. Most corepressors bind a specific segment of the AF1. As GR and MR differ the most in their NTDs, differential recruitment of cell-specific corepressors theoretically provides for differentially regulated gene transcription (120, 131, 345, 423, 461). The list of coregulatory proteins for the MR is still growing and includes members of the large steroid receptor coactivator family (SRC), PBP/TRAP220, and CREB-binding protein (CBP) as coactivators, and NCoR and SMRT as corepressors (293, 294, 490, 495). For example, small ubiquitin-related modifier-1 (SUMO-1) ubiquitin9 and steroid receptor coactivator-1 (SRC-1) form a coactivating complex with the NTD of the activated MR and enhance its transcriptional activity for ENaC, a prototypical MR-regulated gene in nephron aldo target epithelia expressing both MR and 11β-HSD2 (494). When 11β-HSD2 activity is deficient or absent, as in Apparent Mineralocorticoid Excess syndrome or licorice abuse, endogenous cortisol or corticosterone produce the same transcriptional effect on the ENaC gene (311, 428). The distinct anatomical distribution of different splice variants of SRC-1 in neurons may be responsible for the opposite effect that stress levels of corticosterone have on the release of corticotrophin releasing hormone from neurons of the PVN and central amygdala through MR and GR (299).

To identify cofactors specific for the MR, those that differentiate MR from GR transactivation, the NTD of the human MR was used as bait in a yeast two-hybrid assay, resulting in the isolation and identification of ELL (11-19 lysine-rich leukemia), an RNA polymerase II elongation factor. Subsequent transcription assays in several cell systems demonstrated that ELL is a potent coactivator for human MR-mediated transcription and significant corepressor of GR-mediated transcription, but did not alter transcriptional activity of AR or PR (346). A similar type of study using a human brain cDNA library and a segment of the human MR AF1 sequence as bait demonstrated that DAXX and FLASH were coactivators for both MR and GR, while FAF-1 only coactivated MR (333). Further analysis of coregulator specificity should provide information about the complex and cell type specific actions mediated by the MR, the GR and their interactions necessary for the development of MR:ligand-selective peptide antagonists to target MR in specific cells under specific contexts, for example, in the injured or poorly perfused cardiomyocyte (489), but not hippocampal neurons (402).

Ligand independent transcriptional activation of the MR has been suggested. While MR and GR are primarily in the cytoplasm of cells in the adrenalectomized animal, a few receptors are found in the nuclei, and MR have been reported to be activated in under conditions of high oxidative stress despite no increase in circulating agonists. Ras-related C3 botulinum toxin substrate 1 (Rac1) is a Rho-family small GTPase expressed fairly ubiquitously.

Activated Rac1 has been proposed as mediator of ligand-independent MR transcriptional activity under high reactive oxygen stress in several tissues, including the chronically failing heart and kidney (128,320,413). Under normal conditions NO suppresses transcriptional MR activity, suggesting that NO treatment mitigates excessive and pathophysiological effects. In contrast, peroxynitrite formed by the reaction of NO with excessive ROS was found to induce ligand independent MR nuclear translocation and transactivation without activating GR (388). An alternative proposal is that in many nonepithelial cells the MR is bound to glucocorticoid in a quiescent conformation that is rendered active under conditions of severe oxidative stress such as that of heart failure, resulting in inappropriate MR activation (135).

The regulation of MR and GR expression is crucial for their function. Two promoter sites on the MR gene have been identified, P1 and P2. The transcription factors initiating MR gene transcription through these promoter sites may be cell-type specific. In one highly synthetic system, MR gene transcription was activated by GR homodimers at both sites, MR homodimers initiated transcription only at P2, and together, MR and GR induced transcription of the MR gene more efficiently, however mutational analysis found that this synergy did not occur at the MR gene HRE; the mechanism of transcriptional activation has not been reported (505). In other cell types expressing GR and MR, cortisol and corticosterone, but not the synthetic glucocorticoid dexamethasone, efficiently promote transcription of the MR gene through P1 and P2, while aldosterone increased transcription primarily through the less efficient P2 promoter (461). In contrast, MR gene expression in murine embryonic stem cells (ESCs) was initiated by aldosterone activation of MR at both the P1 and P2 promoter sites on the MR HRE during and after their differentiation into neurons (315). The nuclear transcription factors Spl and AP-2 bind to both the P1and P2 promoters providing addition transcriptional regulation of the MR (344, 505).

Discrepant reports about the effects of adrenalectomy and steroid treatment on MR and GR mRNA may well be due to differences in the part of the brain studied and the use of very large amounts of corticosterone or aldosterone that may activate both MR or GR. (5, 204). More physiological levels of replacement in the adrenalectomized rat had different effects on MR and GR expression and activation in tubular epithelial cells of different segments of the nephron (2). Levels of MR mRNA and protein were found to be increased in the PVN of rats on a chronically low, compared to high, sodium intake. Predictably, plasma aldosterone concentration were significantly greater in the rats on a low salt diet, while corticosterone was similar in both groups (71). This suggests that MR transcription in the PVN may be modulated by aldosterone as reported from *in vitro* studies (315, 461). Progesterone is generally an MR antagonist; however, it has been shown to increase neuronal MR promoter activity and increase MR mRNA *in vitro* and in rats whose ovaries and adrenals were removed (67). The MR promoter region also has a potential estrogen response element (266), which is interesting in the context of the mammary ductal epithelial cell that expresses both MR and 11β-HSD2 (396) and the finding that 11β-HSD2 expression is increased by estrogen (170).

The G protein-coupled receptor 48 (GPR48) deletion mouse develops peudohypoaldosteronism, with high aldosterone levels but renal salt wasting due to deficient of MR expression. This model revealed the importance of GPR48 in stimulating MR

expression through the cAMP/protein kinase A pathway and a noncanonical cAMP-responsive element located in the MR promoter (468).

Splice variants of the MR mRNA found in the rat and human are of uncertain physiological significance (256, 504, 510). *In situ* hybridization studies of the developing rat hippocampus demonstrated significant differences in the proportions of three MR spice variants comprising the same coding regions in different parts of the hippocampus that correlated with stages in neuronal development (460). The expression of these MR variants in the different areas of the hippocampus was disrupted by adrenalectomy. The authors proposed that the different MR transcripts contributed to the regulation of the complex processes of neurogenesis, migration, and maturation in the developing hippocampus (460). The MR and GR genes both have two strong Kozac consensus sites, however, to date studies demonstrating a significant difference in transcriptional efficiency between the two MR transcripts have been limited to highly artificial systems and have as yet not proven to be physiologically important (345). Gain or loss of function mutations of MR and GR genes resulting in severe disease (74, 151, 332) and polymorphisms with more subtle implications have been described in the human (40, 99, 421, 454, 456), some of which are known to alter the risk for hypertension and/or depression which will be described more fully below.

Epigenetic events allow for the silencing of gene expression necessary for cell differentiation by altering the degree of DNA methylation, covalent modification of histones adjacent to a given gene thereby controlling access of transcription factors, and noncoding RNAs, including microRNAs that modulate protein coding RNA (230). While most epigenetic events occur during cell differentiation, they also provide a mechanism for long-term and relatively stable adaptation to the environment. Methylation of cytosines adjacent to guanines (CpG sites) in gene promoter regions generally decreases transcription and tends to be more resistant to reversal than histone modification by acetylation, methylation, and phosphorylation.

Methyl-CpG-binding protein 2 (MECP2) is an example of a mechanism for transcriptional repression. MECP2 binds to symmetrically positioned methylated CpG sites in the promoter regions of genes subject to transcriptional silencing after DNA methylation, including the GR and MR genes. Upon binding to the chromatin, MeCP2 interacts with histone deacetylase and the transcriptional corepressor SIN3A, resulting in deacetylation of core histones, causing them to adhere more closely to the DNA, preventing access to transcription factors (13). Loss of function MeCP2 mutations have been documented in most Rett syndrome patients and transgenic mice bearing these mutations recapitulate many aspects of this progressive and devastating developmental disorder, including anxiety, loss of sleep/activity cycle, and motor and cognitive deficits, demonstrating the importance of normal repression of gene transcription during the development (87). Treatment of these mice with corticosterone during their first week of postnatal life is reported to produce paradoxical changes in MR and GR expression in the hippocampus and partial normalization their behavior after weaning (87).

An example of a factor that enhances transcription through epigenetic changes is nerve growth factor-inducible factor A (NGFI-A), a member of a family of immediate-early gene-

encoded transcription activators that is highly expressed in the hippocampus. NGFI-A binds specific structures in the promoter regions of target genes to promote histone acetylation and chromatin demethylation by DNA demethylases (472). The GR gene is among those targeted by NGFI-A.

As might be predicted, DNA methylation of exon 1 of the gene for 11β-HSD2 is least in aldosterone target tissues, where its expression is highest (9). Activation of the MR in the renal tubule by aldosterone increases the transcription of several genes including Sgk1 and ENaCα. Murine histone H3 lysine-79 methyltransferase (mDot1a) forms a repressor complex with Af9 which hypermethylates the ENaCα gene, thus represses its transcription. Sgk1 phosphorylates Af9, inactivating the repressor complex, thus allowing the ENaCα promoter to become hypomethylated, thus more accessible for transcription (507, 508). Polymorphisms in the human Sgk1 gene has been associated with blood pressure in two different cohorts of men (57). Epigenetic changes altering the expression of enzymes required for the synthesis and catabolism of adrenal steroids are important determinants of cell-type specific function (232).

The epigenetic effects of stress and glucocorticoids on the limbic system and HPA were recognized long before the molecular bases for these changes were known (230). Ontogeny of the MR and GR continues after birth in mammals, reaching adult levels in rats at about 1 and 3 weeks of age, respectively (393). The number of GR but not MR are significantly influenced by the early environment (296, 297, 393), a phenomenon now known to be a crucial epigenetic event influencing the ability to cope with psychological stress, as well as energy metabolism and cardiovascular health as an adult (68). Pioneering work by Meaney on the long-term effects of different levels of maternal attention to their pups on their behavior as adults. Adult rats raised by more interactive dams with high licking and grooming behavior, compared to those who had been adequately fed and groomed by less interactive dams, have greater hippocampal GR expression, dampened hypothalamic-pituitaryadrenal (HPA) activation and less fear behaviors in response to acute stress (296, 297, 407, 472, 506). These effects on the adult progeny were reversed by cross-fostering. This relatively mild and benign increased stimulation during the first week of postnatal life increased hippocampal serotonin (5-hydroxytryptamine, 5-HT) turnover and NGFI-A expression. Increased NGFI-A was associated with increased demethylation of hippocampal GR, thus greater GR expression in the progeny of the high licking/grooming dams persisting into adulthood (390, 434, 471). The degree of GR gene methylation at the NGFI-A binding site was similarly correlated with HPA activity and cortisol levels in women (109).

More severe and/or chronic stress, iatrogenic glucocorticoid excess, or inhibition of the 11β-HSD2 during gestation and early life result in a hyperreactive HPA, and deleterious effects on energy metabolism, cardiovascular function, cognition, and greater anxiety behavior in the adult in experimental animals and humans (208, 317, 337, 406, 422). Effects of glucocorticoids on phenotype programming can persist over generations and be transmitted by the sire as well as the dam in experimental animals (104). Part of the mechanism for these effects is a decrease in the methylation of MeCP2 binding sites on the arginine vasopressin gene, resulting in increased aVP expression and stimulation of ACTH release,

thus increased glucocorticoid synthesis by the adrenal upon relative minor stress, resulting in deleterious effects of chronically high glucocorticoids on many systems (316).

Epigenetic changes induced by stress are not limited to early life experiences (230, 291). Biochemical and behavioral consequences of chronic social stress in adolescent mice were evident immediately after cessation of the stress regimen, including a significant decrease in the expression of hippocampal MR and GR mRNA, increased corticosterone levels with dampening of the circadian rhythm, and greater anxiety related behaviors compared to unstressed mice (426). Twelve months later the relative decrease in MR expression and increased anxiety-like behavior were still evident, suggesting epigenetic effects (426). The transcriptional response to an acute stress level dose of glucocorticoids differs between naïve rats and those having experienced chronic stress in the past, including altered expression of genes for enzymes involved in DNA and histone modulation and an increase in those associated with apoptosis in the dentate gyrus (85).

Excessive continuous GR activation in depression and Cushing's disease increases arousal at the expense of cognition (29). As in animal studies, methylation of the GR gene differs in different areas of the brain in humans, however no differences were found when GR methylation patterns were compared between those with major depressive disorder and controls (11). Comparative little is yet known about the epigenetic regulation of the MR (230).

In summary, due to their homology, MR and GR share ligands and many chaperones, HREs, and transcription coregulatory proteins. Coregulatory proteins and relative expression of MR:GR, as well as the expression of 11β-HSD1 and 2, enzymes that modulate the concentrations of cortisol and corticosterone within the cell, are cell-type and context dependent. MR and GR form homodimers and heterodimers depending on the relative amounts of activated receptors, the functional consequence of which we are just beginning to appreciate. Clearly, the transcriptional functions of the MR and GR do not conform to the simple lock and key model of receptor activation, Figure 3. In addition to providing a mechanism to silence genes during cell differentiation, epigenetic changes modulating the expression of proteins including the GR and MR, are a mechanism for adaptation to the environment that under some circumstances is pathological.

Rapid nongenomic actions of the membrane-associated MR and other members of the steroid hormone receptor superfamily are mediated by classical cell signaling pathways and do not require transcription (72, 195). Rapid steroid effects were reported 70 years ago by Hans Selye (410) and for aldosterone within 3 years of its isolation (145). It was later demonstrated that aldosterone mediated both rapid efflux of ^{22}Na from arterial smooth muscle that was inhibited by MR antagonists, but not the transcription inhibitor actinomycin, as well as delayed effects that were dependent upon transcription and protein synthesis (313). Rapid nongenomic MR effects may result secondarily in transcriptional events, obscuring the separation between transcriptional and rapid signaling effects. Studies have also been complicated by confusion of rapid nongenomic effects mediated by steroid hormone receptors and those mediated by steroid hormones through G-protein coupled receptors independently of their cognate steroid hormone receptor (124, 190).

Methods similar to those used to demonstrate the membrane association of the estrogen receptors (ERα and β) (205, 207) have been used to study the MR, including the use of aldosterone conjugated to BSA that prevents the steroid from crossing the plasma membrane (43, 150, 191, 271). MR was shown to colocalize with the EGFR within the plasma membrane by coimmunoprecipitation and FRET and disruption of the membrane with cyclodextrin decreased this association (196). A 24 h incubation with very high levels of aldosterone caused most MR, including those associated with EGRF, to enter the nucleus, however inhibition of Hsp90 prevented MR nuclear translocation without altering the number of MR associated with EGRF (196). cSrc is a cytosolic tyrosine kinase important for rapid nongenomic functions of ER, PR and MR. While most of the MR molecule comprising the ligand binding, DNA binding, hinge, and N-terminal domains where coactivators and corepressors bind is necessary for classical MR transcriptional activity, a truncated MR comprising only the EF domain (C-terminal) that includes the LBD and cSrc binding site suffices for rapid EGFR transactivation and ERK1/2 phosphorylation (194). Rapid MR initiation of the cSrc dependent EGFR transactivation and ERK1/2 phosphorylation increases collagen III synthesis, a crucial component for normal repair that in excess leads to pathological vascular and cardiac remodeling (194, 473).

A palmitoylation site on the ER is thought to allow its anchoring to the plasma membrane (281, 370); however, such a sequence has not been identified in the MR sequence. MR associate with caveolins, proteins associated with lipid rafts and plasma membrane invaginations called caveoli (64, 231, 358) and caveolin-1, (Cav-1) does have a palmitoylation site to which c-Src tyrosine kinase is bound (263). Activation of MR increases the expression of both Cav1 (231) and Src (265). C-Src is implicated in the nongenomic activation by MR of mitogen-activated protein (MAP) kinase, resulting in the increase in NADPH-driven generation of reactive oxygen species, an important signaling event for normal function, but which in excess leads to vascular inflammatory damage (62, 64).

Cell signaling pathways mediating nongenomic MR effects differ for different cells and include protein kinase C (PKC), cyclic adenosine 3′, 5′-monophosphate (cAMP), and Phosphoinositide 3-kinases (PI3K), with downstream activation of a variety of cell-type specific kinases, ion channels and pumps (134, 193). PI3Ks, along with PLC, generate IP3 a second messenger crucial to many intracellular signaling events. As described above, among the events involved in rapid extra-nuclear MR effects are epidermal growth factor receptor (EGFR)-dependent phosphorylation of ERK1/2 and c-Jun NH2-terminal kinase (JNK) 1/2 kinases, and activation of MAPK kinase (MEK) and cSrc kinase (62, 63, 191, 192). While some rapid MR-mediated effects are ephemeral, for example, inotropic and chronotropic changes in cardiomyocytes (59), others persist for a relatively long time (191, 261).

Rapid transient movement of Ca^{++} is an important nongenomic effector of MR rapid action in renal tubular epithelial cells, cardiomyocytes, vascular smooth muscle cells, and neurons. Rapid nongenomic MR activation of the N^+/H^+ exchanger NHE-1 results in rapid changes in ion transport in the tubular epithelial cells of the kidney and in intracellular Ca^{++} transients necessary for vasoconstriction of mesenteric resistance vessels (303). Stretch-triggered reactive oxygen species generation in the cardiomyocytes was found to activate

redox-sensitive kinases upstream of the NHE-1, resulting in mobilization of intracellular Ca^{++} (59, 102).

Activation of NADPH oxidase and generation of reactive oxygen species (ROS) is an important mechanism of normal MR signaling in various types of cells including the macula densa, renal tubular epithelia, cardiomyocyte, and neurons of the PVN and hippocampus (59, 187, 244, 360, 513). In renal tubular epithelia rapid MR signaling through ROS derived from NADPH oxidase activation is critical for acute ion homeostasis (400); transcriptional MR effects are slower, providing tonic regulation of ion transport. MR signaling through NADPH oxidase-derived ROS produces stretch-induced slow force generation during each heart beat (59), activates presympathetic neurons of the PVN of the hypothalamus (118, 239, 487), and leads to Rac1 dependent ERK1/2 phosphorylation in hippocampal neurons, enhancing excitatory potentials (244). ROS in vascular smooth muscle cells are crucial for the rapid regulation of vascular tone by increasing IP3-mediated cytosolic Ca^{++} accumulation through the inhibition of sarcoplasmic/ER Ca^{++}-ATPase and stimulation of Ca^{++} influx through Ca^{++} channels to increase intracellular Ca^{++} (442).

MR-mediates rapid EGFR activation. EGF is a regulator of cell differentiation and proliferation, as well as repair. MR facilitates the EGF-EGFR-MEK1/2-ERK1/2 signaling cascade in several cell models by increasing phosphorylation of c-Src and EGFR (191, 195, 228, 253). MR-mediated rapid EGFR transactivation synergizes with the activation of the angiotensin II receptor type 1 (AT1R) (59, 195, 228) and is potentiated by non-MR-mediated aldosterone action through GPR30 (GPER) at physiological concentrations (24).

Na^+/K^+-ATPase pump as a mediator of rapid MR signaling. Increasing Na^+/K^+-ATPase pump activity on the basal side of transport epithelial cells is a prototypical mineralocorticoid transcriptional function ascribed to aldosterone and MR activation (3, 285); however, the complexity of the relationship of the MR with the Na^+/K^+-ATPase pump was demonstrated over 20 years ago when it was shown that the rapid suppression of baroreceptor function by aldosterone (maximal within 15 min of aldosterone infusion) was inhibited by either the MR antagonist spironolactone or ouabain, a cardenolide isolated from plants of the *Strophanthus* and *Acokanthera* genuses (262, 469). Like other cardenolides, ouabain inhibits the ion-pumping function of Na^+/K^+-ATPase; it differs from the others in that it also increases the activity of other ion channels in vascular smooth muscle and other excitable cells (38) by activating the Na^+/K^+-ATPase-associated Src, resulting in the stimulation of protein tyrosine phosphorylation (264). Depending on the cell type, this may stimulate growth and proliferation pathways, sometimes at concentrations of ouabain below those needed to inhibit Na^+/K^+-ATPase ion pump (29, 248). Na^+/K^+-ATPase and Src can be coimmunoprecipitated and are concentrated in caveoli along with the membrane associated MR (265).

An endogenous cardiotonic steroid or ouabain-like factor has been implicated hypertension and heart failure (37, 38, 176, 203, 226, 467, 470). A large amount of evidence has accumulated supporting a proposed aldosterone-endogenous ouabain pathway for slower tonic central control of the sympathetic nervous system and blood pressure (140, 226); however, the concept remains controversial because despite over 30 years of effort, the

mechanism for the synthesis of a ouabain-like molecule in a mammal has not been discovered, nor have intermediates or metabolites been isolated (202, 444).

Rapid signaling effects of the MR are cell-type and context specific. In endothelial cells, MR activation stimulates the PI3K pathway and increases NO synthase (267); in vascular smooth muscle cells, it increases myosin light chain phosphorylation (119). Aldosterone causes rapid vascular dilation and attenuation of α-adrenergic constriction of intact rat aortic arterial rings, but increases α-adrenergic constriction of aortic rings denuded of endothelium (119, 267). Thus, vascular endothelial dysfunction tips the balance between rapid aldosterone induced dilation in favor of constriction and explains discordant results of studies of human forearm blood flow (116, 327).

Genomic and nongenomic effects of the MR may act in opposition in the same cell. Increased synthesis of ENaC and Na^+/K^+-ATPase subunits are classical MR transcriptional functions (12, 247, 285). MR also rapidly activates ERK1/2 and EGF; both inhibit sodium transport through ENaC (192). MR also acutely inhibits vascular Na^+/K^+-ATPase activity, an effect that is not altered by inhibitors of gene transcription or protein synthesis, but blocked by inhibitors of the MR and protein kinase C (PKC) (12). Increased transcription of striatin by MR indirectly counters its nongenomic stimulation of vascular smooth muscle proliferation by enhancing nongenomic ER effects (357, 376).

Rapid nongenomic effects are avenues for steroid hormone receptor interaction and fine tuning of physiological effects. Aldosterone, glucocorticoids, and estradiol act through their cognate receptors to shift the balance from net secretion to net absorption in epithelia of various types, as well as cell growth and migration (212-214, 231, 377). The interaction between ER, MR, and GR may underlie gender differences that disappear after menopause, including the lower risk for cardiovascular diseases and higher risk for anxiety and depression in women compared to men with PA (14).

Striatin is a scaffolding protein first isolated from the brain that is involved with vesicular transport and interaction with the neuronal membrane. In vascular tissue striatin provides an anchor for the membrane association of ERα and is necessary for the vasoprotective ERα-mediated rapid nongenomic signaling through NO synthase (30, 39, 449). MR coprecipitates with both caveolin 1 and striatin (357), suggesting an interaction between the two membrane receptors and the possibility that rapid nongenomic MR effects leading to adaptive repair and hypertrophy that in excess cause deleterious vascular smooth muscle proliferation is countered by nongenomic ER effects inhibiting vascular smooth muscle proliferation, an effect enhanced by transcriptional MR effects increasing the expression of striatin (357, 376). *In vitro* and *in vivo* increases in aldosterone, including physiological increases by feeding a low sodium diet, were reported to increase striatin expression in the heart, vessels and cultured endothelial cells, thereby enhance rapid nongenomic ER effects (357,376). The increase in striatin was blocked by an MR antagonist. However, the mechanism for aldosterone access to MR in tissues devoid of 11β-HSD2 such as the heart was not addressed by this study (or many others). Figure 3 includes the schematic representation of possible ER and MR interaction through striatin.

The interaction between MR- and GR-mediated effects have been most thoroughly studied in the hippocampus (94, 209, 318, 372, 391) where coordinated rapid nongenomic MR and GR actions modulate arousal and anxiety (187, 511). The integration of rapid nongenomic and transcriptional effects of MR and GR are necessary for the integrated response to arousal, stress, and anxiety with that of learning in the forebrain, hippocampus and hypothalamus (187,347,419,511). Mice with a selective forebrain deletion of MR have uncontrolled arousal and anxiety that impedes cognition (29,46), while overexpression of MR (257) or reducing GR in the forebrain reduces anxiety (245). Overexpression of the MR in the dentate gyrus granule cell layer in rats also enhances the consolidation of nonspatial memory, augments short term memory, and protects against the effects of glucocorticoid excess in rats (121, 122), while selective overexpression of the MR in the basolateral amygdala of adult rats is anxiolytic and dampens to the response to acute stress (305). Activation of GR decreases the excitability of neurons produced by a stressful event, thereby restoring normal function (392); 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 (68,85). Expression of a negative transdominant GR in the dentate gyrus in rats reduced the impairment in long-term special memory produced by the administration of stress levels of corticosterone (122). While most studies involve the deleterious effects of a decrease in the MR:GR ratio (209), a decrease in functional GR creates problems as well. Transgenic mice with only half of normal GR function compensate by increasing HPA activation, resulting in a concomitant increase MR activation and hypertension (302). In summary, transgenic mice with tissue-specific alterations in the MR:GR ratio confirm the importance of this balance which varies for the different brain regions (245).

Electrophysiological studies indicate that MR associated with pre- and postsynaptic membranes in hippocampal neurons are essential for the phenomenon of long-term potentiation (LTP) required for memory and learning (187, 236, 278, 340). Corticosterone acting through MR rapidly enhanced the frequency of miniature excitatory postsynaptic potentials in hippocampal CA1 pyramidal neurons and reduce paired-pulse facilitation, probably through increased glutamate release (241). The effect was prevented by MR, but not GR antagonists, however the concentration of corticosterone required for this effect was higher than that required for MR transcriptional activity, though lower than that for GR activation, suggesting that the membrane MR has a lower affinity for corticosterone than the transcriptional or cytosolic MR (241).

Normally plasma glucocorticoid concentrations have pulsatile increases of approximately 1 h superimposed upon their circadian rhythm. The amplitude and frequency of these pulses alter the neuroendocrine and behavioral responses to stress-induced glucocorticoid surges (79, 392) that activate GR and are responsible for the appropriate graded response to and recovery from stress (236, 241, 401, 403). Thus, the health status of an individual may be one of the causes of the discrepant results of the effect of MR antagonists on affect and cognition in human studies. The other is the dose of the MR antagonist. For example, currently spironolactone at 12.5 to 100 mg daily with titration to effect is used in most heart failure regimes and for inoperable PA. As in experimental animals, short-term treatment of healthy men with 300 mg of an MR antagonist increased baseline cortisol secretion and

impaired selective attention, visual-spatial memory, mental flexibility/set shifting, and the ability to learn under stress, but had no effect on experimentally induced panic symptoms (347, 407).

Treatment of PA patients with MR antagonists benefits their cardiovascular and electrolyte parameters, yet does not ameliorate cognitive scores, while removal of an aldosterone producing adenoma and normalization of aldosterone levels significantly improves both systemic and cognitive function (7, 255). As levels of aldosterone in these patients are not high enough to compete with cortisol for MR binding in nonaldosterone target tissues, these results suggest a deleterious role for excessive aldosterone activity through a non-MR-mediated mechanism. As mentioned above, MR antagonists increase performance on psychosocial measures of quality of life and cognitive tests in patients with severe cardiovascular complications (84, 218) associated in part with increased pulmonary function and oxygenation (4), but had deleterious effects in those with milder disease (32), demonstrating the importance of assessing and optimizing the health of the whole organism.

In summary, the optimal balance between MR and GR activation with MR predominating in the hippocampus is necessary for best emotional and cognitive function (47, 209, 235, 241, 347, 511). Evidence of the deleterious effects of chronic GR overexpression and activation suggests that a selective GR antagonist would be a useful adjunct to the treatment of stress-related cognitive disorders (90, 236), as well as systemic problems as diverse as cardiometabolic syndromes (220) and wound healing (497), but to date there is none, in great measure due to the homologies of the LBDs of steroid receptors, as discussed above. RU-486, mifepristone, initially developed in search of a GR antagonist, is also a potent antagonist of the progesterone receptor. Notwithstanding, results of its selective use in psychiatric disorders has been promising (223, 324).

Steroids may act through G-coupled protein receptors. As shown in the flow chart in Figure 1, in addition to rapid effects mediated by membrane-associated steroid hormone receptors that are inhibited by classical steroid receptor antagonists, steroids may have rapid effects that are independent of their cognate ligands (190, 193, 269, 474). Skepticism about rapid nongenomic effects of aldosterone were based on early erroneous reports about their kinetic characteristics and the demonstration that some rapid nontranscriptional aldosterone effects were insensitive to MR antagonists, yet others were (212, 270, 475, 476). Atomic force microscopy demonstrated strong aldosterone binding sites on plasma membranes of cultured human vascular endothelial cell that are blocked by addition of aldosterone to the media, but not by spironolactone or dexamethasone which avidly bind MR and GR, respectively (481). Among the MR-independent aldosterone effects is the rapid increase in cAMP in vascular smooth muscle cells for which aldosterone, not estradiol, was shown to be an agonist at physiological concentrations (73). Aldosterone activates the G protein-coupled receptor GPER, formerly called GPR30, in freshly isolated vascular smooth muscle and endothelial cells at physiological concentrations producing cell type-specific signaling effects (119, 188, 190, 476). Freshly isolated rat aortic endothelial cells which express GPR30, but not MR, respond similarly to a GPR30 agonist and aldosterone with rapid ERK phosphorylation mediating proapoptotic and antiproliferative effects that are prevented by a GPR30 antagonist (189). GPR30 is also bound and activated by estrogen at supraphysiological

concentrations, but not by cortisol, progesterone, or testosterone (119, 124, 137, 188, 190). The implications of an aldosterone signaling mechanism that is not replicated by endogenous levels of glucocorticoids are tremendous. *In vitro*, activation of GPER enhances both ERα and MR responses in vascular smooth muscle (119, 190).

Despite the low affinity of GPR30 for estrogen relative to its maximal circulating concentrations making it highly unlikely that estrogen is an endogenous ligand, GPR30 was renamed the G-protein coupled estrogen receptor (GPER). The issue of the endogenous ligand for this receptor remains contentious (23, 124, 137, 189). It was reported that GPR30 activation induces the expression of the ERα variant ERα36 and that the cell signaling cascade initiated by estrogen is prevented by an antibody against ERα36, suggesting that ERα36, not GPER is the receptor for the membrane effects of estrogen (238). Another study using similar methods found that the vasodilation of the rat middle cerebral artery produced by estradiol was mediated by both ERα36 and GPR30 (348). This controversy demonstrates the importance of considering physiological levels of agonists when interpreting effector actions and interactions.

MR-independent aldosterone actions may be important for glycemic control, as resection of an aldosterone producing adenoma usually improves insulin resistance, yet despite their beneficial effects on cardiovascular function and remodeling, MR antagonists do not significantly ameliorate glucose homeostasis or insulin resistance associated with PA, nor impaired endothelial dysfunction in diabetics, suggesting an non-MR-mediated effect of the aldosterone (282). Adrenal steroid signaling through G-protein coupled receptors is beyond the scope of this review of the MR; however, they must not be overlooked in analyzing the effects of pharmacological interventions, particularly since such signaling may provide mechanisms for direct interactions between hormones, for example, aldosterone and glucocorticoids with estrogens and/or with Angiotensin II (24, 188, 190, 491).

Pathophysiological Implications of Inappropriate MR Activation

Pathophysiological implications of inappropriate MR activation reflect the diversity of MR functions. The following is not a comprehensive list, but should serve as examples of the effects of perturbing such a complex system. PA is associated with hypertension, hypokalemia, greater cardiovascular remodeling compared to essential hypertension of similar duration and severity, a greater incidence of cardiovascular and renal disease, and insulin resistance (216). However, even in severe PA, aldosterone concentrations are still two orders of magnitude less than those of free cortisol, therefore, it is not clear how these levels of aldosterone have such marked effects in tissues that do not express 11BHSD2 such as the heart. Nonetheless, treatment with MR antagonists suppress the cardiac remodeling, as well as the hypertension and hypokalemia, in patients with PA and are valuable adjuncts to the treatment of chronic heart failure even when the patient has normal to low plasma aldosterone levels (33, 355, 356).

Hypertension is associated with inappropriate MR activation and sodium accelerates and exacerbates the increase in blood pressure and end-organ damage. Mineralocorticoids were so named because of their marked effects on electrolyte balance and action in the kidney and

toad bladder; a name proposed for aldosterone upon its isolation was “electrocortin” (198, 417). It soon became clear that, in addition to the kidney, mineralocorticoids acted directly upon the vessels and brain to contribute to the hypertension and that elevated sodium consumption exacerbated these nonrenal effects (27, 44, 51, 78, 108, 201, 237, 259, 272, 457). While the model of excess mineralocorticoid-salt hypertension has been used profitable to study mechanisms of hypertension and cardiovascular pathology, normally aldosterone production is suppressed by sodium intake and increased by low blood pressure through the renin-angiotensin-aldosterone system (RAAS). Blood pressure has been simplified as the result of [cardiac output] X [total peripheral resistance]; MR-mediated effects support both sides of the equation. On the cardiac output side, MR activation increases sodium appetite, sodium reabsorption through renal and colonic epithelia resulting in water retention, and inotropic effects. On the resistance side, MR increase vasoconstriction through MR in vessels and those modulating sympathetic nervous system drive to the vessels.

The anterior hypothalamus and brain stem, identified by autoradiography as areas of prominent aldosterone binding (35, 430), were demonstrated by ablation studies to be essential for mineralocorticoid-salt hypertension (50). Mineralocorticoid-salt excess and renovascular hypertension were found to be abrogated by a lesion of the area anteroventral to the third ventricle (AV3V). The components of this lesion, the organum vasculosum of the lamina terminalis, ventral portion of the median preoptic nucleus, anteroventral periventricular nucleus, and the PVN, plus nerve fibers that relay information between these structures and areas receiving and integrating hemodynamic information from the periphery, including the NTS and lateral parabrachial nucleus in the medulla, and PVN, supraoptic and median preoptic nuclei of the hypothalamus (50) were further studied with more discrete lesions and shown to involve multiple regulatory systems including those for osmoreception, water and sodium homeostasis, integration of baroreceptor and autonomic nervous system information, and secretion of vasopressin and natriuretic factor (25, 144). The pivotal role of the sympathetic nervous system in mineralocorticoid hypertension was also recognized early (26-28, 295).

Chronic lateral intracerebroventricular (icv) infusions of MR agonists at doses too small to increase sodium appetite or have an effect when infused systemically, were shown to produce hypertension associated with an increase sympathetic nervous system activation and release of vasopressin and a decrease in baroreceptor sensitivity (162, 233) [reviewed in (175)]. More germane to deciphering the role of central control of the blood pressure, the icv infusion of a MR antagonist at a concentration too small to have an effect when infused systemically prevents mineralocorticoid excess-salt hypertension (167). The icv infusion of small interfering RNA (siRNA) for the MR or AT1a angiotensin II receptor (AT1aR) confirmed the specificity of these studies and previous evidence of the significant synergism between Angiotensin II and aldosterone signaling through the AT1R and MR in stimulating the sympathetic nervous system (487). The icv infusion of an antagonist of the ENaC, a major effector of MR-mediated activities in ion transport epithelia, also prevents the hypertension and sympathetic nervous system activation (1, 172, 225, 226). The icv infusion of an MR antagonist prevents the hypertension of carbenoxolone and glycyrrhizic and glycyrrhetinic acid, nonselective 11β-HSD antagonists administered systemically or orally,

suggesting that, as in Apparent Mineralocorticoid Excess, endogenous glucocorticoids was the agonist of central MR (171), however the concomitant icv infusion of corticosterone inhibited the hypertensinogenic effect icv aldosterone in a dose related fashion (180). The molecular basis for this inhibition has not been ascertained.

The effects of excessive MR activation on blood pressure, salt appetite, and cardiovascular pathology are separable. Aldosterone infused into the lateral ventricle at small concentrations produces hypertension without increasing sodium appetite or causing cardiac and renal hypertrophy after 8 weeks of hypertension (162,163). Prevention of the hypertension produced by systemic mineralocorticoid-salt excess with the icv infusion of a low dose of MR antagonist does not prevent the extensive renal, vascular and cardiac damage (498). These studies and several more since (123) demonstrated that hypertension and end-organ disease produced by excessive MR activation are separable. While low hypertensinogenic concentrations of aldosterone infused icv did not increase the sodium appetite, they do when infused into the fourth ventricle (126), near the aldosterone selective neurons of the NTS that express both MR and 11β-HSD (149, 425). These neurons receive information about sodium intake and plasma concentration from the vagus nerve and about osmolality from area postrema neurons (149, 414, 425) and project to neurons in the parabrachial nuclei, which in turn project to the central nucleus of the amygdala, another area of the brain mediating salt appetite. Infusion of an MR antagonist or MR antisense oligonucleotides into the amygdala inhibits the increase in salt appetite produced by mineralocorticoid excess (389).

Inflammation and excessive ROS are caused by inappropriate MR activation, particularly in the context of high salt intake, and result in sympathetic nervous system overactivation, hypertension, kidney, vessel and heart hypertrophy, and fibrosis (33, 156, 159, 175, 273, 319, 477, 487, 513). Experimentally, the inflammation that precedes these events is prevented by the inhibition of MR, as well as NADPH oxidase inhibitors and ROS scavengers, such as apocynin and tempol, respectively, and the tumor necrosis factor antagonist, etanercept (239, 244, 361, 362, 387, 487, 513). In addition to mitigating the cardiovascular pathology, inhibition of TNF after in experimental heart failure also alleviated the anhedonia, a surrogate symptom of depression, in rats (185). While aldosterone is implicated as the activator of the MR responsible for tissue inflammation in human clinical situations, including in the heart where 11β-HSD2 expression is limited (61), it has been difficult to explain how the MR is activated because circulating aldosterone concentrations are most often normal or low. Increased ROS from any source has been found experimentally to activate MR independently of ligand (118, 128, 175, 388). An alternative proposal is that in many nonepithelial tissues, for example, the heart, occupation of MR by glucocorticoids limits MR function; oxidative stress changes the conformation and activates the quiescent MR:cort complexes (135, 258).

Circulating proinflammatory cytokines stimulate the sympathetic nervous system (118, 433, 501), however they do not cross the blood brain barrier. They produce sympathetic excitation by inducing cyclooxygenase 2 activity in perivascular macrophages leading to the synthesis of prostaglandin E(2) which does diffuse across the blood brain barrier and acts within the PVN to activate MR and NADPH oxidase, leading to sympathetic nervous system

excitation, as well as inflammatory cytokine production in the CNS (240). This cascade of events is inhibited by antagonists of cytokines, COX-2, NADPH oxidase, and MR, as well as ROS scavengers (118, 487, 501). These pharmacological measures also prevent the excessive sympathetic nervous system activation and hypertension in aldo-salt and AII-salt excess models (487). Transgenic mice with reduced ability to produce prostaglandin E were less susceptible to the effects of induced inflammation (31).

Obesity, a component of Metabolic Syndrome or Cardiometabolic Syndrome (119, 220, 383, 478, 503), is associated with increased markers of inflammation, inflammatory cytokines and tissue ROS, insulin resistance, and activation of the RAAS and sympathetic nervous system, in addition to cardiac pathology (156, 286, 412, 478, 503). Treatment with MR antagonists decreases both cardiovascular risk markers and insulin resistance even in insulin-dependent diabetics (260, 440, 463, 503). Aldosterone may have a primary or amplifying role in the Cardiometabolic Syndrome. PA is associated with alterations in the HPA axis (157) and shares obesity-related cardiometabolic risk factors including insulin resistance and diabetes mellitus that are ameliorated with treatment (115,155,384). Subjects with the highest quartile of plasma aldosterone within the normal range have the highest risk for the development of hypertension, deleterious cardiac remodeling, obesity, and insulin resistance (16,182,458,459). Conversely, weight loss in young obese adults lowers aldosterone along with cardiometabolic risk factors (383). HIV-infected women who develop visceral obesity on retroviral treatment have higher aldosterone production, blood pressure and hemoglobin A1c compared to age- and BMI-matched HIV-infected women without visceral obesity and healthy controls (268).

Feedback sensitivity of the HPA axis of Zucker obese rats is less than that of lean rats and associated with decreased expression of hypothalamic MR and 11β-HSD1, but not GR (288). Lowered reductase activity means less conversion of cortisone to cortisol within CRH neurons and corticotrophs, resulting in higher baseline circulating cortisol levels to produce negative feedback. Obese men, compared to age matched control of normal BMI were also found to have a dampened negative HPA feedback response (289).

In contrast, net increase in reductase activity resulting in the conversion of cortisone to cortisol in other tissues, whether due to increased 11β-HSD1 or decreased 11β-HSD2, is thought to allow cortisol to activate the MR inappropriately in the cardiometabolic syndrome (16, 69, 219, 398, 503). MR, 11β-HSD2 and 11β-HSD1 are expressed in vascular smooth muscle and vascular endothelial cells. 11β-HSD1, but not 11β-HSD2, is increased in aortic vascular smooth muscle cells by inflammatory cytokines (58). This increase is adaptive in acute injury or stress, however increased 11β-HSD1 and glucocorticoid action due to the chronic inflammation in cardiometabolic syndrome or diabetes leads to inappropriate MR and GR activation (69, 70). It has been proposed that structural damage and remodeling of vessels associated with age, is caused by a relative increase in 11β-HSD1 over 11β-HSD2 activity, allowing cortisol to activate the MR, as well as the GR, upsetting the normal MR:GR activation ratio (200,221). Limited early trials with selective 11β-HSD1 antagonists improved glycemic control in obese type 2 diabetics (20, 219, 466). Selective 11β-HSD1 antagonists may also accelerate wound healing by decreasing GR-mediated effects that impede MR trophic and fibrotic repair effects (473, 497). Epigenetic events

during gestation and early childhood related to growth restriction and/or stress increase the relative expression of 11β-HSD1:11β-HSD2 and are associated with cardiometabolic risk in the adult (81, 220, 375, 484).

Activation of MR is required for adipocyte maturation. Glucocorticoids and aldosterone activate the MR-mediated transcription of several genes, in particular PPARγ required for preadipocyte maturation, while selective agonists of the GR prevent maturation (66, 286). Drospirenone is an antagonist of the MR and AR and agonist of the progesterone receptor (PR) used in some contraceptives. Drospirenone inhibits adipocyte differentiation *in vitro* by blocking the MR which may add to its efficacy in the treatment of polycystic ovarian syndrome which is often, not invariably, associated with increased BMI, insulin resistance, hypertension, and hirsutism (65). In animal experiments aldosterone administration inhibits the expression of uncoupling protein-1 (thus decreases energy expenditure), impairs insulin-induced glucose uptake, and increases mRNA for the proinflammatory adipokines leptin and monocyte chemo-attractant protein-1 in adipocytes isolated from brown fat (250). MR antagonists decrease the inflammatory profile in visceral fat of obese and diabetic ob/ob mice (199). Over the last two decades, it has been proposed that the adipocyte may release yet unidentified factors that stimulate aldosterone synthesis by the adrenal gland (111, 182, 399), perhaps through the action of adiponectin (385), or that aldosterone may be synthesized by the adipocyte itself (48). Other laboratories have not been able to demonstrate CYP17 (17α-hydroxylase), CYP11B1 (11β-hydroxylase), and CYP11B2 (aldosterone synthase) transcription required for either cortisol/corticosterone or aldosterone in adipose tissue, however the requisite enzymes for 11-deoxycorticosterone, also a mineralocorticoid were found to be significantly expressed (277).

Macrophages and T lymphocytes are also critically involved in MR-mediated hypertension, inflammation, and fibrosis (36, 156, 210, 211, 283, 284, 380). Transgenic mice with targeted MR deletion in monocytes are resistant to DOCA-salt hypertension and cardiac fibrosis (378). MR in macrophages are also required for the cardiac inflammation and fibrosis produced by L-NAME, an inhibitor of nitric oxide synthase, an inflammatory insult that does not involve the MR directly or increased aldosterone levels (33). Like cardiomyocytes, macrophages are not protected by 11β-HSD2; however, they do express abundant 11β-HSD1, suggesting that cortisol binding to their MR or GR is regulated (438).

Inappropriate sympathetic nervous system activation is one mechanism bridging inflammation, hypertension and insulin resistance (16, 249). In addition to being activated by circulating inflammatory cytokines (118,433,501), among the many adaptive functions of the sympathetic nervous system is to ensure adequate energy by increasing gluconeogenesis through the release of epinephrine and glucagon and induction of peripheral insulin resistance (331). Reduction of blood pressure with chlorthalidone, a diuretic commonly used in the treatment of hypertension and heart failure, activates the RAAS and sympathetic nervous system and promotes insulin resistance. Addition of an MR antagonist to the treatment regimen for these patients normalized both the sympathetic nervous system activation and insulin sensitivity (366). Early evidence for a role of the sympathetic nervous system as a mediator of aldosterone action in humans was inconsistent in part due to inappropriate methods and controls (175). As in experimental animals, the infusion of

aldosterone in human volunteers to raise plasma levels to the pathophysiologic range increased muscle sympathetic nerve activity and impaired baroreflex responses (309). Sympathetic nervous system activity is elevated in essential hypertension, as well as untreated PA (248, 326). Treatment with an MR antagonist or resection of the aldosterone producing adenoma in PA decreases blood pressure and sympathetic nervous system activity. Removal of an aldosteronoma resulting in normal aldo levels has a greater normalizing effect upon pathological remodeling of the heart, glycemic control, and the depression associated with PA (280, 282, 420), suggesting that MR-independent aldosterone actions are partially responsible for these effects.

Development and function of neurons and neuron networks requires the appropriate balance of MR:GR activation. Aldosterone increased MR expression in ESC-derived neurons through both P1 and P2 promoters, leading to an increase in their resistance to oxidative stress and survival (315). Corticosterone, but not aldosterone produced apoptosis in these stem cell derived neurons. Increasing the MR:GR ratio in these ESC-derived neurons protected them against apoptosis when treated with concentrations of corticosterone that activated both receptors (146, 314). These *in vitro* results confirmed those described in live animals. In general, excessive and chronic GR activation leads to hippocampal neuron atrophy and eventually death; MR activation is antiapoptotic and supports neurogenesis (290) Adrenalectomy in the adult rat causes apoptosis of granule cells in the dentate gyrus which was shown to be completely reversed by aldosterone replacement, but only partially by a selective glucocorticoid agonist (483). In the adult brain excessive GR activation increased the expression of the tumor suppressor protein p53, a direct transcriptional regulator of the proapoptotic bax and bcl-2 genes, and induced hippocampal granule cell apoptosis, while MR activation suppresses p53 transcription in developing and mature hippocampal neurons and is protective (10, 82). Overexpression of the MR in the mouse forebrain protected neurons from transient global ischemia (257).

Changes in the relative expression of 11β-HSD1 and 2 in the placenta and fetus throughout ontogeny is crucial for the proportional activation of MR and GR required for the development of fetal organs, particularly the brain, and there is a great deal of literature describing the effects of deleterious consequences of interrupting this balance, particularly by treatment of the mother with synthetic glucocorticoids not metabolized by 11β-HSD1 (69, 222, 306, 406) including epigenetic changes in the expression of the GR (337, 422, 472).

Response to stress is modulated by different levels of cort binding to MR and GR and interaction between rapid nongenomic and slower genomic (transcriptional) effects mediated by these receptors (91, 187, 278). Under normal conditions glucocorticoids activate MR in hippocampal neurons to mediate arousal and trophic effects that are dampened by higher stress levels of glucocorticoids through GR (89). The differential regulation of the 5-HT1A receptor in different parts of the hippocampus is an example of integrated GR and MR effects (325). At lower corticosterone levels MR activation alone downregulates 5-HT1A receptors and suppresses of serotonin-related activity in the raphe-hippocampal system. Transient increases in glucocorticoid concentrations producing GR occupation rapidly increases the ability for hippocampal neurons to respond to 5-HT1A receptor stimulation,

attenuates 5-HT autoinhibition, and facilitates stress-induced increases in 5-HT release, in part by increasing calcium influx and depolarizing the neurons (234,298). These concentrations also bind MR which through transrepression of the 5-HT1A receptor promoter by the MR:GR heterodimer, restores normal 5-HT1A receptor signaling after an appropriate delay and allows the brain to adapt to stress (343). However, chronic stress leads to chronic heterodimer formation and repression of 5-HT1A receptor transcription and depression-related behavior that led to the development of the selective serotonin reuptake inhibitors in use today (242, 298). As described in the section on epigenetic modifications of the MR and GR, chronic stress produces in rats many of the same biochemical changes found in depression (426).

Clinical depression is associated with plasma cortisol levels that remain relatively high with a flat circadian rhythm. Compared to control subjects, total MR and the ratio of MR:GR mRNAs in the prefrontal and anterior cingulate cortex and hippocampus is significantly decreased in persons with major depression, as well as bipolar disorder and schizophrenia (341, 359, 485). Conversely, MR message in the PVN was found to be increased in depressed patients (359). This increase in hypothalamic MR may be relevant to the consistent finding that depression and cardiovascular disease including hypertension are independent risk factors for one another. They also share neuroendocrine and inflammatory derangements, including inappropriate HPA, RAAS, and sympathetic nervous system activation and increases in circulating inflammatory cytokines, in particular TNFα (186,433).

Depression is a common comorbidity in PA (254, 280, 420). The choice of treatment of PA depends on the etiology of the autonomous aldo production. Removal of an aldosteronoma resulting in normal aldo levels ameliorates the hypertension, pathological remodeling of the heart and depression (280, 420). While medical treatment with an MR antagonist for bilateral hyperplasia or in lieu of aldosteronoma resection significantly ameliorates the cardiovascular components, there was no improvement in mood and cognition (254). As aldo levels remain high in medically treated patients, aldosterone may have MR-independent aldosterone actions in the brain, as well as on glycemic control (282). Alternatively or in addition, inhibition of some brain MR may be detrimental, as discussed below.

The addition of MR antagonists to standard treatment of heart and renal failure not only decreases morbidity and mortality, it has been shown in many studies to increase quality of life measures (386, 431, 502, 509). In addition, treatment of hypertensive subjects was reported to increase their score on a cognitive test (488). Quality of life measures are a complex distillation of multiple factors, including mood. The mechanisms of these beneficial effects of the MR antagonist may relate to the decrease in inflammation and cerebrovascular pathology, as well as general cardiovascular and renal functional improvement and decreased stress in these patients, as other clinical and experimental evidence indicates that MR function is crucial for normal mood and cognition and that MR inhibition has negative effects on neuronal function required for cognition.

In normotensive human subjects short-term blockade of the MR, increased cortisol and impaired selective attention, working and visual-spatial memory, and mental flexibility,

results that parallel those in animal models (80,342,492,511). Moreover, in a randomized, double blinded, placebo controlled study of treatment-naïve depressed patients, addition of a low dose of MR *agonist*, fludrocortisone, to an SSRI accelerated the onset of the antidepressant effect compared to the placebo or MR antagonist groups (there was no difference between the latter) (341). MR function is important for the performance of cognitive tasks under stress (403). Studies in normal volunteers studied using functional magnetic resonance imaging demonstrate that different learning strategies are used when learning under stress and that this adaptive compensation is prevented by pharmacologic blockade of the MR, resulting in suboptimal performance under stress (403).

LTP formation is essential for memory and learning. Early studies on the effect of adrenocorticosteroids on LTP formation demonstrated that activation of MR enhances and of GR suppresses LTPs in the dentate gyrus and CA1 & 3 areas of the hippocampus (349,350). MR at both pre- and postsynaptic membranes of hippocampal neurons appear to participate in LTP formation (187,278,340) and MR antagonists block both the formation and retrieval of memories (235, 347, 511). Corticosterone acts through MR to rapidly enhance the frequency of miniature excitatory postsynaptic potentials in hippocampal CA1 pyramidal neurons and reduce paired-pulse facilitation, probably through increased glutamate release (241). The effect was prevented by MR, but not GR antagonists; however, the concentration of corticosterone required for this effect was higher than that required for MR transcriptional activity, suggesting that the membrane-associated MR has a lower affinity for corticosterone than the transcriptional or cytosolic MR (241).

Adrenalectomized mice receiving low corticosterone replacement that primarily activated MR were rapid learners, more exploratory and less anxious than controls, while those receiving stress levels of corticosterone were more aroused and had learning deficits (47). It was shown that mice use different learning strategies under low and high stress/ corticosterone situations and that the switch to learning under high corticosterone situations depended upon MR-mediated functions. MR antagonists prevented this switch, significantly impairing learning and memory (402). Transgenic mice in which the MR is deleted only in the forebrain have normal circadian levels and cycling of corticosterone, hypothalamic effects, but profound learning deficits, including loss of perseverance and exaggerated response to stress, associated with an increase in GR, and morphological changes in neurons (29, 46). Diabetes mellitus in humans is associated with increased glucocorticoid secretion and cognitive defects. In a streptozotocin mouse model of diabetes both the hippocampal morphology and cognitive abilities were partially normalized by treatment with a GR antagonist (374).

The acute administration of an MR antagonist in normal people increased plasma cortisol levels, thus the ratio of activated MR:GR was decreased both by decreasing activated MR and increasing GR (80). This imbalance was associated with impairment in selective attention, learning and memory and recapitulated many studies done in animals. As an example, formation and use of spatial memory is particularly dependent upon MR in both experimental animals (103, Oitzl, 1998, 121, p. 4208, 257, 492) and humans (342).

The effects of sleep disruption on MR functions are still unclear. HPA suppression through the MR during early slow wave sleep is crucial for the formation of declarative memory in humans. Interruption of the normal sleep cycle by sleep apnea prevents memory (79). As obesity is frequently associated with sleep apnea and increased cortisol (60,181,354), this may be a mechanism for the lower cognitive function associated with obesity and the metabolic syndrome in humans (20, 56).

MR polymorphisms in the human impart varying degrees of altered function. Loss of function MR mutations produce pseudohypoaldosteronism with neonatal sodium loss (394, 395). Patients with the very rare MR S810L substitution have pseudohyperaldosteronism with hypertension that is exacerbated during pregnancy because progesterone, rather than being an antagonist, is a full agonist of MR S810L (151). It is now known that rather than being constitutively active, the MR S810L is activated by cortisol, cortisone and progesterone, as well as the synthetic MR antagonists eplerenone and spironolactone (229, 365). Several MR polymorphisms with less dramatic effects on electrolyte and blood pressure homeostasis have been studied primarily in the context of affect and cognitive function (40, 99, 100, 422, 454). The relatively common MR-I180V polymorphism has lower transactivation capacity and has not been associated with blood pressure changes. Subjects with the MR-I180V polymorphism have mildly altered the HPA axis, normal levels of cortisol upon awakening, and significant mild stress-induced learning deficits and risk for depression (40, 100, 246, 455). The MR c.-2G>C has a substitution of guanine for cytosine two nucleotides before the start codon, decreasing *in vitro* translational efficiency. The effect of SSRIs upon the HPA axis differs depending on MR c.-2G/C status and gender. Compared to homozygotes for the MR c.-2C/C allele, MR c.-2G/G subjects had lower MR protein expression in peripheral blood cells, higher renin and aldo levels as expected for a mild loss of function of peripheral MR, and in men, significant mild elevation of blood pressures (455). The higher blood pressure may be due to MR-independent actions of the higher aldosterone levels. Similarly, there are several GR polymorphisms associated with depression, as well as ability to perform cognitive tasks when distractors are present and decreased risk for dementia (421). With the development of less expensive methods of genotyping, current studies of the biology of common MR and GR polymorphisms should guide the choice of therapy for depression and cognitive disorders and will hopefully lead to early assessment of risk and development of rational prevention strategies.

Conclusion

The adrenal steroids aldosterone, cortisol, corticosterone and the adrenal androgens, as do other hormonal steroids, coordinate cellular activities throughout the body via cognate steroid hormone receptors. Steroid hormone receptors are ligand activated transcription factors that interact directly with the DNA and also initiate rapid nonnuclear events through secondary cell signaling mechanisms while associated with the plasma membrane. The GR and MR are often expressed in the same cells and are unique among the steroid hormone receptors in the complexity of their interactions as transcription factors; many transcriptional events depend on the balance of activated GR and MR. Cortisol and corticosterone are the primary ligands for both MR and GR in most nonepithelial cells. Prereceptor modulation of their concentrations through 11β-hydroxylation or reduction is crucial for cellular and whole

body homeostasis and occurs in selected cell populations. Evidence is accruing for a third mechanism of adrenal steroid function through the interaction with G-protein coupled receptors, the molecular mechanisms for which are not yet well understood.

Mineralocorticoids evolved under the pressures of maintaining an internal balance of water and electrolytes in an external environment where water and sodium were often limited and glucocorticoids took on the task of ensuring energy homeostasis to meet large and often rapidly changes in rates of energy expenditure. MR and GR often work in concert, often in counterpoint, to meet environmental challenges and appropriately terminate responses. Therefore, the ratio of MR to GR activation can be crucial for normal function, particularly in the brain, where highest concentrations of MR are expressed. Inappropriate MR and GR function are associated with Hypertension, Metabolic Syndrome or the most recent and encompassing term Cardiometabolic Syndrome, and Depression, diseases common in the Developed World where sodium and calories are not limited and stressors at many levels, disruption of the circadian rhythm by 24 h lighting is but one example, are chronic and often unremitting. Addition of MR antagonists to treatment regimens clearly mitigates symptoms of chronic heart failure and Cardiometabolic Syndrome, including small vessel disease in the brain that leads to ischemia and stroke with a net benefit to cognitive function despite reducing the MR:GR ratio. Use of GR antagonists have been hampered by lack of specificity, leading to the development and testing of 11β-HSD1 inhibitors. As we learn more about specific cellular mechanisms of MR- and GR-mediated function we should be able to identify and selectively target those responsible for inappropriate action producing disease.

Acknowledgements

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. 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–R1510. [PubMed: 20926762]
2. Ackermann D, Gresko N, Carrel M, Loffing-Cueni D, Habermehl D, Gomez-Sanchez C, Rossier BC, Loffing J. 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–F1485. [PubMed: 20861076]
3. Agarwal MK, Mirshahi M. General overview of mineralocorticoid hormone action. Pharmacol Ther. 1999; 84:273–326. [PubMed: 10665831]
4. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M, Cattadori G, Palermo P. Spironolactone improves lung diffusion in chronic heart failure. Eur Heart J. 2005; 26:159–164. [PubMed: 15618072]
5. Ahima R, Krozowski Z, Harlan R. Type I corticosteroid receptor-like immunoreactivity in the rat CNS: Distribution and regulation by corticosteroids. J Comp Neurol. 1991; 313:522–538. [PubMed: 1770174]
6. Ahmad N, Romero DG, Gomez-Sanchez EP, Gomez-Sanchez CE. Do human vascular endothelial cells produce aldosterone? Endocrinology. 2004; 145:3626–3629. [PubMed: 15117882]

7. Ahmed AH, Gordon RD, Sukor N, Pimenta E, Stowasser M. Quality of life in patients with bilateral primary aldosteronism before and during treatment with spironolactone and/or amiloride, including a comparison with our previously published results in those with unilateral disease treated surgically. J Clin Endocrinol Metab. 2011; 96:2904–2911. [PubMed: 21778218]
8. 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–E346. [PubMed: 20962019]
9. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. J Clin Invest. 2004; 114:1146–1157. [PubMed: 15489962]
10. Almeida OF, Conde GL, Crochemore C, Demeneix BA, Fischer D, Hassan AH, Meyer M, Holsboer F, Michaelidis TM. Subtle shifts in the ratio between pro- and antiapoptotic molecules after activation of corticosteroid receptors decide neuronal fate. FASEB J. 2000; 14:779–790. [PubMed: 10744634]
11. Alt SR, Turner JD, Klok MD, Meijer OC, Lakke EA, Derijk RH, Muller CP. Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. Psychoneuroendocrinology. 2010; 35:544–556. [PubMed: 19782477]
12. Alzamora R, Marusic ET, Gonzalez M, Michea L. Nongenomic effect of aldosterone on Na+,K+-adenosine triphosphatase in arterial vessels. Endocrinology. 2003; 144:1266–1272. [PubMed: 12639909]
13. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet. 1999; 23:185–188. [PubMed: 10508514]
14. Apostolopoulou K, Kunzel HE, Gerum S, Merkle K, Schulz S, Fischer E, Pallauf A, Brand V, Bidlingmaier M, Endres S, Beuschlein F, Reincke M. Gender differences in anxiety and depressive symptoms in patients with primary hyperaldosteronism: A cross-sectional study. World J Biolo Psychiatry. 2012; 15:26–35.
15. Arampatzis S, Kadereit B, Schuster D, Balazs Z, Schweizer RA, Frey FJ, Langer T, Odermatt A. Comparative enzymology of 11beta-hydroxysteroid dehydrogenase type 1 from six species. J Mol Endocrinol. 2005; 35:89–101. [PubMed: 16087724]
16. Aroor AR, McKarns S, Demarco VG, Jia G, Sowers JR. Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance. Metabolism. 2013; 62:1543–1552. [PubMed: 23932846]
17. 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]
18. Arriza JW, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, Evans RM. Cloning of human mineralocorticoid receptor complementary DNA: Structural and functional kinship with the glucocorticoid receptor. Science. 1987; 237:268–275. [PubMed: 3037703]
19. 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; 571:129–133. [PubMed: 15280030]
20. 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; 7:125–140. [PubMed: 17584152]
21. Baker ME. Co-evolution of steroidogenic and steroid-inactivating enzymes and adrenal and sex steroid receptors. Mol Cell Endocrinol. 2004; 215:55–62. [PubMed: 15026175]
22. Bao AM, Swaab DF. Corticotropin-releasing hormone and arginine vasopressin in depression focus on the human postmortem hypothalamus. Vitam Horm. 2010; 82:339–365. [PubMed: 20472147]
23. Barton M. Position paper: The membrane estrogen receptor GPER–Clues and questions. Steroids. 2012; 77:935–942. [PubMed: 22521564]
24. 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; 94:136–143. [PubMed: 22260839]

25. Bealer SL. Anteroventral third ventricle periventricular tissue contributes to cardiac baroreflex responses. Clin Exp Pharmacol Physiol. 2000; 27:460–464. [PubMed: 10831253]
26. 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):1146–1152.
27. Berecek KH, Bohr DF. Whole body vascular reactivity during the development of deoxycorticosterone acetate hypertension in the pig. Circ Res. 1978; 42:764–771. [PubMed: 657435]
28. Berecek KH, Murray RD, Gross F. Significance of sodium, sympathetic innervation and central adrenergic structures on renal vascular responsiveness in DOCA-treated rats. Circ Res. 1980; 47:675–683. [PubMed: 7418127]
29. Berger S, Wolfer DP, Selbach O, Alter H, Erdmann G, Reichardt HM, Chepkova AN, Welzl H, Haas HL, Lipp HP, Schutz G. Loss of the limbic mineralocorticoid receptor impairs behavioral plasticity. Proc Natl Acad Sci U S A. 2006; 103:195–200. [PubMed: 16368758]
30. Bernelot Moens SJ, Schnitzler GR, Nickerson M, Guo H, Ueda K, Lu Q, Aronovitz MJ, Nickerson H, Baur WE, Hansen U, Iyer LK, Karas RH. Rapid estrogen receptor signaling is essential for the protective effects of estrogen against vascular injury. Circulation. 2012; 126:1993–2004. [PubMed: 22997253]
31. Berry A, Carnevale D, Giorgio M, Pelicci PG, de Kloet ER, Alleva E, Minghetti L, Cirulli F. Greater resistance to inflammation at adulthood could contribute to extended life span of p66(Shc −/−) mice. Exp Gerontol. 2010; 45:343–350. [PubMed: 20085805]
32. Berry C, Murphy NF, De Vito G, Galloway S, Seed A, Fisher C, Sattar N, Vallance P, Hillis WS, McMurray J. Effects of aldosterone receptor blockade in patients with mild-moderate heart failure taking a beta-blocker. Eur J Heart Fail. 2007; 9:429–434. [PubMed: 17126073]
33. Bienvenu LA, Morgan J, Rickard AJ, Tesch GH, Cranston GA, Fletcher EK, Delbridge LM, Young MJ. Macrophage mineralocorticoid receptor signaling plays a key role in aldosterone-independent cardiac fibrosis. Endocrinology. 2012; 153:3416–3425. [PubMed: 22653557]
34. Biglieri EG, Kater CE. Steroid characteristics of mineralocorticoid adrenocortical hypertension. Clin Chem. 1991; 37:1843–1848. [Review] [25 refs]. [PubMed: 1914200]
35. Birmingham MD, Stumpf WE, Sar M. Nuclear Iocalization of aldosterone in rat brain cells assessed by autoradiography. Experientia. 1979; 35:1240–1241. [PubMed: 488294]
36. 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; 63:1791–1800. [PubMed: 12675855]
37. Blaustein MP, Hamlyn JM. Pathogenesis of essential hypertension. A link between dietary salt and high blood pressure. Hypertension. 1991; 18:III184–III195. [PubMed: 1937683]
38. Blaustein MP, Hamlyn JM. Signaling mechanisms that link salt retention to hypertension: Endogenous ouabain, the Na(+) pump, the Na(+)/Ca(2+) exchanger and TRPC proteins. Biochim Biophys Acta. 2010; 1802:1219–1229. [PubMed: 20211726]
39. Bobik A. Striatin-dependent membrane estrogen receptor signaling and vasoprotection by estrogens. Circulation. 2012; 126:1941–1943. [PubMed: 22997252]
40. Bogdan R, Perlis RH, Fagerness J, Pizzagalli DA. The impact of mineralocorticoid receptor ISO/VAL genotype (rs5522) and stress on reward learning. Genes Brain Behav. 2010; 9:658–667. [PubMed: 20528958]
41. Boschitsch E, Mayerhofer S, Magometschnigg D. Hypertension in women: The role of progesterone and aldosterone. Climacteric. 2010; 13:307–313. [PubMed: 20443718]
42. Bratton MR, Gomez-Sanchez EP, Gomez-Sanchez CE, Subauste JS. The myosin binding protein is a novel mineralocorticoid receptor binding partner. Mol Cell Endocrinol. 2004; 217:221–227. [PubMed: 15134821]
43. Braun S, Losel R, Wehling M, Boldyreff B. Aldosterone rapidly activates Src kinase in M-1 cells involving the mineralocorticoid receptor and HSP84. FEBS Lett. 2004; 570:69–72. [PubMed: 15251441]
44. Bravo EL, Tarazi RC, Dustan HP. Multifactorial analysis of chronic hypertension by electrolyte active steroids in trained, unanesthetized dogs. Circ Res. 1977; 40:140–145.

45. Bridgham JT, Carroll SM, Thornton JW. Evolution of hormone-receptor complexity by molecular exploitation. Science. 2006; 312:97–101. [PubMed: 16601189]
46. Brinks V, Berger S, Gass P, de Kloet ER, Oitzl MS. Mineralocorticoid receptors in control of emotional arousal and fear memory. Horm Behav. 2009; 56:232–238. [PubMed: 19447109]
47. Brinks V, van der Mark MH, de Kloet ER, Oitzl MS. Differential MR/GR activation in mice results in emotional states beneficial or impairing for cognition. Neural Plast. 2007; 2007:90163. [PubMed: 17710249]
48. Briones AM, Cat AN, Callera GE, Yogi A, Burger D, He Y, Correa JW, Gagnon AM, Gomez-Sanchez CE, Gomez-Sanchez EP, Sorisky A, Ooi TC, Ruzicka M, Burns KD, Touyz RM. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: Implications in diabetes mellitus-associated obesity and vascular dysfunction. Hypertension. 2012; 59:1069–1078. [PubMed: 22493070]
49. Brody MJ. Central nervous system and mechanisms of hypertension. Clin Physiol Biochem. 1988; 6:230–239. [PubMed: 3060299]
50. 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.
51. Brody MJ, Haywood JR, Touw KB. Neural mechanisms in hypertension. Ann Rev Physiol. 1978; 42:441–453. [PubMed: 6996591]
52. Bujalska IJ, Draper N, Michailidou Z, Tomlinson JW, White PC, Chapman KE, Walker EA, Stewart PM. Hexose-6-phosphate dehydrogenase confers oxo-reductase activity upon 11 beta-hydroxysteroid dehydrogenase type 1. J Mol Endocrinol. 2005; 34:675–684. [PubMed: 15956339]
53. 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; 87:1205–1210. [PubMed: 11889189]
54. Bulow HE, Bernhardt R. Analyses of the CYP11B gene family in the guinea pig suggest the existence of a primordial CYP11B gene with aldosterone synthase activity. Eur J Biochem. 2002; 269:3838–3846. [PubMed: 12153581]
55. Bumke-Vogt C, Bahr V, Diederich S, Herrmann SM, Anagnostopoulos I, Oelkers W, Quinkler M. Expression of the progesterone receptor and progesterone-metabolising enzymes in the female and male human kidney. J Endocrinol. 2002; 175:349–364. [PubMed: 12429033]
56. Burkhalter TM, Hillman CH. A narrative review of physical activity, nutrition, and obesity to cognition and scholastic performance across the human lifespan. Adv Nutr. 2011; 2:201S–206S. [PubMed: 22332052]
57. Busjahn A, Aydin A, Uhlmann R, Krasko C, Bahring S, Szelestei T, Feng Y, Dahm S, Sharma AM, Luft FC, Lang F. Serum- and glucocorticoid-regulated kinase (SGK1) gene and blood pressure. Hypertension. 2002; 40:256–260. [PubMed: 12215463]
58. 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; 77:117–122. [PubMed: 11377976]
59. Caldiz CI, Diaz RG, Nolly MB, Chiappe de Cingolani GE, Ennis IL, Cingolani HE, Perez NG. Mineralocorticoid receptor activation is crucial in the signalling pathway leading to the Anrep effect. J Physiol. 2011; 589:6051–6061. [PubMed: 22174146]
60. Calhoun DA, Nishizaka MK, Zaman MA, Harding SM. Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. Chest. 2004; 125:112–117. [PubMed: 14718429]
61. Calhoun DA, Sharma K. The role of aldosteronism in causing obesity-related cardiovascular risk. Cardiol Clin. 2010; 28:517–527. [PubMed: 20621254]
62. Callera GE, Montezano AC, Yogi A, Tostes RC, He Y, Schiffrin EL, Touyz RM. c-Src-dependent nongenomic signaling responses to aldosterone are increased in vascular myocytes from spontaneously hypertensive rats. Hypertension. 2005; 46:1032–1038. [PubMed: 16157790]
63. Callera GE, Touyz RM, Tostes RC, Yogi A, He Y, Malkinson S, Schiffrin EL. Aldosterone activates vascular p38MAP kinase and NADPH oxidase via c-Src. Hypertension. 2005; 45:773–779. [PubMed: 15699470]

64. Callera GE, Yogi A, Briones AM, Montezano AC, He Y, Tostes RC, Schiffrin EL, Touyz RM. Vascular proinflammatory responses by aldosterone are mediated via c-Src trafficking to cholesterol-rich microdomains: Role of PDGFR. Cardiovasc Res. 2011; 91:720–731. [PubMed: 21576132]

65. Caprio M, Antelmi A, Chetrite G, Muscat A, Mammi C, Marzolla V, Fabbri A, Zennaro MC, Feve B. Antiadipogenic effects of the mineralocorticoid receptor antagonist drospirenone: Potential implications for the treatment of metabolic syndrome. Endocrinology. 2011; 152:113–125. [PubMed: 21084448]

66. Caprio M, Feve B, Claes A, Viengchareun S, Lombes M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. FASEB J. 2007; 21:2185–2194. [PubMed: 17384139]

67. Castren M, Patchev VK, Almeida OF, Holsboer F, Trapp T, Castren E. Regulation of rat mineralocorticoid receptor expression in neurons by progesterone. Endocrinology. 1995; 136:3800–3806. [PubMed: 7649087]

68. Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, Joels M, Krugers H. Maternal care and hippocampal plasticity: Evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. J Neurosci. 2008; 28:6037–6045. [PubMed: 18524909]

69. Chapman K, Holmes M, Seckl J. 11beta-hydroxysteroid dehydrogenases: Intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev. 2013; 93:1139–1206. [PubMed: 23899562]

70. Chapman KE, Coutinho AE, Zhang Z, Kipari T, Savill JS, Seckl JR. Changing glucocorticoid action: 11beta-Hydroxysteroid dehydrogenase type 1 in acute and chronic inflammation. J Steroid Biochem Mol Biol. 2013; 137:82–92. [PubMed: 23435016]

71. 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; 306:R328–R340. [PubMed: 24381176]

72. Cheskis BJ. Regulation of cell signalling cascades by steroid hormones. J Cell Biochem. 2004; 93:20–27. [PubMed: 15352158]

73. Christ M, Gunther A, Heck M, Schmidt BM, Falkenstein E, Wehling M. Aldosterone, not estradiol, is the physiological agonist for rapid increases in cAMP in vascular smooth muscle cells. Circulation. 1999; 99:1485–1491. [PubMed: 10086974]

74. Chung E, Hanukoglu A, Rees M, Thompson R, Dillon M, Hanukoglu IB, Kuhnle U, Seckl J, Gardiner RM. Exclusion of the locus for autosomal recessive pseudohypoaldosteronism type 1 from the mineralocorticoid receptor gene region on human chromosome 4q by linkage analysis. J Clin Endocrinol Metab. 1995; 80:3341–3345. [PubMed: 7593448]

75. 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; 70:349–352. [PubMed: 2137132]

76. 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; 37:354–360. [PubMed: 6316188]

77. Cole MA, Kalman BA, Pace TW, Topczewski F, Lowrey MJ, Spencer RL. Selective blockade of the mineralocorticoid receptor impairs hypothalamic-pituitary-adrenal axis expression of habituation. J Neuroendocrinol. 2000; 12:1034–1042. [PubMed: 11012846]

78. Coleman TG, Grange HJ, Guyton AC. Whole-body autoregulation and hypertension. Circ Res 28. 1971; 29:11–76.

79. Conway-Campbell BL, Sarabdjitsingh RA, McKenna MA, Pooley JR, Kershaw YM, Meijer OC, De Kloet ER, Lightman SL. Glucocorticoid ultradian rhythmicity directs cyclical gene pulsing of the clock gene period 1 in rat hippocampus. J Neuroendocrinol. 2010; 22:1093–1100. [PubMed: 20649850]

80. Cornelisse S, Joels M, Smeets T. A randomized trial on mineralocorticoid receptor blockade in men: Effects on stress responses, selective attention, and memory. Neuropsychopharmacology. 2011; 36:2720–2728. [PubMed: 21881569]

81. Cottrell EC, Holmes MC, Livingstone DE, Kenyon CJ, Seckl JR. Reconciling the nutritional and glucocorticoid hypotheses of fetal programming. FASEB J. 2012; 26:1866–1874. [PubMed: 22321728]
82. Crochemore C, Lu J, Wu Y, Liposits Z, Sousa N, Holsboer F, Almeida OF. Direct targeting of hippocampal neurons for apoptosis by glucocorticoids is reversible by mineralocorticoid receptor activation. Mol Psychiatry. 2005; 10:790–798. [PubMed: 15940303]
83. Czar MJ, Galigniana MD, Silverstein AM, Pratt WB. Geldanamycin, a heat shock protein 90-binding benzoquinone ansamycin, inhibits steroid-dependent translocation of the glucocorticoid receptor from the cytoplasm to the nucleus. Biochemistry. 1997; 36:7776–7785. [PubMed: 9201920]
84. Daniel KR, Wells G, Stewart K, Moore B, Kitzman DW. Effect of aldosterone antagonism on exercise tolerance, Doppler diastolic function, and quality of life in older women with diastolic heart failure. Congest Heart Fail. 2009; 15:68–74. [PubMed: 19379452]
85. 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; 154:3261–3272. [PubMed: 23633533]
86. Davies E, MacKenzie SM. Extra-adrenal production of corticosteroids. Clin Exp Pharmacol Physiol. 2003; 30:437–445. [PubMed: 12823256]
87. De Filippis B, Ricceri L, Fuso A, Laviola G. Neonatal exposure to low dose corticosterone persistently modulates hippocampal mineralocorticoid receptor expression and improves locomotor/exploratory behaviour in a mouse model of Rett syndrome. Neuropharmacology. 2013; 68:174–183. [PubMed: 22709945]
88. De Kloet ER. Brain corticosteroid receptor balance and homeostatic control. Front Neuroendocrinol. 1991; 12:95–164.
89. De Kloet ER. Hormones and the stressed brain. AnnNY Acad Sci. 2004; 1018:1–15.
90. 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; 3:168–179. [PubMed: 17237843]
91. de Kloet ER, Karst H, Joels M. Corticosteroid hormones in the central stress response: Quick-and-slow. Front Neuroendocrinol. 2008; 29:268–272. [PubMed: 18067954]
92. De Kloet ER, Ratka A, Reul J, Sutanto W, Van Eekelen JAM. Corticosteroid receptor types in brain: Regulation and putative function. Ann N Y Acad Sci. 1987; 512:351–361. [PubMed: 3327424]
93. De Kloet ER, Van Acker SA, Sibug RM, Oitzl MS, Meijer OC, Rahmouni K, de Jong W. Brain mineralocorticoid receptors and centrally regulated functions. Kidney Int. 2000; 57:1329–1336. [PubMed: 10760063]
94. De Kloet ER, Versteeg DHG, Kovacs GL. Aldosterone blocks the response to corticosterone in the raphe-hippocampal serotonin system. Brain Res. 1983; 264:323–327. [PubMed: 6850304]
95. De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. Endocr Rev. 1998; 19:269–301. [PubMed: 9626555]
96. Dekker MJ, Tiemeier H, Luijendijk HJ, Kuningas M, Hofman A, de Jong FH, Stewart PM, Koper JW, Lamberts SW. The effect of common genetic variation in 11beta-hydroxysteroid dehydrogenase type 1 on hypothalamic-pituitary-adrenal axis activity and incident depression. J Clin Endocrinol Metab. 972012:E233–E237.
97. Delcayre C, Silvestre JS, Garnier A, Oubenaissa A, Cailmail S, Tatara E, Swynghedauw B, Robert V. Cardiac aldosterone production and ventricular remodeling. Kidney Int. 2000; 57:1346–1351. [PubMed: 10760065]
98. Derfoul A, Robertson NM, Hall DJ, Litwack G. The N-terminal domain of the mineralocorticoid receptor modulates both mineralocorticoid receptor- and glucocorticoid receptor-mediated transactivation from Na/K ATPase beta1 target gene promoter. Endocrine. 2000; 13:287–295. [PubMed: 11216640]
99. Derijk RH. Single nucleotide polymorphisms related to HPA axis reactivity. Neuroimmunomodulation. 2009; 16:340–352. [PubMed: 19571595]

100. DeRijk RH, de Kloet ER, Zitman FG, van Leeuwen N. Mineralocorticoid receptor gene variants as determinants of HPA axis regulation and behavior. Endocr Dev. 2011; 20:137–148. [PubMed: 21164267]

101. Dhabhar FS, Miller AH, McEwen BS, Spencer RL. Differential activation of adrenal steroid receptors in neural and immune tissues of Sprague Dawley, Fischer 344, and Lewis rats. J Neuroimmunol. 1995; 56:77–90. [PubMed: 7822484]

102. Diaz RG, Perez NG, Morgan PE, Villa-Abrille MC, Caldiz CI, Nolly MB, Portiansky EL, Ennis IL, Cingolani HE. Myocardial mineralocorticoid receptor activation by stretching and its functional consequences. Hypertension. 2013; 63:112–118. [PubMed: 24126173]

103. Douma BR, Korte SM, Buwalda B, la Fleur SE, Bohus B, Luiten PG. Repeated blockade of mineralocorticoid receptors, but not of glucocorticoid receptors impairs food rewarded spatial learning. 1998; 23:33–44.

104. Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol. 2004; 288:R34–R38. [PubMed: 15178540]

105. Draper N, Stewart PM. 11beta-hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. J Endocrinol. 2005; 186:251–271. [PubMed: 16079253]

106. 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; 7:357–363. [PubMed: 11279298]

107. Du J, McEwen B, Manji HK. Glucocorticoid receptors modulate mitochondrial function: A novel mechanism for neuroprotection. Commun Integr Biol. 2009; 2:350–352. [PubMed: 19721888]

108. Dupont JJ, Hill MA, Bender SB, Jaisser F, Jaffe IZ. Aldosterone and vascular mineralocorticoid receptors: Regulators of ion channels beyond the kidney. Hypertension. 2013 [Epub ahead of print].

109. Edelman S, Shalev I, Uzefovsky F, Israel S, Knafo A, Kremer I, Mankuta D, Kaitz M, Ebstein RP. Epigenetic and genetic factors predict women's salivary cortisol following a threat to the social self. PLoS One. 2012; 7:e48597. [PubMed: 23155396]

110. Edwards CRW, Burt D, McIntyre MA, De Kloet ER, Stewart PM, Brett L, Sutanto WS, Monder C. Localisation of 11b-hydroxysteroid dehydrogenase-tissue specific protector of the mineralocorticoid receptor. Lancet. 1988; ii:986–989. [PubMed: 2902493]

111. Ehrhart-Bornstein M, Arakelyan K, Krug AW, Scherbaum WA, Bornstein SR. Fat cells may be the obesity-hypertension link: Human adipogenic factors stimulate aldosterone secretion from adrenocortical cells. Endocr Res. 2004; 30:865–870. [PubMed: 15666838]

112. Ellman P, Cudkowicz L. Comparative effects of cortisone, ACTH, and DOCA in a case of rheumatoid arthritis with Addison's disease. Ann Rheum Dis. 1952; 11:225–229. [PubMed: 12977058]

113. Evans RM. The steroid and thyroid hormone receptor superfamily. Science. 1988; 240:889–895. [PubMed: 3283939]

114. Evans RM, Arriza JL. A molecular framework for the actions of glucocorticoid hormones in the nervous system. Neuron. 1989; 45:1–27.

115. Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, Rabbia F, Federspil G, Mulatero P. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J Clin Endocrinol Metab. 2006; 91:454–459. [PubMed: 16291704]

116. Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction in vivo in humans: Evidence for an aldosterone-induced vasculopathy. Clin Sci (Lond). 2002; 103:425–431. [PubMed: 12241543]

117. Fejes-Toth G, Pearce D, Naray-Fejes-Toth A. Subcellular localization of mineralocorticoid receptors in living cells: Effects of receptor agonists and antagonists. Proc Natl Acad Sci U S A. 1998; 95:2973–2978. [PubMed: 9501200]

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

119. Feldman RD, Gros R. Unraveling the mechanisms underlying the rapid vascular effects of steroids: Sorting out the receptors and the pathways. Br J Pharmacol. 2011; 163:1163–1169. [PubMed: 21545416]
120. Fenelon VS, Poulain DA, Theodosis DT. Fos synthesis and neuronal activation: Analysis of fos immunoreactivity in identified magnocellular neurons during lactation. AnnNY Acad Sci. 1993; 689:508–511.
121. Ferguson D, Sapolsky R. Mineralocorticoid receptor overexpression differentially modulates specific phases of spatial and nonspatial memory. J Neurosci. 2007; 27:8046–8052. [PubMed: 17652595]
122. Ferguson D, Sapolsky R. Overexpression of mineralocorticoid and transdominant glucocorticoid receptor blocks the impairing effects of glucocorticoids on memory. Hippocampus. 2008; 18:1103–1111. [PubMed: 18651616]
123. Fiebeler A, Schmidt F, Muller DN, Park JK, Dechend R, Bieringer M, Shagdarsuren E, Breu V, Haller H, Luft FC. Mineralocorticoid receptor affects AP-1 and nuclear factor-kappab activation in angiotensin II-induced cardiac injury. Hypertension. 2001; 37:787–793. [PubMed: 11230374]
124. Filardo EJ, Thomas P. Minireview: G protein-coupled estrogen receptor-1, GPER-1: its mechanism of action and role in female reproductive cancer, renal and vascular physiology. Endocrinology. 2012; 153:2953–2962. [PubMed: 22495674]
125. Fischer K, Kelly SM, Watt K, Price NC, McEwan IJ. Conformation of the mineralocorticoid receptor N-terminal domain: Evidence for induced and stable structure. Mol Endocrinol. 2010; 24:1935–1948. [PubMed: 20685853]
126. 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–R259. [PubMed: 23193117]
127. Frey FJ, Odermatt A, Frey BM. Glucocorticoid-mediated mineralocorticoid receptor activation and hypertension. Curr Opin Nephrol Hypertens. 2004; 13:451–458. [PubMed: 15199296]
128. Fujita T. Mineralocorticoid receptors, salt-sensitive hypertension, and metabolic syndrome. Hypertension. 2010; 55:813–818. [PubMed: 20176994]
129. Fuller PJ, Brennan FE, Burgess JS. Acute differential regulation by corticosteroids of epithelial sodium channel subunit and Nedd4 mRNA levels in the distal colon. Pflugers Arch. 2000; 441:94–101. [PubMed: 11205067]
130. Fuller PJ, Lim-Tio SS, Brennan FE. Specificity in mineralocorticoid versus glucocorticoid action. Kidney Int. 2000; 57:1256–1264. [PubMed: 10760051]
131. Fuller PJ, Young MJ. Mechanisms of mineralocorticoid action. Hypertension. 2005; 46:1227–1235. [PubMed: 16286565]
132. Funder J, Myles K. Exclusion of corticosterone from epithelial mineralocorticoid receptors is insufficient for selectivity of aldosterone action: *In vivo* binding studies. Endocrinology. 1996; 137:5264–5268. [PubMed: 8940344]
133. Funder JW. Corticosteroid hypertension. CurrOpin Nephand Hyper. 1995; 4:432–437.
134. Funder JW. Non-genomic actions of aldosterone: Role in hypertension. Curr Opin Nephrol Hypertens. 2001; 10:227–230. [PubMed: 11224698]
135. Funder JW. Mineralocorticoid receptor activation and oxidative stress. Hypertension. 2007a; 50:840–841. [PubMed: 17923584]
136. Funder JW. Why are mineralocorticoid receptors so nonselective? Curr Hypertens Rep. 2007b; 9:112–116. [PubMed: 17442221]
137. Funder JW. GPR30, mineralocorticoid receptors, and the rapid vascular effects of aldosterone. Hypertension. 2011; 57:370–372. [PubMed: 21242458]
138. Funder JW, Pearce PT, Myles K, Roy LP. Apparent mineralocorticoid excess, pseudohypoaldosteronism, and urinary electrolyte excretion: Toward a redefinition of mineralocorticoid action. FASEB J. 1990; 4:3234–3238. [PubMed: 2172062]
139. Funder JW, Pearce PT, Smith R, Smith AI. Mineralocorticoid action: Target tissue specificity is enzyme, not receptor, mediated. Science. 1988; 242:583–585. [PubMed: 2845584]
140. Gabor A, Leenen FH. Central neuromodulatory pathways regulating sympathetic activity in hypertension. J Appl Physiol. 2012; 113:1294–1303. [PubMed: 22773773]

141. Galigniana MD, Erlejman AG, Monte M, Gomez-Sanchez C, Piwien-Pilipuk G. The hsp90-FKBP52 complex links the mineralocorticoid receptor to motor proteins and persists bound to the receptor in early nuclear events. Mol Cell Biol. 2010; 30:1285–1298. [PubMed: 20038533]

142. Galigniana MD, Harrell JM, Murphy PJ, Chinkers M, Radanyi C, Renoir JM, Zhang M, Pratt WB. Binding of hsp90-associated immunophilins to cytoplasmic dynein: Direct binding and in vivo evidence that the peptidylprolyl isomerase domain is a dynein interaction domain. Biochemistry. 2002; 41:13602–13610. [PubMed: 12427021]

143. Galigniana MD, Scruggs JL, Herrington J, Welsh MJ, Carter-Su C, Housley PR, Pratt WB. Heat shock protein 90-dependent (geldanamycin-inhibited) movement of the glucocorticoid receptor through the cytoplasm to the nucleus requires intact cytoskeleton. Mol Endocrinol. 1998; 12:1903–1913. [PubMed: 9849964]

144. Ganong WF. Circumventricular organs: Definition and role in the regulation of endocrine and autonomic function. Clin Exp Pharmacol Physiol. 2000; 27:422–427. [PubMed: 10831247]

145. Ganong WF, Mulrow PJ. Rate of change in sodium and potassium excretion after injection of aldosterone into the aorta and renal artery of the dog. Am J Physiol. 1958; 195:337–342. [PubMed: 13583172]

146. Gass P, Kretz O, Wolfer DP, Berger S, Tronche F, Reichardt HM, Kellendonk C, Lipp HP, Schmid W, Schutz G. Genetic disruption of mineralocorticoid receptor leads to impaired neurogenesis and granule cell degeneration in the hippocampus of adult mice. EMBO Rep. 2000; 1:447–451. [PubMed: 11258486]

147. Geerling JC, Kawata M, Loewy AD. Aldosterone-sensitive neurons in the rat central nervous system. J Comp Neurol. 2006; 494:515–527. [PubMed: 16320254]

148. 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]

149. Geerling JC, Loewy AD. Aldosterone in the brain. Am J Physiol Renal Physiol. 2009; 297:F559–F576. [PubMed: 19261742]

150. Gekle M, Silbernagl S, Wunsch S. Non-genomic action of the mineralocorticoid aldosterone on cytosolic sodium in cultured kidney cells. J Physiol. 1998; 511:255–263. Pt 1. [PubMed: 9679179]

151. Geller DS, Farhi A, Pinkerton N, Fradley M, Moritz M, Spitzer A, Meinke G, Tsai FT, Sigler PB, Lifton RP. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science. 2000; 289:119–123. [PubMed: 10884226]

152. Gennari-Moser C, Escher G, Kramer S, Dick B, Eisele N, Baumann M, Raio L, Frey FJ, Surbek D, Mohaupt MG. Normotensive blood pressure in pregnancy: The Role of salt and aldosterone. Hypertension. 2013; 63:362–368. [PubMed: 24296282]

153. Gennari-Moser C, Khankin EV, Schuller S, Escher G, Frey BM, Portmann CB, Baumann MU, Lehmann AD, Surbek D, Karumanchi SA, Frey FJ, Mohaupt MG. Regulation of placental growth by aldosterone and cortisol. Endocrinology. 2011; 152:263–271. [PubMed: 21068161]

154. Gesing A, Bilang-Bleuel A, Droste SK, Linthorst AC, Holsboer F, Reul JM. Psychological stress increases hippocampal mineralocorticoid receptor levels: Involvement of corticotropin-releasing hormone. J Neurosci. 2001; 21:4822–4829. [PubMed: 11425909]

155. Giacchetti G, Turchi F, Boscaro M, Ronconi V. Management of primary aldosteronism: Its complications and their outcomes after treatment. Curr Vasc Pharmacol. 2009; 7:244–249. [PubMed: 19356005]

156. Gilbert KC, Brown NJ. Aldosterone and inflammation. Curr Opin Endocrinol Diabetes Obes. 2010; 17:199–204. [PubMed: 20422780]

157. Giordano R, Pellegrino M, Picu A, Bonelli L, Oleandri SE, Pellissetto C, Limone P, Migliaretti G, Maccario M, Ghigo E, Arvat E. Primary hyperaldosteronism is associated with derangement in the regulation of the hypothalamus-pituitary-adrenal axis in humans. J Endocrinol Invest. 2007; 30:558–563. [PubMed: 17848838]

158. Gomez-Sanchez CE, Gomez-Sanchez EP. Editorial: Cardiac steroidogenesis—New sites of synthesis, or much ado about nothing? J Clin Endocrinol Metab. 2001; 86:5118–5120. [PubMed: 11701662]

159. Gomez-Sanchez CE, Gomez-Sanchez EP. The protective side of the mineralocorticoid receptor. Endocrinology. 2012; 153:1565–1567. [PubMed: 22408177]
160. Gomez-Sanchez CE, Zhou MY, Cozza EN, Morita H, Eddleman FC, Gomez-Sanchez EP. Corticosteroid synthesis in the central nervous system. Endocr Res. 1996; 22:463–470. [PubMed: 8969897]
161. Gomez-Sanchez CE, Zhou MY, Cozza EN, Morita H, Foecking MF, Gomez-Sanchez EP. Aldosterone biosynthesis in the rat brain. Endocrinology. 1997; 138:3369–3373. [PubMed: 9231789]
162. Gomez-Sanchez EP. Intracerebroventricular infusion of aldosterone induces hypertension in rats. Endocrinology. 1986; 118:819–823. [PubMed: 3943493]
163. Gomez-Sanchez EP. Dose-response studies of intracerebroventricular infusion of aldosterone in sensitized and nonsensitized rats. J Hypertension. 1988; 6:437–442.
164. Gomez-Sanchez EP. The mammalian mineralocorticoid receptor: Tying down a promiscuous receptor. Exp Physiol. 2010; 95:13–18. [PubMed: 19648477]
165. Gomez-Sanchez EP, Ahmad N, Romero DG, Gomez-Sanchez CE. Origin of aldosterone in the rat heart. Endocrinology. 2004; 145:4796–4802. [PubMed: 15308609]
166. Gomez-Sanchez EP, Ahmad N, Romero DG, Gomez-Sanchez CE. Is aldosterone synthesized within the rat brain? Am J Physiol Endocrinol Metab. 2005; 288:E342–E346. [PubMed: 15479953]
167. Gomez-Sanchez EP, Fort CM, Gomez-Sanchez CE. Intracerebroventricular infusions of RU28318 blocks aldosterone-salt hypertension. Am J Physiol. 1990; 258:E482–E484. [PubMed: 2316642]
168. Gomez-Sanchez EP, Ganjam V, Chen YJ, Cox DL, Zhou MY, Thanigaraj S, Gomez-Sanchez CE. The sheep kidney contains a novel unidirectional, high affinity $NADP^+$-dependent 11b-hydroxysteroid dehydrogenase (11-HSD3). Steroids. 1997; 62:444–450. [PubMed: 9178432]
169. 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; 66:845–848. [PubMed: 11576624]
170. Gomez-Sanchez EP, Ganjam V, Chen YJ, Liu Y, Zhou MY, Toroslu C, Romero DG, Hughson MD, de Rodriguez A, Gomez-Sanchez CE. Regulation of 11 beta-hydroxysteroid dehydrogenase enzymes in the rat kidney by estradiol. Am J Physiol Endocrinol Metab. 2003; 285:E272–E279. [PubMed: 12700160]
171. Gomez-Sanchez EP, Gomez-Sanchez CE. Central hypertensinogenic effects of glycyrrhizic acid and carbenoxolone. Am J Physiol. 1992; 263:E1125–E1130. [PubMed: 1476186]
172. Gomez-Sanchez EP, Gomez-Sanchez CE. Effect of central amiloride infusion on mineralocorticoid hypertension. Am J Physiol. 1994; 267:E754–E758. [PubMed: 7977727]
173. Gomez-Sanchez EP, Gomez-Sanchez CE. Editorial: First there was one, then two … why more 11b-hydroxysteroid dehydrogenases? Endocr. 1997; 138:5087–5088.
174. Gomez-Sanchez EP, Gomez-Sanchez CE. Is aldosterone synthesized in the CNS regulated and functional? Trends Endocrinol Metab. 2003; 14:444–446. [PubMed: 14643057]
175. Gomez-Sanchez EP, Gomez-Sanchez CE. Central regulation of blood pressure by the mineralocorticoid receptor. Mol Cell Endocrinol. 2012; 350:289–298. [PubMed: 21664417]
176. Gomez-Sanchez EP, Gomez-Sanchez CE, Fort C. Immunization of Dahl SS/jr rats with a ouabain conjugate mitigates salt-induced hypertension. Am J Hypertens. 1994; 7:591–596. [PubMed: 7946159]
177. Gomez-Sanchez EP, Gomez-Sanchez CM, Plonczynski M, Gomez-Sanchez CE. Aldosterone synthesis in the brain contributes to Dahl salt-sensitive rat hypertension. Exp Physiol. 2010; 95:120–130. [PubMed: 19837774]
178. 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; 149:525–533. [PubMed: 18039793]
179. Gomez-Sanchez EP, Samuel J, Vergara G, Ahmad N. Effect of 3{beta}-hydroxysteroid dehydrogenase inhibition by trilostane on blood pressure in the Dahl salt-sensitive rat. Am J Physiol Regul Integr Comp Physiol. 2005; 288:R389–R393. [PubMed: 15458970]

180. Gomez-Sanchez EP, Venkataraman MT, Thwaites D. ICV infusion of Corticosterone antagonizes ICV-aldosterone hypertension. Am J Physiol. 1990; 258:E649–E653. [PubMed: 2333961]
181. Goodfriend TL, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone: Theory and therapy. Hypertension. 2004; 43:518–524. [PubMed: 14732721]
182. Goodfriend TL, Egan BM, Kelley DE. Aldosterone in obesity. Endocr Res. 1998; 24:789–796. [PubMed: 9888579]
183. Gray MJ, Strausfeld KS, Watanabe M, Sims EA, Solomon S. Aldosterone secretory rates in the normal menstrual cycle. J Clin Endocrinol Metab. 1968; 28:1269–1275. [PubMed: 5679990]
184. Grillo C, Vallee SM, Piroli G, McEwen BS, De Nicola AF. Transformation and nuclear translocation of brain type L corticosteroid receptors complexed with the mineralocorticoid antagonist ZK 91587, aldosterone or dexamethasone. J Steroid Biochem Mol Biol. 1992; 42:515–520. [PubMed: 1616881]
185. Grippo AJ, Francis J, Weiss RM, Felder RB, Johnson AK. Cytokine mediation of experimental heart failure-induced anhedonia. Am J Physiol Regul Integr Comp Physiol. 2003; 284:R666–R673. [PubMed: 12611391]
186. 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]
187. 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]
188. Gros R, Ding Q, Davis M, Shaikh R, Liu B, Chorazyczewski J, Pickering JG, Feldman RD. Delineating the receptor mechanisms underlying the rapid vascular contractile effects of aldosterone and estradiol. Can J Physiol Pharmacol. 2011; 89:655–663. [PubMed: 21854125]
189. 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–C540. [PubMed: 23283935]
190. Gros R, Ding Q, Sklar LA, Prossnitz EE, Arterburn JB, Chorazyczewski J, Feldman RD. GPR30 expression is required for the mineralocorticoid receptor-independent rapid vascular effects of aldosterone. Hypertension. 2011; 57:442–451. [PubMed: 21242460]
191. Grossmann C, Benesic A, Krug AW, Freudinger R, Mildenberger S, Gassner B, Gekle M. Human mineralocorticoid receptor expression renders cells responsive for nongenotropic aldosterone actions. Mol Endocrinol. 2005; 19:1697–1710. [PubMed: 15761031]
192. Grossmann C, Freudinger R, Mildenberger S, Krug AW, Gekle M. Evidence for epidermal growth factor receptor as negative-feedback control in aldosterone-induced Na +reabsorption. Am J Physiol Renal Physiol. 2004; 286:F1226–F1231. [PubMed: 14749256]
193. Grossmann C, Gekle M. Non-classical actions of the mineralocorticoid receptor: Misuse of EGF receptors? Mol Cell Endocrinol. 2007; 277:6–12. [PubMed: 17692454]
194. Grossmann C, Gekle M. Nongenotropic aldosterone effects and the EGFR: Interaction and biological relevance. Steroids. 2008; 73:973–978. [PubMed: 18249428]
195. Grossmann C, Gekle M. New aspects of rapid aldosterone signaling. Mol Cell Endocrinol. 2009; 308:53–62. [PubMed: 19549592]
196. Grossmann C, Husse B, Mildenberger S, Schreier B, Schuman K, Gekle M. Colocalization of mineralocorticoid and EGF receptor at the plasma membrane. Biochim Biophys Acta. 2010; 1803:584–590. [PubMed: 20211660]
197. Grossmann C, Ruhs S, Langenbruch L, Mildenberger S, Stratz N, Schumann K, Gekle M. Nuclear shuttling precedes dimerization in mineralocorticoid receptor signaling. Chem Biol. 2012; 19:742–751. [PubMed: 22726688]
198. Grundy HM, Simpson SA, Tait JF. Isolation of a highly active mineralocorticoid from beef adrenal extract. Nature. 1952; 169:795–796. [PubMed: 14941045]
199. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, Li J, Williams GH, Adler GK. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation. 2008; 117:2253–2261. [PubMed: 18427128]

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

201. 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. J Physiol Pharmacol. 1969; 47:81–86.

202. Hamlyn JM, Laredo J, Shah JR, Lu ZR, Hamilton BP. 11-Hydroxylation in the biosynthesis of endogenous ouabain: Multiple implications. Ann N Y Acad Sci. 2003; 986:685–693. [PubMed: 12763919]

203. Hamlyn JM, Schenden JA, Zyren J, Baczynskyj L. Purification and characterization of digitalis-like factors from human plasma. Hypertension. 1987; 10(Suppl I):I-71–I-77. [PubMed: 2824370]

204. Han F, Ozawa H, Matsuda KI, Lu H, De Kloet ER, Kawata M. Changes in the expression of corticotrophin-releasing hormone, mineralocorticoid receptor and glucocorticoid receptor mRNAs in the hypothalamic paraventricular nucleus induced by fornix transection and adrenalectomy. J Neuroendocrinol. 2007; 19:229–238. [PubMed: 17244200]

205. Han HJ, Lee YH, Park SH. Estradiol-17beta-BSA stimulates Ca(2+) uptake through nongenomic pathways in primary rabbit kidney proximal tubule cells: Involvement of cAMP and PKC. J Cell Physiol. 2000; 183:37–44. [PubMed: 10699964]

206. Hardy MP, Gao HB, Dong Q, Ge R, Wang Q, Chai WR, Feng X, Sottas C. Stress hormone and male reproductive function. Cell Tissue Res. 2005; 322:147–153. [PubMed: 16079965]

207. Harrington WR, Kim SH, Funk CC, Madak-Erdogan Z, Schiff R, Katzenellenbogen JA, Katzenellenbogen BS. Estrogen dendrimer conjugates that preferentially activate extranuclear, nongenomic versus genomic pathways of estrogen action. Mol Endocrinol. 2006; 20:491–502. [PubMed: 16306086]

208. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. Horm Behav. 2011; 59:279–289. [PubMed: 20591431]

209. 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; 38:648–658. [PubMed: 22980941]

210. Harrison DG, Marvar PJ, Titze JM. Vascular inflammatory cells in hypertension. Front Physiol. 2012; 3:128. [PubMed: 22586409]

211. Harrison DG, Vinh A, Lob H, Madhur MS. Role of the adaptive immune system in hypertension. Curr Opin Pharmacol. 2010; 10:203–207. [PubMed: 20167535]

212. Harvey BJ, Alzamora R, Healy V, Renard C, Doolan CM. Rapid responses to steroid hormones: From frog skin to human colon. A homage to Hans Ussing. Biochim Biophys Acta. 2002; 1566:116–128. [PubMed: 12421543]

213. 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; 108:310–317. [PubMed: 17951051]

214. Harvey BJ, Doolan CM, Condliffe SB, Renard C, Alzamora R, Urbach V. Non-genomic convergent and divergent signalling of rapid responses to aldosterone and estradiol in mammalian colon. Steroids. 2002; 67:483–491. [PubMed: 11960625]

215. Hattangady NG, Olala LO, Bollag WB, Rainey WE. Acute and chronic regulation of aldosterone production. Mol Cell Endocrinol. 2012; 350:151–162. [PubMed: 21839803]

216. Hawkins UA, Gomez-Sanchez EP, Gomez-Sanchez CM, Gomez-Sanchez CE. The ubiquitous mineralocorticoid receptor: Clinical implications. Curr Hypertens Rep. 2012; 14:573–580. [PubMed: 22843494]

217. Hernandez-Diaz I, Giraldez T, Arnau MR, Smits VA, Jaisser F, Farman N, Alvarez de la Rosa D. The mineralocorticoid receptor is a constitutive nuclear factor in cardiomyocytes due to hyperactive nuclear localization signals. Endocrinology. 2010; 151:3888–3899. [PubMed: 20484457]

218. Hollenberg NK, Williams GH, Anderson R, Akhras KS, Bittman RM, Krause SL. Symptoms and the distress they cause: Comparison of an aldosterone antagonist and a calcium channel blocking

agent in patients with systolic hypertension. Arch Intern Med. 2003; 163:1543–1548. [PubMed: 12860576]

219. Hollis G, Huber R. 11beta-Hydroxysteroid dehydrogenase type 1 inhibition in type 2 diabetes mellitus. Diabetes Obes Metab. 2011; 13:1–6. [PubMed: 21114597]
220. Holmes MC, Abrahamsen CT, French KL, Paterson JM, Mullins JJ, Seckl JR. The mother or the fetus? 11beta-hydroxysteroid dehydrogenase type 2 null mice provide evidence for direct fetal programming of behavior by endogenous glucocorticoids. J Neurosci. 2006; 26:3840–3844. [PubMed: 16597738]
221. Holmes MC, Carter RN, Noble J, Chitnis S, Dutia A, Paterson JM, Mullins JJ, Seckl JR, Yau JL. 11beta-hydroxysteroid dehydrogenase type 1 expression is increased in the aged mouse hippocampus and parietal cortex and causes memory impairments. J Neurosci. 2010; 30:6916–6920. [PubMed: 20484633]
222. Holmes MC, Seckl JR. The role of 11beta-hydroxysteroid dehydrogenases in the brain. Mol Cell Endocrinol. 2006; 248:9–14. [PubMed: 16413106]
223. Howland RH. Mifepristone as a therapeutic agent in psychiatry. J Psychosoc Nurs Ment Health Serv. 2013; 51:11–14.
224. Hu X, Funder JW. The evolution of mineralocorticoid receptors. Mol Endocrinol. 2005; 20:1471–1478. [PubMed: 16195247]
225. 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–H2497. [PubMed: 15615845]
226. Huang BS, Leenen FH. The brain renin-angiotensin-aldosterone system: A major mechanism for sympathetic hyperactivity and left ventricular remodeling and dysfunction after myocardial infarction. Curr Heart Fail Rep. 2009; 6:81–88. [PubMed: 19486591]
227. 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]
228. Huang S, Zhang A, Ding G, Chen R. Aldosterone-induced mesangial cell proliferation is mediated by EGF receptor transactivation. Am J Physiol Renal Physiol. 2009; 296:F1323–F1333. [PubMed: 19339632]
229. Hultman ML, Krasnoperova NV, Li S, Du S, Xia C, Dietz JD, Lala DS, Welsch DJ, Hu X. The ligand-dependent interaction of mineralocorticoid receptor with coactivator and corepressor peptides suggests multiple activation mechanisms. Mol Endocrinol. 2005; 19:1460–1473. [PubMed: 15761029]
230. Hunter RG. Epigenetic effects of stress and corticosteroids in the brain. Front Cell Neurosci. 2012; 6:18. [PubMed: 22529779]
231. Igarashi J, Hashimoto T, Shoji K, Yoneda K, Tsukamoto I, Moriue T, Kubota Y, Kosaka H. Dexamethasone induces caveolin-1 in vascular endothelial cells: Implications for attenuated responses to VEGF. Am J Physiol Cell Physiol. 2013; 304:C790–C800. [PubMed: 23426970]
232. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther. 2007; 116:496–526. [PubMed: 18001838]
233. Janiak PC, Lewis SJ, Brody MJ. Role of central mineralocorticoid binding sites in development of hypertension. Am J Physiol. 1990; 259:R1025–R1034. [PubMed: 2240262]
234. Joels M. Corticosteroid actions in the hippocampus. J Neuroendocrinol. 2001; 13:657–669. [PubMed: 11489082]
235. Joels M, Karst H, DeRijk R, de Kloet ER. The coming out of the brain mineralocorticoid receptor. Trends Neurosci. 2008; 31:1–7. [PubMed: 18063498]
236. 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; 64:901–938. [PubMed: 23023031]
237. Jones AW, Hart RG. Altered ion transport in aortic smooth muscle during deoxycorticosterone acetate hypertension in rats. Circ Res. 1975; 37:333–341. [PubMed: 1157222]

238. Kang L, Zhang X, Xie Y, Tu Y, Wang D, Liu Z, Wang ZY. Involvement of estrogen receptor variant ER-alpha36, not GPR30, in nongenomic estrogen signaling. Mol Endocrinol. 2010; 24:709–721. [PubMed: 20197310]

239. Kang YM, Zhang ZH, Johnson RF, Yu Y, Beltz T, Johnson AK, Weiss RM, Felder RB. Novel effect of mineralocorticoid receptor antagonism to reduce proinflammatory cytokines and hypothalamic activation in rats with ischemia-induced heart failure. Circ Res. 2006; 99:758–766. [PubMed: 16960100]

240. 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–H236. [PubMed: 18487441]

241. 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; 102:19204–19207. [PubMed: 16361444]

242. Karten YJ, Nair SM, van Essen L, Sibug R, Joels M. Long-term exposure to high corticosterone levels attenuates serotonin responses in rat hippocampal CA1 neurons. Proc Natl Acad Sci U S A. 1999; 96:13456–13461. [PubMed: 10557342]

243. Kassahn KS, Ragan MA, Funder JW. Mineralocorticoid receptors: Evolutionary and pathophysiological considerations. Endocrinology. 2011; 152:1883–1890. [PubMed: 21343255]

244. Kawakami-Mori F, Shimosawa T, Mu S, Wang H, Ogura S, Yatomi Y, Fujita T. 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–E432. [PubMed: 22114025]

245. 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]

246. Klok MD, Vreeburg SA, Penninx BW, Zitman FG, de Kloet ER, Derijk RH. Common functional mineralocorticoid receptor polymorphisms modulate the cortisol awakening response: Interaction with SSRIs. Psychoneuroendocrinology. 2010; 36:484–494. [PubMed: 20884124]

247. Kolla V, Litwack G. Transcriptional regulation of the human Na/K ATPase via the human mineralocorticoid receptor. Molr Cell Biochem. 2000; 204:35–40.

248. Kontak AC, Wang Z, Arbique D, Adams-Huet B, Auchus RJ, Nesbitt SD, Victor RG, Vongpatanasin W. Reversible sympathetic overactivity in hypertensive patients with primary aldosteronism. J Clin Endocrinol Metab. 2010; 95:4756–4761. [PubMed: 20660053]

249. Koska P, Dojcsak Kiss-Toth E, Juhasz Szalai A, Kovacs GL, Barkai L, Racz O, Fodor B. Brain glucose sensing and counterregulatory response to hypoglycaemia. Acta Physiol Hungarica. 2013; 100:133–139.

250. Kraus D, Jager J, Meier B, Fasshauer M, Klein J. Aldosterone inhibits uncoupling protein-1, induces insulin resistance, and stimulates proinflammatory adipokines in adipocytes. Horm Metab Res. 2005; 37:455–459. [PubMed: 16034720]

251. Krozowski Z, Stuchberry S, White PC, Monder C, Funder JW. Characterization of 11b-hydroxysteroid dehydrogenase gene expression: Identification of multiple unique forms of messenger ribonucleic acid in the rat kidney. Endocrinology. 1990; 127:3009–3013. [PubMed: 2249639]

252. 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; 80:6056–6060. [PubMed: 6310613]

253. Krug AW, Schuster C, Gassner B, Freudinger R, Mildenberger S, Troppmair J, Gekle M. Human epidermal growth factor receptor-1 expression renders Chinese hamster ovary cells sensitive to alternative aldosterone signaling. J Biol Chem. 2002; 277:45892–45897. [PubMed: 12244120]

254. Kunzel HE. Psychopathological symptoms in patients with primary hyperaldosteronism—Possible pathways. Horm Metab Res. 2012; 44:202–207. [PubMed: 22351473]

255. Kunzel HE, Apostolopoulou K, Pallauf A, Gerum S, Merkle K, Schulz S, Fischer E, Brand V, Bidlingmaier M, Endres S, Beuschlein F, Reincke M. 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; 46:1650–1654. [PubMed: 23017810]

256. Kwak SP, Patel PD, Thompson RC, Akil H, Watson SJ. 5′-Heterogeneity of the mineralocorticoid receptor messenger ribonucleic acid: Differential expression and regulation of splice variants within the rat hippocampus. Endocrinology. 1993; 133:2344–2350. [PubMed: 8404687]

257. Lai M, Horsburgh K, Bae SE, Carter RN, Stenvers DJ, Fowler JH, Yau JL, Gomez-Sanchez CE, Holmes MC, Kenyon CJ, Seckl JR, Macleod MR. Forebrain mineralocorticoid receptor overexpression enhances memory, reduces anxiety and attenuates neuronal loss in cerebral ischaemia. Eur J Neurosci. 2007; 25:1832–1842. [PubMed: 17432969]

258. Lam EY, Funder JW, Nikolic-Paterson DJ, Fuller PJ, Young MJ. Mineralocorticoid receptor blockade but not steroid withdrawal reverses renal fibrosis in DOC/salt rats. Endocrinology. 2006; 147:3623–3639. [PubMed: 16627578]

259. Langford HG, Snavely JR. Effect of DCA on development of renoprival hypertension. Amer J Physiol. 1959; 196:449–450. [PubMed: 13627199]

260. 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; 8:203–207. [PubMed: 18625117]

261. Le Menuet D, Munier M, Meduri G, Viengchareun S, Lombes M. Mineralocorticoid receptor overexpression in embryonic stem cell-derived cardiomyocytes increases their beating frequency. Cardiovasc Res. 2010; 87:467–475. [PubMed: 20299331]

262. Leal T, Crabbé J. Effects of aldosterone on (Na^++K^+)-ATPase of amphibian sodium-transporting epithelial cells (A6) in culture. J Steroid Biochem. 1989; 34:581–584. [PubMed: 2560522]

263. Lee H, Woodman SE, Engelman JA, Volonte D, Galbiati F, Kaufman HL, Lublin DM, Lisanti MP. Palmitoylation of caveolin-1 at a single site (Cys-156) controls its coupling to the c-Src tyrosine kinase: Targeting of dually acylated molecules (GPI-linked, transmembrane, or cytoplasmic) to caveolae effectively uncouples c-Src and caveolin-1 (TYR-14). J Biol Chem. 2001; 276:35150–35158. [PubMed: 11451957]

264. Li Z, Xie Z. The Na/K-ATPase/Src complex and cardiotonic steroid-activated protein kinase cascades. Pflugers Arch. 2009; 457:635–644. [PubMed: 18283487]

265. Liang M, Cai T, Tian J, Qu W, Xie ZJ. Functional characterization of Src-interacting Na/K-ATPase using RNA interference assay. J Biol Chem. 2006; 281:19709–19719. [PubMed: 16698801]

266. Listwak SJ, Gold PW, Whitfield HJ Jr. The human mineralocorticoid receptor gene promoter: Its structure and expression. J Steroid Biochem Mol Biol. 1996; 58:495–506. [PubMed: 8918975]

267. Liu SL, Schmuck S, Chorazcyzewski JZ, Gros R, Feldman RD. Aldosterone regulates vascular reactivity: Short-term effects mediated by phosphatidylinositol 3-kinase-dependent nitric oxide synthase activation. Circulation. 2003; 108:2400–2406. [PubMed: 14557368]

268. Lo J, Looby SE, Wei J, Adler GK, Grinspoon SK. Increased aldosterone among HIV-infected women with visceral fat accumulation. Aids. 2009; 23:2366–2370. [PubMed: 19770620]

269. Losel R, Feuring M, Wehling M. Non-genomic aldosterone action: From the cell membrane to human physiology. J Steroid Biochem Mol Biol. 2002; 83:167–171. [PubMed: 12650713]

270. Losel R, Schultz A, Wehling M. A quick glance at rapid aldosterone action. Mol Cell Endocrinol. 2004; 217:137–141. [PubMed: 15134812]

271. Losel RM, Falkenstein E, Feuring M, Schultz A, Tillmann HC, Rossol-Haseroth K, Wehling M. Nongenomic steroid action: Controversies, questions, and answers. Physiol Rev. 2003; 83:965–1016. [PubMed: 12843413]

272. Luft R, Sjogren B. The effect of desoxycorticosterone acetate and sodium chloride on blood pressure and renal function. Acta Endocrinol (Copenh). 1949; 3:56–70. [PubMed: 15396700]

273. Luther JM, Gainer JV, Murphey LJ, Yu C, Vaughan DE, Morrow JD, Brown NJ. Angiotensin II induces interleukin-6 in humans through a mineralocorticoid receptor-dependent mechanism. Hypertension. 2006; 48:1050–1057. [PubMed: 17043157]

274. MacKenzie SM, Clark CJ, Ingram MC, Lai M, Seckl J, Gomez-Sanchez CE, Fraser R, Connell JM, Davies E. Corticosteroid production by fetal rat hippocampal neurons. Endocr Res. 2000; 26:531–535. [PubMed: 11196425]

275. MacKenzie SM, Dewar D, Stewart W, Fraser R, Connell JM, Davies E. The transcription of steroidogenic genes in the human cerebellum and hippocampus: A comparative survey of normal and Alzheimer's tissue. J Endocrinol. 2008; 196:123–130. [PubMed: 18180323]
276. MacKenzie SM, Fraser R, Connell JM, Davies E. Local renin-angiotensin systems and their interactions with extra-adrenal corticosteroid production. J Renin Angiotensin Aldosterone Syst. 2002; 3:214–221. [PubMed: 12584665]
277. MacKenzie SM, Huda SS, Sattar N, Fraser R, Connell JM, Davies E. Depot-specific steroidogenic gene transcription in human adipose tissue. Clin Endocrinol (Oxf). 2008; 69:848–854. [PubMed: 18410552]
278. Maggio N, Segal M. Cellular basis of a rapid effect of mineralocorticosteroid receptors activation on LTP in ventral hippocampal slices. Hippocampus. 2012; 22:267–275. [PubMed: 21080413]
279. Maksymowych AB, Hsu TC, Litwack G. A novel, highly conserved structural motif is present in all members of the steroid receptor superfamily. Receptor. 1992; 2:225–240. [PubMed: 1299410]
280. Malinow KC, Lion JR. Hyperaldosteronism (Conn's disease) presenting as depression. J Clin Psychiatry. 1979; 40:358–359. [PubMed: 468762]
281. Marino M, Ascenzi P. Steroid hormone rapid signaling: The pivotal role of S-palmitoylation. IUBMB Life. 2006; 58:716–719. [PubMed: 17424910]
282. Marney AM, Brown NJ. Aldosterone and end-organ damage. Clin Sci (Lond). 2007; 113:267–278. [PubMed: 17683282]
283. Marvar PJ, Harrison DG. Stress-dependent hypertension and the role of T lymphocytes. Exp Physiol. 2012; 97:1161–1167. [PubMed: 22941978]
284. Marvar PJ, Vinh A, Thabet S, Lob HE, Geem D, Ressler KJ, Harrison DG. T lymphocytes and vascular inflammation contribute to stress-dependent hypertension. Biol Psychiatry. 2012; 71:774–782. [PubMed: 22361077]
285. Marver D. Models of aldosterone action on sodium transport: Emerging concepts. Adv Exptl Med Biol. 1986; 196:153–171. [PubMed: 3012976]
286. Marzolla V, Armani A, Zennaro MC, Cinti F, Mammi C, Fabbri A, Rosano GM, Caprio M. The role of the mineralocorticoid receptor in adipocyte biology and fat metabolism. Mol Cell Endocrinol. 2012; 350:281–288. [PubMed: 21945603]
287. Mattos GE, Heinzmann JM, Norkowski S, Helbling JC, Minni AM, Moisan MP, Touma C. Corticosteroid-binding globulin contributes to the neuroendocrine phenotype of mice selected for extremes in stress reactivity. J Endocrinol. 2013; 219:217–229. [PubMed: 24048966]
288. Mattsson C, Lai M, Noble J, McKinney E, Yau JL, Seckl JR, Walker BR. Obese Zucker rats have reduced mineralocorticoid receptor and 11beta-hydroxysteroid dehydrogenase type 1 expression in hippocampus-implications for dysregulation of the hypothalamic-pituitary-adrenal axis in obesity. Endocrinology. 2003; 144:2997–3003. [PubMed: 12810555]
289. Mattsson C, Reynolds RM, Simonyte K, Olsson T, Walker BR. Combined receptor antagonist stimulation of the hypothalamic-pituitaryadrenal axis test identifies impaired negative feedback sensitivity to cortisol in obese men. J Clin Endocrinol Metab. 2009; 94:1347–1352. [PubMed: 19141586]
290. McEwen BS. Corticosteroids and hippocampal plasticity. Ann N Y Acad Sci. 1994; 746:134–142. discussion 142-144, 178-139. [PubMed: 7825871]
291. McEwen BS, Eiland L, Hunter RG, Miller MM. Stress and anxiety: Structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology. 2012; 62:3–12. [PubMed: 21807003]
292. McEwen BS, Weiss JM, Schwartz LS. Selective retention of corticosterone by limbic structures in rat brain. Nature. 1968; 220:911–912. [PubMed: 4301849]
293. McKenna NJ, O'Malley BW. Minireview: Nuclear receptor coactivators—An update. Endocrinology. 2002; 143:2461–2465. [PubMed: 12072374]
294. McKenna NJ, O'Malley BW. Nuclear receptors, coregulators, ligands, and selective receptor modulators: Making sense of the patchwork quilt. AnnNY Acad Sci. 2001; 949:3–5.
295. McManus F, MacKenzie SM, Freel EM. Central mineralocorticoid receptors, sympathetic activity, and hypertension. Curr Hypertens Rep. 2009; 11:224–230. [PubMed: 19442333]

296. Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, Caldji C, Sharma S, Seckl JR, Plotsky PM. Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. Dev Neurosci. 1996; 18:49–72. [PubMed: 8840086]

297. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: Life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci. 2005; 7:103–123. [PubMed: 16262207]

298. Meijer OC, de Kloet ER. Corticosterone and serotonergic neurotransmission in the hippocampus: Functional implications of central corticosteroid receptor diversity. Crit Rev Neurobiol. 1998; 12:1–20. [PubMed: 9444479]

299. Meijer OC, Steenbergen PJ, De Kloet ER. Differential expression and regional distribution of steroid receptor coactivators SRC-1 and SRC-2 in brain and pituitary. Endocrinology. 2000; 141:2192–2199. [PubMed: 10830308]

300. Mellon SH, Deschepper CF. Neurosteroid biosynthesis: Genes for adrenal steroidogenic enzymes are expressed in the brain. Brain Res. 1993; 629:283–292. [PubMed: 8111631]

301. Michael AE, Glenn C, Wood PJ, Webb RJ, Pellatt L, Mason HD. Ovarian 11beta-hydroxysteroid dehydrogenase (11betaHSD) activity is suppressed in women with anovulatory Polycystic Ovary Syndrome (PCOS): Apparent role for ovarian androgens. J Clin Endocrinol Metab. 2013; 98:3375–3383. [PubMed: 23678035]

302. Michailidou Z, Carter RN, Marshall E, Sutherland HG, Brownstein DG, Owen E, Cockett K, Kelly V, Ramage L, Al-Dujaili EA, Ross M, Maraki I, Newton K, Holmes MC, Seckl JR, Morton NM, Kenyon CJ, Chapman KE. Glucocorticoid receptor haploinsufficiency causes hypertension and attenuates hypothalamic-pituitary-adrenal axis and blood pressure adaptions to high-fat diet. FASEB J. 2008; 22:3896–3907. [PubMed: 18697839]

303. Michea L, Delpiano AM, Hitschfeld C, Lobos L, Lavandero S, Marusic ET. Eplerenone blocks nongenomic effects of aldosterone on the Na^+/H^+ exchanger, intracellular Ca^{2+} levels and vasoconstriction in mesenteric resistance vessels. Endocrinology. 2004; 146:973–980. [PubMed: 15550504]

304. Mihailidou AS, Loan Le TY, Mardini M, Funder JW. Glucocorticoids activate cardiac mineralocorticoid receptors during experimental myocardial infarction. Hypertension. 2009; 54:1306–1312. [PubMed: 19841288]

305. Mitra R, Ferguson D, Sapolsky RM. Mineralocorticoid receptor overexpression in basolateral amygdala reduces corticosterone secretion and anxiety. Biol Psychiatry. 2009; 66:686–690. [PubMed: 19500777]

306. Moisan M-P, Edwards CRW, Seckl JR. Ontogeny of 11b-hydroxysteroid dehydrogenase in rat brain and kidney. Endocrinology. 1992; 130:400–404. [PubMed: 1727713]

307. Moisan M-P, Seckl JR, Edwards CRW. 11b-Hydroxysteroid dehydrogenase bioactivity and messenger RNA expression in rat forebrain: Localization in hypothalamus, hippocampus, and cortex. Endocrinology. 1990; 127:1450–1455. [PubMed: 2387261]

308. Moisan MP, Minni AM, Dominguez G, Helbling JC, Foury A, Henkous N, Dorey R, Beracochea D. Role of corticosteroid binding globulin in the fast actions of glucocorticoids on the brain. Steroids. 2013; 81C:109–115. [PubMed: 24252379]

309. Monahan KD, Leuenberger UA, Ray CA. Aldosterone impairs baroreflex sensitivity in healthy adults. Am J Physiol Heart Circ Physiol. 2007; 292:H190–H197. [PubMed: 16920805]

310. Monder C. The forms and functions of 11b-hydroxysteroid dehydrogenase. J Steroid Biochem Mol Biol. 1993; 45:161–165. [PubMed: 8481341]

311. Monder C, Shackleton CH, Bradlow HL, New MI, Stoner E, Iohan F, Lakshmi V. 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; 63:550–557. [PubMed: 3460996]

312. Morgan SA, Gathercole LL, Simonet C, Hassan-Smith ZK, Bujalska I, Guest P, Abrahams L, Smith DM, Stewart PM, Lavery GG, Tomlinson JW. Regulation of lipid metabolism by glucocorticoids and 11beta-HSD1 in skeletal muscle. Endocrinology. 2013; 154:2374–2384. [PubMed: 23633532]

313. Moura A-M, Worcel M. Direct action of aldosterone on transmembrane 22Na efflux from arterial smooth muscle: Rapid and delayed effects. Hypertension. 1984; 6:425–430. [PubMed: 6329952]

314. Munier M, Law F, Meduri G, Le Menuet D, Lombes M. Mineralocorticoid receptor overexpression facilitates differentiation and promotes survival of embryonic stem cell-derived neurons. Endocrinology. 2012; 153:1330–1340. [PubMed: 22234470]

315. Munier M, Meduri G, Viengchareun S, Leclerc P, Le Menuet D, Lombes M. Regulation of mineralocorticoid receptor expression during neuronal differentiation of murine embryonic stem cells. Endocrinology. 2010; 151:2244–2254. [PubMed: 20207834]

316. Murgatroyd C. Epigenetic programming of neuroendocrine systems during early life. Exp Physiol. 2014; 99:62–65. [PubMed: 24036596]

317. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmuhl Y, Fischer D, Holsboer F, Wotjak CT, Almeida OF, Spengler D. Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nat Neurosci. 2009; 12:1559–1566. [PubMed: 19898468]

318. Murphy D, Costall B, Smythe JW. Regulation of hippocampal theta activity by corticosterone: Opposing functions of mineralocorticoid and glucocorticoid receptors. Brain Res Bull. 1998; 45:631–635. [PubMed: 9566508]

319. Nagase M, Fujita T. Aldosterone and glomerular podocyte injury. Clin Exp Nephrol. 2008; 12:233–242. [PubMed: 18317876]

320. Nagase M, Fujita T. Role of Rac1-mineralocorticoid-receptor signalling in renal and cardiac disease. Nat Rev Nephrol. 2013; 9:86–98. [PubMed: 23296296]

321. Nair S, Lee YH, Lindsay RS, Walker BR, Tataranni PA, Bogardus C, Baier LJ, Permana PA. 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; 47:1088–1095. [PubMed: 15156315]

322. Naray-Fejes-Toth A, Fejes-Toth G. Extranuclear localization of endogenous 11beta-hydroxysteroid dehydrogenase-2 in aldosterone target cells. Endocrinology. 1998; 139:2955–2959. [PubMed: 9607806]

323. 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; 271:15436–15442. [PubMed: 8663122]

324. Nelson EB. Psychotic depression–beyond the antidepressant/antipsychotic combination. Curr Psychiatry Rep. 2012; 14:619–623. [PubMed: 22936518]

325. Neumaier JF, Sexton TJ, Hamblin MW, Beck SG. Corticosteroids regulate 5-HT(1A) but not 5-HT(1B) receptor mRNA in rat hippocampus. Brain Res Mol Brain Res. 2000; 82:65–73. [PubMed: 11042358]

326. Nicholls MG, Espiner EA, Ikram H, Maslowski AH, Hamilton EJ, Bones PJ. Hormone and blood pressure relationships in primary aldosteronism. Clin Exp Hypertension A. 1984; 6:1441–1458.

327. Nietlispach F, Julius B, Schindler R, Bernheim A, Binkert C, Kiowski W, Brunner-La Rocca HP. Influence of acute and chronic mineralocorticoid excess on endothelial function in healthy men. Hypertension. 2007; 50:82–88. [PubMed: 17502494]

328. Nishi M, Ogawa H, Ito T, Matsuda KI, Kawata M. Dynamic changes in subcellular localization of mineralocorticoid receptor in living cells: In comparison with glucocorticoid receptor using dual-color labeling with green fluorescent protein spectral variants. Mol Endocrinol. 2001; 15:1077–1092. [PubMed: 11435609]

329. Nishi M, Tanaka M, Matsuda K, Sunaguchi M, Kawata M. Visualization of glucocorticoid receptor and mineralocorticoid receptor interactions in living cells with GFP-based fluorescence resonance energy transfer. J Neurosci. 2004; 24:4918–4927. [PubMed: 15163683]

330. Nonaka Y, Takemori H, Halder SK, Sun T, Ohta M, Hatano O, Takakusu A, Okamoto M. Frog cytochrome P-450 (11 beta,aldo), a single enzyme involved in the final steps of glucocorticoid and mineralocorticoid biosynthesis. Eur J Biochem. 1995; 229:249–256. [PubMed: 7744036]

331. Nunn N, Womack M, Dart C, Barrett-Jolley R. Function and pharmacology of spinally-projecting sympathetic pre-autonomic neurones in the paraventricular nucleus of the hypothalamus. Curr Neuropharmacol. 2011; 9:262–277. [PubMed: 22131936]

332. Nystrom AM, Bondeson ML, Skanke N, Martensson J, Stromberg B, Gustafsson J, Anneren G. A novel nonsense mutation of the mineralocorticoid receptor gene in a Swedish family with pseudohypoaldosteronism type I (PHA1). J Clin Endocrinol Metab. 2004; 89:227–231. [PubMed: 14715854]
333. Obradovic D, Tirard M, Nemethy Z, Hirsch O, Gronemeyer H, Almeida OF. DAXX, FLASH, and FAF-1 modulate mineralocorticoid and glucocorticoid receptor-mediated transcription in hippocampal cells— Toward a basis for the opposite actions elicited by two nuclear receptors? Mol Pharmacol. 2004; 65:761–769. [PubMed: 14978255]
334. 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; 276:28484–28492. [PubMed: 11350956]
335. Ohnishi T, Wada A, Nonaka Y, Sugiyama T, Yamano T, Okamoto M. Effect of calmodulin on aldosterone synthesis by a cytochrome P-450^{11b}-reconstituted system from bovine adrenocortical mitochondria. J Biochem (Tokyo). 1986; 100:1065–1076. [PubMed: 3493242]
336. Ohno S, Nakagawara S, Honda Y, Nakajin S. Evidence for expression of 11beta-hydroxysteroid dehydrogenase type3 (HSD11B3/HSD11B1L) in neonatal pig testis. Mol Cell Biochem. 2013; 381:145–156. [PubMed: 23881245]
337. Oitzl MS, Champagne DL, van der Veen R, de Kloet ER. Brain development under stress: Hypotheses of glucocorticoid actions revisited. Neurosci Biobehav Rev. 2010; 34:853–866. [PubMed: 19631685]
338. Oitzl MS, van Haarst AD, Sutanto W, De Kloet ER. Corticosterone, brain mineralocorticoid receptors (MRs) and the activity of the hypothalamic-pituitary-adrenal (HPA) axis: The Lewis rat as an example of increased central MR capacity and a hyporesponsive HPA axis. Psychoneuroendocr. 1995; 20:655–675.
339. Okamoto M, Nonaka Y, Takemori H, Doi J. Molecular identity and gene expression of aldosterone synthase cytochrome P450. Biochem Biophys Res Commun. 2005; 338:325–330. [PubMed: 16105656]
340. 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; 27:2542–2550. [PubMed: 18547242]
341. Otte C, Hinkelmann K, Moritz S, Yassouridis A, Jahn H, Wiedemann K, Kellner M. 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; 44:339–346. [PubMed: 19909979]
342. Otte C, Moritz S, Yassouridis A, Koop M, Madrischewski AM, Wiedemann K, Kellner M. Blockade of the mineralocorticoid receptor in healthy men: Effects on experimentally induced panic symptoms, stress hormones, and cognition. Neuropsychopharmacology. 2007; 32:232–238. [PubMed: 17035932]
343. Ou XM, Storring JM, Kushwaha N, Albert PR. Heterodimerization of mineralocorticoid and glucocorticoid receptors at a novel negative response element of the 5-HT1A receptor gene. J Biol Chem. 2001; 276:14299–14307. [PubMed: 11278286]
344. Pascual-Le Tallec L, Demange C, Lombes M. Human mineralocorticoid receptor A and B protein forms produced by alternative translation sites display different transcriptional activities. Eur J Endocrinol. 2004; 150:585–590. [PubMed: 15080790]
345. Pascual-Le Tallec L, Lombes M. The mineralocorticoid receptor: A journey exploring its diversity and specificity of action. Mol Endocrinol. 2005; 19:2211–2221. [PubMed: 15802372]
346. Pascual-Le Tallec L, Simone F, Viengchareun S, Meduri G, Thirman MJ, Lombes M. The elongation factor ELL (eleven-nineteen lysine-rich leukemia) is a selective coregulator for steroid receptor functions. Mol Endocrinol. 2005; 19:1158–1169. [PubMed: 15650021]
347. Pasricha N, Joels M, Karst H. Rapid effects of corticosterone in the mouse dentate gyrus via a nongenomic pathway. J Neuroendocrinol. 2011; 23:143–147. [PubMed: 21092068]
348. Patkar S, Farr TD, Cooper E, Dowell FJ, Carswell HV. Differential vasoactive effects of oestrogen, oestrogen receptor agonists and selective oestrogen receptor modulators in rat middle cerebral artery. Neurosci Res. 2011; 71:78–84. [PubMed: 21624404]

349. Pavlides C, McEwen BS. Effects of mineralocorticoid and glucocorticoid receptors on long-term potentiation in the CA3 hippocampal field. Brain Res. 1999; 851:204–214. [PubMed: 10642845]
350. Pavlides C, Ogawa S, Kimura A, McEwen BS. Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. Brain Res. 1996; 738:229–235. [PubMed: 8955517]
351. Pearce D, Naray-Fejes-Toth A, Fejes-Toth G. Determinants of subnuclear organization of mineralocorticoid receptor characterized through analysis of wild type and mutant receptors. J Biol Chem. 2002; 277:1451–1456. [PubMed: 11677231]
352. Penning TM. Hydroxysteroid dehydrogenases and pre-receptor regulation of steroid hormone action. Hum Reprod Update. 2003; 9:193–205. [PubMed: 12861966]
353. Pilipuk GP, Vinson GP, Gomez-Sanchez CE, Galigniana MD. Evidence for NL1-independent nuclear translocation of the mineralocorticoid receptor. Biochemistry. 2007; 46:1389–1397. [PubMed: 17260968]
354. Pimenta E, Calhoun DA, Oparil S. Sleep apnea, aldosterone, and resistant hypertension. Prog Cardiovasc Dis. 2009; 51:371–380. [PubMed: 19249443]
355. Pitt B. Effect of aldosterone blockade in patients with systolic left ventricular dysfunction: Implications of the RALES and EPHESUS studies. Mol Cell Endocrinol. 2004; 217:53–58. [PubMed: 15134801]
356. Pitt B, Stier CT Jr. Rajagopalan S. Mineralocorticoid receptor blockade: New insights into the mechanism of action in patients with cardiovascular disease. J Renin Angiotensin Aldosterone Syst. 2003; 4:164–168. [PubMed: 14608520]
357. Pojoga LH, Coutinho P, Rivera A, Yao TM, Maldonado ER, Youte R, Adler GK, Williams J, Turchin A, Williams GH, Romero JR. Activation of the mineralocorticoid receptor increases striatin levels. Am J Hypertens. 2012; 25:243–249. [PubMed: 22089104]
358. Pojoga LH, Romero JR, Yao TM, Loutraris P, Ricchiuti V, Coutinho P, Guo C, Lapointe N, Stone JR, Adler GK, Williams GH. Caveolin-1 ablation reduces the adverse cardiovascular effects of N-omega-nitro-L-arginine methyl ester and angiotensin II. Endocrinology. 2010; 151:1236–1246. [PubMed: 20097717]
359. Qi XR, Kamphuis W, Wang S, Wang Q, Lucassen PJ, Zhou JN, Swaab DF. Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients. Psychoneuroendocrinology. 2012; 38:863–870. [PubMed: 23137715]
360. Queisser N, Fazeli G, Schupp N. Superoxide anion and hydrogen peroxide-induced signaling and damage in angiotensin II and aldosterone action. Biol Chem. 2010; 391:1265–1279. [PubMed: 20868230]
361. Queisser N, Schupp N. Aldosterone, oxidative stress, and NF-kappaB activation in hypertension-related cardiovascular and renal diseases. Free Radic Biol Med. 2012; 53:314–327. [PubMed: 22609249]
362. Queisser N, Schupp N, Stopper H, Schinzel R, Oteiza PI. Aldosterone increases kidney tubule cell oxidants through calcium-mediated activation of NADPH oxidase and nitric oxide synthase. Free Radic Biol Med. 2011; 51:1996–2006. [PubMed: 21946068]
363. 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; 171:21–24. [PubMed: 11165007]
364. Quinkler M, Meyer B, Bumke-Vogt C, Grossmann C, Gruber U, Oelkers W, Diederich S, Bahr V. Agonistic and antagonistic properties of progesterone metabolites at the human mineralocorticoid receptor. Eur J Endocrinol. 2002; 146:789–799. [PubMed: 12039699]
365. Rafestin-Oblin ME, Souque A, Bocchi B, Pinon G, Fagart J, Vandewalle A. The severe form of hypertension caused by the activating S810L mutation in the mineralocorticoid receptor is cortisone related. Endocrinology. 2003; 144:528–533. [PubMed: 12538613]
366. Raheja P, Price A, Wang Z, Arbique D, Adams-Huet B, Auchus RJ, Vongpatanasin W. Spironolactone prevents chlorthalidone-induced sympathetic activation and insulin resistance in hypertensive patients. Hypertension. 2012; 60:319–325. [PubMed: 22733474]

367. Rahmouni K, Barthelmebs M, Imbs JL, de Jong W. Brain mineralocorticoid receptor and blood pressure control in the conscious normotensive rat. Arch Maladies du Coeur et Vaisseaux. 1998; 91:1009–1012.

368. Rahmouni K, Sibug RM, De Kloet ER, Barthelmebs M, Grima M, Imbs JL, De Jong W. Effects of brain mineralocorticoid receptor blockade on blood pressure and renal functions in DOCA-salt hypertension. Eur J Pharmacol. 2002; 436:207–216. [PubMed: 11858800]

369. Rainey WE, Nakamura Y. Regulation of the adrenal androgen biosynthesis. J Steroid Biochem Mol Biol. 2008; 108:281–286. [PubMed: 17945481]

370. Razandi M, Alton G, Pedram A, Ghonshani S, Webb P, Levin ER. Identification of a structural determinant necessary for the localization and function of estrogen receptor alpha at the plasma membrane. Mol Cell Biol. 2003; 23:1633–1646. [PubMed: 12588983]

371. Rege J, Nakamura Y, Satoh F, Morimoto R, Kennedy MR, Layman LC, Honma S, Sasano H, Rainey WE. Liquid chromatography-tandem mass spectrometry analysis of human adrenal vein 19-carbon steroids before and after ACTH stimulation. J Clin Endocrinol Metab. 2013; 98:1182–1188. [PubMed: 23386646]

372. Reul JMH, De Kloet ER. Two receptor systems for coticosterone in rat brain: Microdistribution and differential occupation. Endocrinology. 1985; 117:2505–2511. [PubMed: 2998738]

373. Reul JMHM, van den Bosch FR, De Kloet ER. Relative occupation of type-I and type-II corticosteroid receptors in rat brain following stress and dexamethasone treatment: Functional implications. J Endocrinol. 1987; 115:459–467. [PubMed: 3443807]

374. Revsin Y, Rekers NV, Louwe MC, Saravia FE, De Nicola AF, de Kloet ER, Oitzl MS. Glucocorticoid receptor blockade normalizes hippocampal alterations and cognitive impairment in streptozotocin-induced type 1 diabetes mice. Neuropsychopharmacology. 2009; 34:747–758. [PubMed: 18784648]

375. Reynolds RM, Walker BR, Phillips DI, Dennison EM, Fraser R, Mackenzie SM, Davies E, Connell JM. Programming of hypertension: Associations of plasma aldosterone in adult men and women with birthweight, cortisol, and blood pressure. Hypertension. 2009; 53:932–936. [PubMed: 19380612]

376. Ricchiuti V, Lapointe N, Pojoga L, Yao T, Tran L, Williams GH, Adler GK. Dietary sodium intake regulates angiotensin II type 1, mineralocorticoid receptor, and associated signaling proteins in heart. J Endocrinol. 2011; 211:47–54. [PubMed: 21746791]

377. Rickard AJ, Funder JW, Fuller PJ, Young MJ. The role of the glucocorticoid receptor in mineralocorticoid/salt-mediated cardiac fibrosis. Endocrinology. 2006; 147:5901–5906. [PubMed: 16990342]

378. Rickard AJ, Morgan J, Tesch G, Funder JW, Fuller PJ, Young MJ. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. Hypertension. 2009; 54:537–543. [PubMed: 19635989]

379. Rigas AC, Ozanne DM, Neal DE, Robson CN. The scaffolding protein RACK1 interacts with androgen receptor and promotes cross-talk through a protein kinase C signaling pathway. J Biol Chem. 2003; 278:46087–46093. [PubMed: 12958311]

380. Rocha R, Rudolph AE, Frierdich GE, Nachowiak DA, Kekec BK, Blomme EA, McMahon EG, Delyani JA. Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol. 2002; 283:H1802–H1810. [PubMed: 12384457]

381. Rogoff D, Gomez-Sanchez CE, Foecking MF, Wortsman J, Slominski A. Steroidogenesis in the human skin: 21-hydroxylation in cultured keratinocytes. J Steroid Biochem Mol Biol. 2001; 78:77–81. [PubMed: 11530287]

382. Romero DG, Plonczynski M, Vergara GR, Gomez-Sanchez EP, Gomez-Sanchez CE. Angiotensin II early regulated genes in H295R human adrenocortical cells. Physiol Genomics. 2004; 19:106–116. [PubMed: 15375197]

383. 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; 60:319–325.

384. Rossi GP, Sechi LA, Giacchetti G, Ronconi V, Strazzullo P, Funder JW. Primary aldosteronism: Cardiovascular, renal and metabolic implications. Trends Endocrinol Metab. 2008; 19:88–90. [PubMed: 18314347]

385. Rossi GP, Sticchi D, Giuliani L, Bernante P, Zavattiero S, Pessina AC, Nussdorfer GG. Adiponectin receptor expression in the human adrenal cortex and aldosterone-producing adenomas. Int J Mol Med. 2006; 17:975–980. [PubMed: 16685404]

386. 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; 58:1958–1966. [PubMed: 22032706]

387. Rude MK, Duhaney TA, Kuster GM, Judge S, Heo J, Colucci WS, Siwik DA, Sam F. Aldosterone stimulates matrix metalloproteinases and reactive oxygen species in adult rat ventricular cardiomyocytes. Hypertension. 2005; 46:555–561. [PubMed: 16043662]

388. Ruhs S, Stratz N, Schlor K, Meinel S, Mildenberger S, Rabe S, Gekle M, Grossmann C. Modulation of transcriptional mineralocorticoid receptor activity by nitrosative stress. Free Radic Biol Med. 2012; 53:1088–1100. [PubMed: 22749806]

389. Sakai RR, McEwen BS, Fluharty SJ, Ma LY. The amygdala: Site of genomic and nongenomic arousal of aldosterone-induced sodium intake. Kidney Int. 2000; 57:1337–1345. [PubMed: 10760064]

390. Sapolsky RM. Mothering style and methylation. Nat Neurosci. 2004; 7:791–792. [PubMed: 15280887]

391. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000; 21:55–89. [PubMed: 10696570]

392. Sarabdjitsingh RA, Joels M, de Kloet ER. Glucocorticoid pulsatility and rapid corticosteroid actions in the central stress response. Physiol Behav. 2012; 106:73–80. [PubMed: 21971364]

393. Sarrieau A, O'Donnell D, Alonso R, Meaney MJ. Regulation of glucocorticosteroid receptor expression in rat hippocampal cell cultures by nerve growth factor. Neurosci Lett. 1996; 206:207–211. [PubMed: 8710188]

394. Sartorato P, Cluzeaud F, Fagart J, Viengchareun S, Lombes M, Zennaro MC. New naturally occurring missense mutations of the human mineralocorticoid receptor disclose important residues involved in dynamic interactions with DNA, intracellular trafficking and ligand binding. Mol Endocrinol. 2004; 18:2151–2165. [PubMed: 15192075]

395. Sartorato P, Khaldi Y, Lapeyraque AL, Armanini D, Kuhnle U, Salomon R, Caprio M, Viengchareun S, Lombes M, Zennaro MC. Inactivating mutations of the mineralocorticoid receptor in Type I pseudohypoaldosteronism. Mol Cell Endocrinol. 2004; 217:119–125. [PubMed: 15134810]

396. Sasano H, Frost AR, Saitoh R, Matsunaga G, Nagura H, Krozowski ZS, Silverberg SG. Localization of mineralocorticoid receptor and 11 beta-hydroxysteroid dehydrogenase type II in human breast and its disorders. Anticancer Res. 1997; 17:2001–2007. [PubMed: 9216657]

397. Savory JG, Prefontaine GG, Lamprecht C, Liao M, Walther RF, Lefebvre YA, Hache RJ. Glucocorticoid receptor homodimers and glucocorticoid-mineralocorticoid receptor heterodimers form in the cytoplasm through alternative dimerization interfaces. Mol Cell Biol. 2001; 21:781–793. [PubMed: 11154266]

398. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A. 2009; 106:4453–4458. [PubMed: 19255424]

399. Schinner S, Willenberg HS, Krause D, Schott M, Lamounier-Zepter V, Krug AW, Ehrhart-Bornstein M, Bornstein SR, Scherbaum WA. Adipocyte-derived products induce the transcription of the StAR promoter and stimulate aldosterone and cortisol secretion from adrenocortical cells through the Wnt-signaling pathway. Int J Obes (Lond). 2007; 31:864–870. [PubMed: 17211444]

400. Schreck C, O'Connor PM. NAD(P)H oxidase and renal epithelial ion transport. Am J Physiol Regul Integr Comp Physiol. 2011; 300:R1023–R1029. [PubMed: 21270341]

401. Schwabe L, Hoffken O, Tegenthoff M, Wolf OT. Stress-induced enhancement of response inhibition depends on mineralocorticoid receptor activation. Psychoneuroendocrinology. 2013; 38:2319–2326. [PubMed: 23831264]

402. Schwabe L, Schachinger H, de Kloet ER, Oitzl MS. Corticosteroids operate as a switch between memory systems. J Cogn Neurosci. 2010; 22:1362–1372. [PubMed: 19445601]

403. Schwabe L, Tegenthoff M, Hoffken O, Wolf OT. Mineralocorticoid receptor blockade prevents stress-induced modulation of multiple memory systems in the human brain. Biol Psychiatry. 2013; 74:801–808. [PubMed: 23871473]

404. Schweizer RA, Zurcher M, Balazs Z, Dick B, Odermatt A. Rapid hepatic metabolism of 7-ketocholesterol by 11beta-hydroxysteroid dehydrogenase type 1: Species-specific differences between the rat, human, and hamster enzyme. J Biol Chem. 2004; 279:18415–18424. [PubMed: 14973125]

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

406. Seckl JR, Holmes MC. Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. Nat Clin Pract Endocrinol Metab. 2007; 3:479–488. [PubMed: 17515892]

407. Seckl JR, Meaney MJ. Glucocorticoid "programming" and PTSD risk. AnnNY Acad Sci. 2006; 1071:351–378.

408. Seckl JR, Morton NM, Chapman KE, Walker BR. Glucocorticoids and 11beta-hydroxysteroid dehydrogenase in adipose tissue. Recent Prog Horm Res. 2004; 59:359–393. [PubMed: 14749510]

409. Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1: A tissue-specific amplifier of glucocorticoid action. Endocrinology. 2001; 142:1371–1376. [PubMed: 11250914]

410. Selye H. The anesthetic effect of steroid hormones. ProSocExpBiolMed. 1941; 46:116–121.

411. Sharma KK, Lindqvist A, Zhou XJ, Auchus RJ, Penning TM, Andersson S. Deoxycorticosterone inactivation by AKR1C3 in human mineralocorticoid target tissues. Mol Cell Endocrinol. 2006; 248:79–86. [PubMed: 16337083]

412. Shibata S, Fujita T. Mineralocorticoid receptors in the pathophysiology of chronic kidney diseases and the metabolic syndrome. Mol Cell Endocrinol. 2012; 350:273–280. [PubMed: 21820485]

413. Shibata S, Mu S, Kawarazaki H, Muraoka K, Ishizawa K, Yoshida S, Kawarazaki W, Takeuchi M, Ayuzawa N, Miyoshi J, Takai Y, Ishikawa A, Shimosawa T, Ando K, Nagase M, Fujita T. Rac1 GTPase in rodent kidneys is essential for salt-sensitive hypertension via a mineralocorticoid receptor-dependent pathway. J Clin Invest. 2011; 121:3233–3243. [PubMed: 21765214]

414. Shin JW, Geerling JC, Loewy AD. Vagal innervation of the aldosterone-sensitive HSD2 neurons in the NTS. Brain Res. 2009; 1249:135–147. [PubMed: 19010311]

415. Silvestre JS, Heymes C, Oubenaissa A, Robert V, Aupetit-Faisant B, Carayon A, Swynghedauw B, Delcayre C. Activation of cardiac aldosterone production in rat myocardial infarction: Effect of angiotensin II receptor blockade and role in cardiac fibrosis. Circulation. 1999; 99:2694–2701. [PubMed: 10338465]

416. Silvestre JS, Robert V, Heymes C, Aupetit-Faisant B, Mouas C, Moalic JM, Swynghedauw B, Delcayre C. Myocardial production of aldosterone and corticosterone in the rat. Physiological regulation. J Biol Chem. 1998; 273:4883–4891. [PubMed: 9478930]

417. Simpson SA, Tait JF, Wettstein A, Neher R, von Euw J, Schindler O, Reichstein T. Konstitution des aldosterons, des neuen mineralocorticoids. Experientia. 1953; 10:132–133. [PubMed: 13161890]

418. Slight SH, Ganjam VK, Gomez-Sanchez CE, Weber KT. High affinity NAD^+-dependent 11b-hydroxysteroid dehydrogenase in the human heart. J Mol Cell Cardiol. 1996; 28:781–787. [PubMed: 8732505]

419. Smythe JW, Murphy D, Timothy C, Costall B. Hippocampal mineralocorticoid, but not glucocorticoid, receptors modulate anxiety-like behaviors in rats. Pharmacol Biochem Behav. 1997; 56:507–513. [PubMed: 9077590]
420. Sonino N, Tomba E, Genesia ML, Bertello C, Mulatero P, Veglio F, Fava GA, Fallo F. Psychological assessment of primary aldosteronism: A controlled study. J Clin Endocrinol Metab. 2011; 96:E878–E883. [PubMed: 21389142]
421. Spijker AT, van Rossum EF. Glucocorticoid receptor polymorphisms in major depression. Focus on glucocorticoid sensitivity and neurocognitive functioning. AnnNY Acad Sci. 2009; 1179:199–215.
422. Spijker AT, van Rossum EF. Glucocorticoid sensitivity in mood disorders. Neuroendocrinology. 2012; 95:179–186. [PubMed: 22076031]
423. Stanisic V, Lonard DM, O'Malley BW. Modulation of steroid hormone receptor activity. Prog Brain Res. 2010; 181:153–176. [PubMed: 20478437]
424. Steiger M, Reichstein T. Desoxy-corticosterone (21-oxy-progesterone). Aus d-3-oxo-etiocholensäure. Helv Chim Acta. 1937; 20:1164.
425. Stein MK, Loewy AD. Area postrema projects to FoxP2 neurons of the pre-locus coeruleus and parabrachial nuclei: Brainstem sites implicated in sodium appetite regulation. Brain Res. 2010; 1359:116–127. [PubMed: 20816675]
426. Sterlemann V, Ganea K, Liebl C, Harbich D, Alam S, Holsboer F, Muller MB, Schmidt MV. Long-term behavioral and neuroendocrine alterations following chronic social stress in mice: Implications for stress-related disorders. Horm Behav. 2008; 53:386–394. [PubMed: 18096163]
427. Stewart PM. Cortisol as a mineralocorticoid in human disease. J Steroid Biochem Mol Biol. 1999; 69:403–408. [PubMed: 10419018]
428. Stewart PM, Corrie JET, Shackleton CHL, Edwards CRW. Syndrome of apparent mineralocorticoid excess. A defect in the cortisol-cortisone shuttle. J Clin Invest. 1988; 82:340–349. [PubMed: 3164727]
429. Stewart PM, Wallace AM, Valentino R, Burt D, Shackleton CHL, Edwards CRW. Mineralocorticoid activity of liquorice: 11-Beta-hydroxysteroid dehydrogenase deficiency comes of age. Lancet. 1987; ii:821–824. [PubMed: 2889032]
430. 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. 137-147.
431. Sukor N, Kogovsek C, Gordon RD, Robson D, Stowasser M. Improved quality of life, blood pressure, and biochemical status following laparoscopic adrenalectomy for unilateral primary aldosteronism. J Clin Endocrinol Metab. 2010; 95:1360–1364. [PubMed: 20089615]
432. Swaab DF, Bao AM. (Re-)activation of neurons in aging and dementia: Lessons from the hypothalamus. Exp Gerontol. 2011; 46:178–184. [PubMed: 20833237]
433. Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T. Brain and cardiovascular diseases: Common neurogenic background of cardiovascular, metabolic and inflammatory diseases. J Physiol Pharmacol. 2010; 61:509–521. [PubMed: 21081794]
434. Szyf M, Weaver I, Meaney M. Maternal care, the epigenome and phenotypic differences in behavior. Reprod Toxicol. 2007; 24:9–19. [PubMed: 17561370]
435. Takeda Y, Yoneda T, Demura M, Furukawa K, Miyamori I, Mabuchi H. Effects of high sodium intake on cardiovascular aldosterone synthesis in stroke-prone spontaneously hypertensive rats. J Hypertens. 2001; 19:635–639. [PubMed: 11327640]
436. Taves MD, Gomez-Sanchez CE, Soma KK. Extra-adrenal glucocorticoids and mineralocorticoids: Evidence for local synthesis, regulation, and function. Am J Physiol Endocrinol Metab. 2011; 301:E11–E24. [PubMed: 21540450]
437. 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; 60:330–335. [PubMed: 9915998]

438. Thieringer R, Le Grand CB, Carbin L, Cai TQ, Wong B, Wright SD, Hermanowski-Vosatka A. 11 Beta-hydroxysteroid dehydrogenase type 1 is induced in human monocytes upon differentiation to macrophages. J Immunol. 2001; 167:30–35. [PubMed: 11418628]

439. Tiganescu A, Tahrani AA, Morgan SA, Otranto M, Desmouliere A, Abrahams L, Hassan-Smith Z, Walker EA, Rabbitt EH, Cooper MS, Amrein K, Lavery GG, Stewart PM. 11β-Hydroxysteroid dehydrogenase blockade prevents age-induced skin structure and function defects. J Clin Invest. 2013; 123:3051–3060. [PubMed: 23722901]

440. Tirosh A, Garg R, Adler GK. Mineralocorticoid receptor antagonists and the metabolic syndrome. Curr Hypertens Rep. 2010; 12:252–257. [PubMed: 20563672]

441. Tomlinson JW, Stewart PM. Mechanisms of disease: Selective inhibition of 11beta-hydroxysteroid dehydrogenase type 1 as a novel treatment for the metabolic syndrome. Nat Clin Pract Endocrinol Metab. 2005; 1:92–99. [PubMed: 16929377]

442. Touyz RM. Reactive oxygen species as mediators of calcium signaling by angiotensin II: Implications in vascular physiology and pathophysiology. Antioxid Redox Signal. 2005; 7:1302–1314. [PubMed: 16115036]

443. Trapp T, Rupprecht R, Castren M, Reul JM, Holsboer F. Heterodimerization between mineralocorticoid and glucocorticoid receptor: A new principle of glucocorticoid action in the CNS. Neuron. 1994; 13:1457–1462. [PubMed: 7993637]

444. Tripodi G, Citterio L, Kouznetsova T, Lanzani C, Florio M, Modica R, Messaggio E, Hamlyn JM, Zagato L, Bianchi G, Staessen JA, Manunta P. Steroid biosynthesis and renal excretion in human essential hypertension: Association with blood pressure and endogenous ouabain. Am J Hypertens. 2009; 22:357–363. [PubMed: 19197249]

445. Tsugita M, Iwasaki Y, Nishiyama M, Taguchi T, Shinahara M, Taniguchi Y, Kambayashi M, Nishiyama A, Gomez-Sanchez CE, Terada Y, Hashimoto K. Glucocorticoid receptor plays an indispensable role in mineralocorticoid receptor-dependent transcription in GR-deficient BE (2)C and T84 cells in vitro. Mol Cell Endocrinol. 2009; 302:18–25. [PubMed: 19146914]

446. Tsutamoto T, Wada A, Maeda K, Hayashi M, Tsutsui T, Ohnishi M, Fujii M, Matsumoto T, Yamamoto T, Takayama T, Ishii C. Transcardiac gradient of aldosterone before and after spironolactone in patients with congestive heart failure. J Cardiovasc Pharmacol. 2003; 41:S19–S22. [PubMed: 12688391]

447. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Swaki M, Fujii M, Matsumoto T, Horie H, Sugimoto Y, Kinoshita M. Spironolactone inhibits the transcardiac extraction of aldosterone in patients with congestive heart failure. J Am Coll Cardiol. 2000; 36:838–844. [PubMed: 10987608]

448. Tytherleigh MY, Vedhara K, Lightman SL. Mineralocorticoid and glucocorticoid receptors and their differential effects on memory performance in people with Addison's disease. Psychoneuroendocrinology. 2004; 29:712–723. [PubMed: 15110920]

449. Ueda K, Lu Q, Baur W, Aronovitz MJ, Karas RH. Rapid estrogen receptor signaling mediates estrogen-induced inhibition of vascular smooth muscle cell proliferation. Arterioscler Thromb Vasc Biol. 2013; 33:1837–1843. [PubMed: 23744991]

450. 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; 49:757–764. [PubMed: 226561]

451. Ulick S, Wang JZ, Blumenfeld JD, Pickering TG. Cortisol inactivation overload: A mechanism of mineralocorticoid hypertension in the ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab. 1992; 74:963–967. [PubMed: 1569172]

452. van Acker SA, Oitzl MS, Fluttert MF, de Kloet ER. Centrally regulated blood pressure response to vasoactive peptides is modulated by corticosterone. J Neuroendocrinol. 2002; 14:56–63. [PubMed: 11903813]

453. 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; 126:118–124. [PubMed: 2293978]

454. van Leeuwen N, Bellingrath S, de Kloet ER, Zitman FG, DeRijk RH, Kudielka BM, Wust S. Human mineralocorticoid receptor (MR) gene haplotypes modulate MR expression and

transactivation: Implication for the stress response. Psychoneuroendocrinology. 2011; 36:699–709. [PubMed: 21095064]

455. van Leeuwen N, Caprio M, Blaya C, Fumeron F, Sartorato P, Ronconi V, Giacchetti G, Mantero F, Fernandes-Rosa FL, Simian C, Peyrard S, Zitman FG, Penninx BW, de Kloet ER, Azizi M, Jeunemaitre X, Derijk RH, Zennaro MC. The functional c.-2G>C variant of the mineralocorticoid receptor modulates blood pressure, renin, and aldosterone levels. Hypertension. 2010; 56:995–1002. [PubMed: 20855654]
456. van Leeuwen N, Kumsta R, Entringer S, de Kloet ER, Zitman FG, DeRijk RH, Wust S. Functional mineralocorticoid receptor (MR) gene variation influences the cortisol awakening response after dexamethasone. Psychoneuroendocrinology. 2010; 35:339–349. [PubMed: 19665310]
457. Vanatta JC, Cottle KE. Effect of desoxycorticosterone acetate on the peripheral vascular reactivity of dogs. Am J Physiol. 1955; 151:119–122. [PubMed: 14376581]
458. Vasan RS, Evans JC, Benjamin EJ, Levy D, Larson MG, Sundstrom J, Murabito JM, Sam F, Colucci WS, Wilson PW. Relations of serum aldosterone to cardiac structure: Gender-related differences in the Framingham Heart Study. Hypertension. 2004; 43:957–962. [PubMed: 15007028]
459. Vasan RS, Evans JC, Larson MG, Wilson PW, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. N Engl J Med. 2004; 351:33–41. [PubMed: 15229305]
460. Vazquez DM, Lopez JF, Morano MI, Kwak SP, Watson SJ. Alpha, beta, and gamma mineralocorticoid receptor messenger ribonucleic acid splice variants: Differential expression and rapid regulation in the developing hippocampus. Endocrinology. 1998; 139:3165–3177. [PubMed: 9645690]
461. 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]
462. Vinson GP. The mislabelling of deoxycorticosterone: Making sense of corticosteroid structure and function. J Endocrinol. 2011; 211:3–16. [PubMed: 21715433]
463. Vogt B, Burnier M. Aldosterone and cardiovascular risk. Curr Hypertens Rep. 2009; 11:450–455. [PubMed: 19895757]
464. Walker BR, Edwards CRW. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. Endocrinol Metab Clin North Am. 1994; 23:359–377. [PubMed: 8070427]
465. Walker BR, Seckl JR. 11beta-Hydroxysteroid dehydrogenase Type 1 as a novel therapeutic target in metabolic and neurodegenerative disease. Expert Opin Ther Targets. 2003; 7:771–783. [PubMed: 14640912]
466. Wan ZK, Chenail E, Li HQ, Kendall C, Wang Y, Gingras S, Xiang J, Massefski WW, Mansour TS, Saiah E. Synthesis of potent and orally efficacious 11beta-hydroxysteroid dehydrogenase type 1 inhibitor HSD-016. J Org Chem. 2011; 76:7048–7055. [PubMed: 21736359]
467. Wang H, Huang BS, Leenen FH. Brain sodium channels and ouabain-like compounds mediate central aldosterone-induced hypertension. Am J Physiol Heart Circ Physiol. 2003; 285:H2516–H2523. [PubMed: 12933342]
468. Wang J, Li X, Ke Y, Lu Y, Wang F, Fan N, Sun H, Zhang H, Liu R, Yang J, Ye L, Liu M, Ning G. GPR48 increases mineralocorticoid receptor gene expression. J Am Soc Nephrol. 2012; 23:281–293. [PubMed: 22135314]
469. Wang W, McClain JM, Zucker IH. Aldosterone reduces baroreceptor discharge in the dog. Hypertension. 1992; 19:270–277. [PubMed: 1532165]
470. Wansapura AN, Lasko VM, Lingrel JB, Lorenz JN. Mice expressing ouabain-sensitive alpha1-Na,K-ATPase have increased susceptibility to pressure overload-induced cardiac hypertrophy. Am J Physiol Heart Circ Physiol. 2011; 300:H347–H355. [PubMed: 20952666]
471. Weaver IC. Epigenetic programming by maternal behavior and pharmacological intervention. Nature versus nurture: Let's call the whole thing off. Epigenetics. 2007; 2:22–28. [PubMed: 17965624]

472. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. Nat Neurosci. 2004; 7:847–854. [PubMed: 15220929]
473. Weber KT, Sun Y, Wodi LA, Munir A, Jahangir E, Ahokas RA, Gerling IC, Postlethwaite AE, Warrington KJ. Toward a broader understanding of aldosterone in congestive heart failure. J Renin Angiotensin Aldosterone Syst. 2003; 4:155–163. [PubMed: 14608519]
474. Wehling M. Effects of aldosterone and mineralocorticoid receptor blockade on intracellular electrolytes. Heart Fail Rev. 2005; 10:39–46. [PubMed: 15947890]
475. Wehling M, Eisen C, Christ M. Aldosterone-specific membrane receptors and rapid non-genomic actions of mineralocorticoids. Mol Cell Endocrinol. 1992; 90:C5–C9. [PubMed: 1338726]
476. Wendler A, Albrecht C, Wehling M. Nongenomic actions of aldosterone and progesterone revisited. Steroids. 2012; 77:1002–1006. [PubMed: 22285849]
477. Whaley-Connell A, Habibi J, Wei Y, Gutweiler A, Jellison J, Wiedmeyer CE, Ferrario CM, Sowers JR. Mineralocorticoid receptor antagonism attenuates glomerular filtration barrier remodeling in the transgenic Ren2 rat. Am J Physiol Renal Physiol. 2009; 296:F1013–F1022. [PubMed: 19261739]
478. Whaley-Connell A, Johnson MS, Sowers JR. Aldosterone: Role in the cardiometabolic syndrome and resistant hypertension. Prog Cardiovasc Dis. 2010; 52:401–409. [PubMed: 20226958]
479. White PC. 11beta-hydroxysteroid dehydrogenase and its role in the syndrome of apparent mineralocorticoid excess. Am J Med Sci. 2001; 322:308–315. [PubMed: 11780688]
480. White PC, Mune T, Agarwal AK. Functional studies of 11 beta-hydroxysteroid dehydrogenase. Steroids. 1995; 60:65–68. [PubMed: 7792818]
481. Wildling L, Hinterdorfer P, Kusche-Vihrog K, Treffner Y, Oberleithner H. Aldosterone receptor sites on plasma membrane of human vascular endothelium detected by a mechanical nanosensor. Pflugers Arch. 2009; 458:223–230. [PubMed: 19018563]
482. Wilson P, Morgan J, Funder JW, Fuller PJ, Young MJ. Mediators of mineralocorticoid receptor-induced profibrotic inflammatory responses in the heart. Clin Sci (Lond). 2009; 116:731–739. [PubMed: 18990085]
483. Woolley CS, Gould E, Sakai RR, Spencer RL, McEwen BS. Effects of aldosterone or RU28362 treatment on adrenalectomy-induced cell death in the dentate gyrus of the adult rat. Brain Res. 1991; 554:312–315. [PubMed: 1933312]
484. Wyrwoll CS, Holmes MC, Seckl JR. 11beta-Hydroxysteroid dehydrogenases and the brain: From zero to hero, a decade of progress. Front Neuroendocrinol. 2010; 32:265–286. [PubMed: 21144857]
485. Xing GQ, Russell S, Webster MJ, Post RM. Decreased expression of mineralocorticoid receptor mRNA in the prefrontal cortex in schizophrenia and bipolar disorder. Int J Neuropsychopharmacol. 2004; 7:143–153. [PubMed: 14741058]
486. Xing Y, Edwards MA, Ahlem C, Kennedy M, Cohen A, Gomez-Sanchez CE, Rainey WE. The effects of ACTH on steroid metabolomic profiles in human adrenal cells. J Endocrinol. 2011; 209:327–335. [PubMed: 21429963]
487. Xue B, Beltz TG, Yu Y, Guo F, Gomez-Sanchez CE, Hay M, Johnson AK. Central interactions of aldosterone and angiotensin II in aldosterone- and angiotensin II-induced hypertension. Am J Physiol Heart Circ Physiol. 2011; 300:H555–H564. [PubMed: 21112947]
488. Yagi S, Akaike M, Aihara K, Iwase T, Yoshida S, Sumitomo-Ueda Y, Ikeda Y, Ishikawa K, Matsumoto T, Sata M. High plasma aldosterone concentration is a novel risk factor of cognitive impairment in patients with hypertension. Hypertens Res. 2011; 34:74–78. [PubMed: 20861841]
489. Yang J, Chang CY, Safi R, Morgan J, McDonnell DP, Fuller PJ, Clyne CD, Young MJ. Identification of ligand-selective peptide antagonists of the mineralocorticoid receptor using phage display. Mol Endocrinol. 2011; 25:32–43. [PubMed: 21106883]
490. Yang J, Young MJ. The mineralocorticoid receptor and its coregulators. J Mol Endocrinol. 2009; 43:53–64. [PubMed: 19617444]
491. Yang S, Roselli F, Patchev AV, Yu S, Almeida OF. Non-receptor-tyrosine kinases integrate fast glucocorticoid signaling in hippocampal neurons. J Biol Chem. 2013; 288:23725–23739. [PubMed: 23818519]

492. Yau JL, Noble J, Seckl JR. Continuous blockade of brain mineralocorticoid receptors impairs spatial learning in rats. Neurosci Lett. 1999; 277:45–48. [PubMed: 10643894]
493. Ye P, Kenyon CJ, MacKenzie SM, Seckl JR, Fraser R, Connell JM, Davies E. Regulation of aldosterone synthase gene expression in the rat adrenal gland and central nervous system by sodium and angiotensin II. Endocrinology. 2003; 144:3321–3328. [PubMed: 12865309]
494. Yokota K, Shibata H, Kurihara I, Kobayashi S, Suda N, Murai-Takeda A, Saito I, Kitagawa H, Kato S, Saruta T, Itoh H. Coactivation of the N-terminal transactivation of mineralocorticoid receptor by Ubc9. J Biol Chem. 2007; 282:1998–2010. [PubMed: 17105732]
495. York B, O'Malley BW. Steroid receptor coactivator (SRC) family: Masters of systems biology. J Biol Chem. 2010; 285:38743–38750. [PubMed: 20956538]
496. Yoshimura M, Nakamura S, Ito T, Nakayama M, Harada E, Mizuno Y, Sakamoto T, Yamamuro M, Saito Y, Nakao K, Yasue H, Ogawa H. Expression of aldosterone synthase gene in failing human heart: Quantitative analysis using modified real-time polymerase chain reaction. J Clin Endocrinol Metab. 2002; 87:3936–3940. [PubMed: 12161536]
497. Youm JK, Park K, Uchida Y, Chan A, Mauro TM, Holleran WM, Elias PM. Local blockade of glucocorticoid activation reverses stress- and glucocorticoid-induced delays in cutaneous wound healing. Wound Repair Regen. 2013; 21:715–722. [PubMed: 23927023]
498. Young M, Head G, Funder JW. Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. Am J Physiol. 1995; 269:E657, E662. [PubMed: 7485478]
499. Young MJ, Rickard AJ. Mechanisms of mineralocorticoid salt-induced hypertension and cardiac fibrosis. Mol Cell Endocrinol. 2012; 350:248–255. [PubMed: 21930186]
500. Yu L, Romero DG, Gomez-Sanchez CE, Gomez-Sanchez EP. Steroidogenic enzyme gene expression in the human brain. Mol Cell Endocrinol. 2002; 190:9–17. [PubMed: 11997174]
501. 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; 55:652–659. [PubMed: 20142564]
502. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364:11–21. [PubMed: 21073363]
503. Zennaro MC, Caprio M, Feve B. Mineralocorticoid receptors in the metabolic syndrome. Trends Endocrinol Metab. 2009; 20:444–451. [PubMed: 19800255]
504. Zennaro MC, Farman N, Bonvalet JP, Lombes M. Tissue-specific expression of alpha and beta messenger ribonucleic acid isoforms of the human mineralocorticoid receptor in normal and pathological states. J Clin Endocrinol Metab. 1997; 82:1345–1352. [PubMed: 9141514]
505. Zennaro MC, Lemenuet D, Lombes M. Characterization of the human mineralocorticoid receptor gene 5′-regulatory region - evidence for differential hormonal regulation of two alternative promoters via non-classical mechanism. Mol Endocrinol. 1996; 10:1549–1560. [PubMed: 8961265]
506. 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; 38:111–123. [PubMed: 22968814]
507. Zhang W, Xia X, Jalal DI, Kuncewicz T, Xu W, Lesage GD, Kone BC. Aldosterone-sensitive repression of ENaCalpha transcription by a histone H3 lysine-79 methyltransferase. Am J Physiol Cell Physiol. 2006; 290:C936–C946. [PubMed: 16236820]
508. Zhang W, Xia X, Reisenauer MR, Rieg T, Lang F, Kuhl D, Vallon V, Kone BC. Aldosterone-induced Sgk1 relieves Dot1a-Af9-mediated transcriptional repression of epithelial Na^+ channel alpha. J Clin Invest. 2007; 117:773–783. [PubMed: 17332896]
509. Zhang Z, Mahoney EM, Kolm P, Spertus J, Caro J, Willke R, Weintraub WS. Cost effectiveness of eplerenone in patients with heart failure after acute myocardial infarction who were taking both ACE inhibitors and beta-blockers: Subanalysis of the EPHESUS. Am J Cardiovasc Drugs. 2011; 10:55–63. [PubMed: 20104935]
510. Zhou M-Y, Gomez-Sanchez CE, Gomez-Sanchez EP. An alternatively spliced mineralocorticoid receptor mRNA causing truncation of the steroid binding domain. Mol Cell Endocrinol. 2000; 159:125–131. [PubMed: 10687858]

511. 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]

512. Zhou MY, Gomez-Sanchez EP, Cox DL, Cosby D, Gomez-Sanchez CE. Cloning, expression and tissue distribution of the rat NAD^+-dependent 11b-hydroxysteroid dehydrogenase. Endocrinology. 1995; 136:3729–3734. [PubMed: 7649078]

513. Zhu X, Manning RD Jr. Lu D, Gomez-Sanchez CE, Fu Y, Juncos LA, Liu R. Aldosterone stimulates superoxide production in macula densa cells. Am J Physiol Renal Physiol. 2011; 301:F529–F535. [PubMed: 21270097]

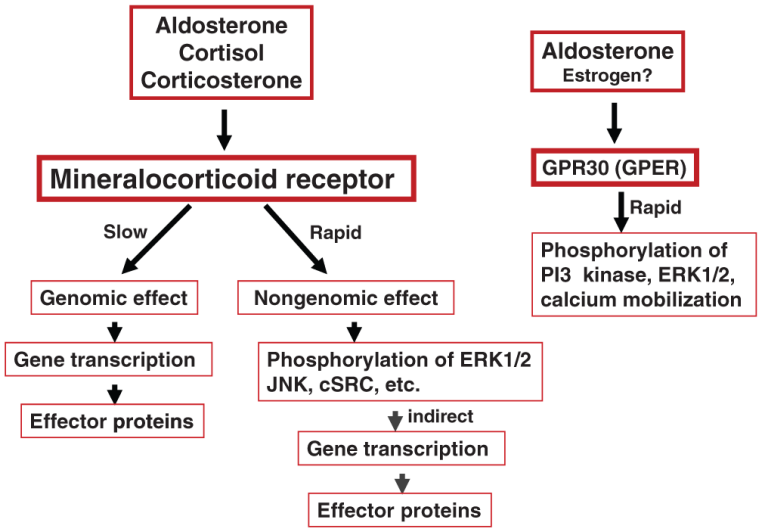

Figure 1.

Aldosterone action. Aldosterone, cortisol, and corticosterone act through the mineralocorticoid receptor for which they have similar binding affinity to initiate transcriptional effects that take more than 3 h or rapid nongenomic effects that occur in seconds to minutes. The glucocorticoid receptor has similar slow transcriptional and rapid nongenomic effects in response to glucocorticoids, but not endogenous levels of aldosterone. Aldosterone, but not cortisol or corticosterone, activates GPR30(GPER) at physiological concentrations. Estrogen has not been demonstrated to activate GPER at physiological concentrations.

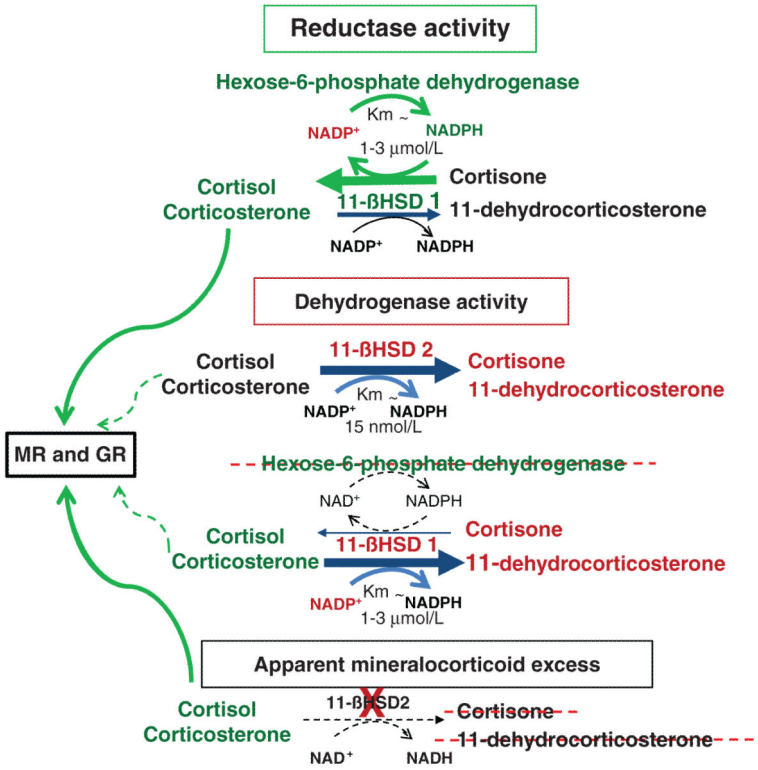

Figure 2.

Microsomal 11β-Hydroxysteroid dehydrogenases 1 and 2 provide prereceptor ligand specificity for MR and GR. 11β-HSD1, a reductase in most tissues, requires NADPH to convert cortisone and 11-dehydrocorticosterone to cortisol and corticosterone with a Km ~1 to 3 µmol/L. In the presence of $NADP^+$ or absence of hexose-6-phosphate dehydrogenase to regenerate NADPH, 11β-HSD1 is a dehydrogenase. 11β-HSD2 is a unidirectional NAD^+-dependent dehydrogenase which converts cortisol and corticosterone to the inactive cortisone and 11-dehydrocorticosterone, Km ~15 nmol/L. Aldosterone is not a substrate for the enzymes. Net dehydrogenase activity within the cell decreases glucocorticoid binding to the MR and GR and provides extrinsic specificity for aldosterone binding to the MR. Reductase activity increases glucocorticoid binding to both receptors.

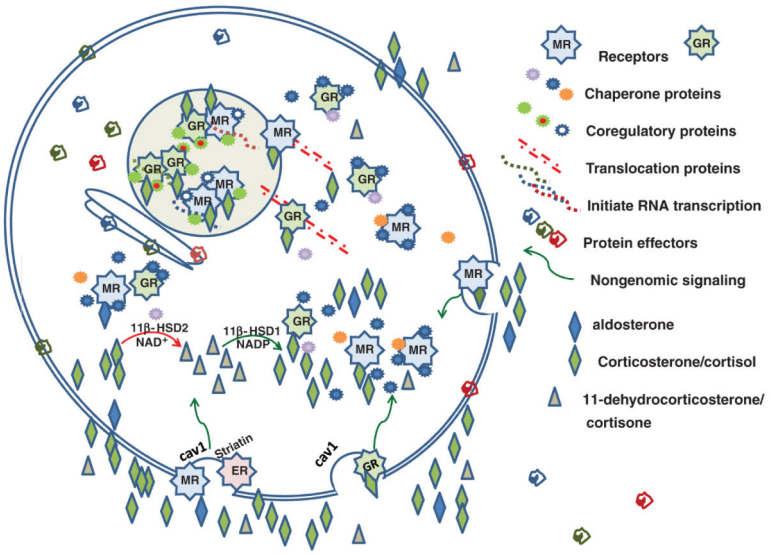

Figure 3.

MR and GR act as ligand activated transcription factors that reside primarily in the cytoplasm bound to chaperone and scaffolding proteins when not bound to an agonist. Upon ligand binding they are transported to the nucleus where they form homodimers and heterodimers that bind hormone response elements on the chromosomes and associate with coactivator and corepressor proteins to modulate the transcription of effector proteins. Some chaperone and co-activator proteins bind both receptors. MR and GR associated with the plasma membrane within caveoli initiate rapid nonnuclear effects through classic cell signaling mechanisms. 11β-HSD enzymes within the endoplasmic reticulum (not depicted) modulate glucocorticoid concentrations for both the GR and MR. Interactions between receptors occur at multiple levels.