The Multifaceted Mineralocorticoid Receptor

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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

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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 ^3H-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

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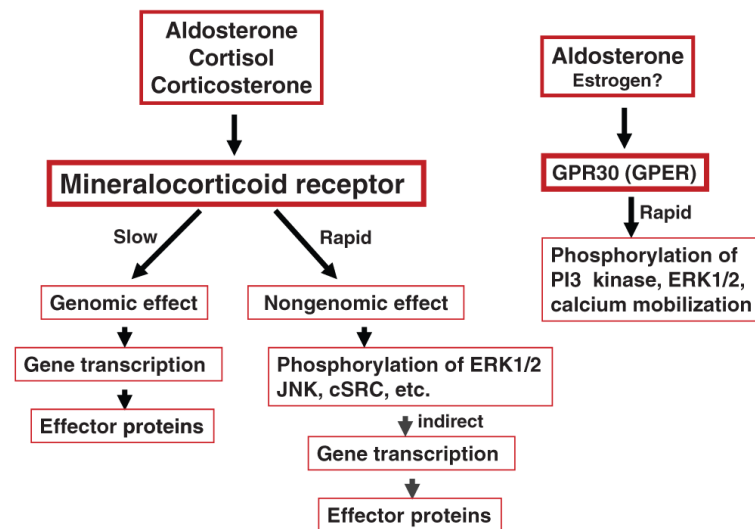
Figure 1.

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.
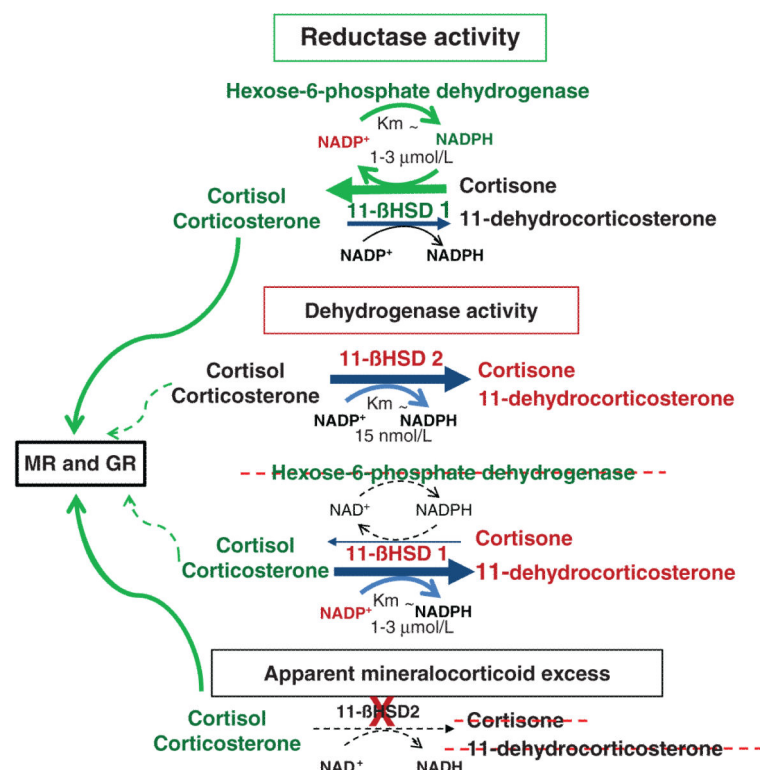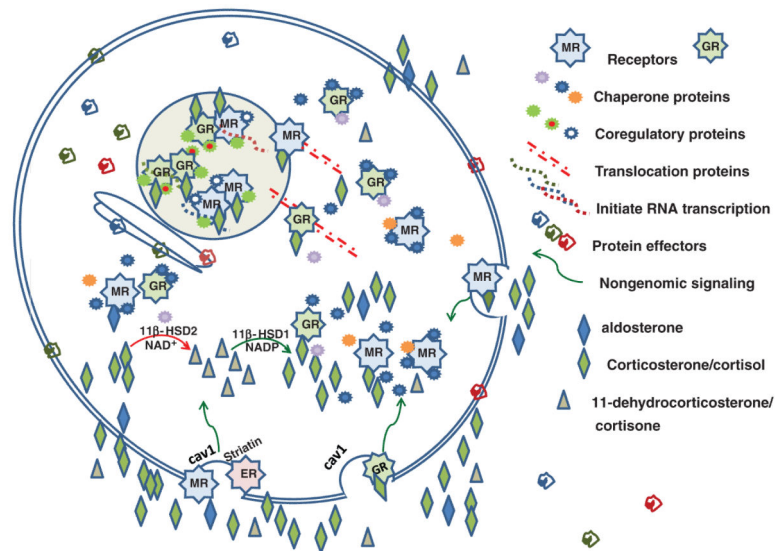
Figure 2.
Microsomal 11β-Hydroxysteroid dehydrogenases 1 and 2 provide prereceptor ligand specificity for MR and GR. 11β-HSD1, a reductase in most tissues, requires NADPH to convert cortisone and 11-dehydrocorticosterone to cortisol and corticosterone with a Km ~1 to 3 μmol/L. In the presence of NADP$^+$ 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.