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Brain mineralocorticoid receptors and centrally regulated functions

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Brain mineralocorticoid receptors and centrally regulated functions. Mineralocorticoid receptors (MRs) expressed in limbic neurons, notably of hippocampus, retain both aldosterone and corticosterone. Basal concentrations of corticosterone already substantially occupy the limbic MR type, suggesting that in hippocampal neurons, MR activity rather than ligand bioavailability is rate limiting. The periventricular region expresses MRs involved in the control of salt homeostasis, which are aldosterone selective because of the presence of 11β-hydroxysteroid dehydrogenase. MR is in hippocampal CA1, CA2, and dentate gyrus colocalized with glucocorticoid receptors (GRs). Both receptor types mediate in a coordinate manner the corticosterone action on information processing critical for behavioral adaptation and associated neuroendocrine responses to stress. MRs operate in proactive mode determining the sensitivity of the stress response system, while GRs facilitate recovery from stress in reactive mode. On the neuronal level, MR-mediated action maintains a stable excitatory tone and attenuates the influence of modulatory signals. In contrast, GR-mediated effects suppress excitability transiently raised by excitatory stimuli. MR is also involved in control of autonomic outflow and volume regulation. This was demonstrated by the effect of an MR antagonist, which was administered centrally, because mdr P-glycoproteins hamper the access of synthetic steroids to the brain. The MR antagonist attenuates pressor responses to a stressor, such as experienced during tail sphygmography. Diuresis and urinary electrolyte excretion are increased after the MR antagonist, but this effect is abolished after bilateral denervation of the kidney. It is presently unknown in which brain cells the MR-mediated effects on these aspects of central cardiovascular regulation occur.

Corticosterone, the principal glucocorticoid secreted by the rat adrenal gland, regulates energy metabolism and the response to stress. These actions are aimed at maintaining homeostasis by control of the sensitivity of the stress response system and by facilitating recovery of homeostasis after a stress-induced disturbance. While the secretion of corticosterone is a rather stereotypical response to every novel stimulus, the steroid has an enormous diversity in action on the target level. Corticosterone has a pleiotropic action and induces multiple changes in peripheral responses that indirectly influence brain function. This has been shown for responses of the immune system and the cardiovascular system and after corticosterone-induced changes in carbohydrate and mineral metabolism. However, the hormone also exerts potent and direct actions on specific neuronal circuits. This direct action of central of B is mediated by high-affinity mineralocorticoid receptors (MRs) and lower affinity glucocorticoid receptors (GRs), which are colocalized in brain cells. MR and GR expression is particularly abundant in hippocampal neurons [1].

We focus on the function of the apparent "nonselective" brain MR and on the aldosterone-selective MRs, which also occur in brain, but are predominantly in periventricular tissue. Beyond periventricular cells, neurons and glial cells of higher brain regions lack significant 11β-hydroxysteroid dehydrogenase (11β-HSD) activity, which confers aldosterone specificity in the epithelial cells. Half-maximal occupation of the "nonselective" brain MR is already at low corticosterone concentrations. It is therefore reasonable to assume that this receptor is, under most circumstances, extensively occupied. Some time ago, we postulated that such MRs would mediate a "tonic" action of corticosterone involving maintenance of homeostasis, as opposed to the "phasic" actions via GR contributing to restoration of homeostasis [1, 2]. Subsequently, by taking into account the integrating function of central mechanisms underlying behavior, we have begun to discriminate between an MR-mediated *proactive* mode maintaining homeostasis versus GR-mediated *reactive* control facilitating recovery from disturbances in homeostasis [3].

In this contribution, we first briefly summarize the present information on properties of central MR and GR and on factors determining access to these receptors. Then data are presented that challenge the view that an

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MR, overwhelmingly occupied with endogenous hormone, would be excluded as a dynamic regulatory component of the stress response system even under conditions of high corticosterone. Finally, we show evidence that brain MR is implicated in central cardiovascular control and volume regulation.

BRAIN CORTICOSTEROID RECEPTORS

Access to receptors

The lipophilic corticosterone diffuses readily through the blood–brain barrier and the plasma membrane of cells to bind to its receptors. An important determinant of corticosteroid receptor activation is access of the ligand to the receptor, which depends on several factors besides the total plasma concentration of corticosterone.

First, circulating hormone is bound to corticosteroid-binding globulin (*CBG/transcortin*) and with a much lower affinity to serum albumin. Of the average corticosterone concentration circulating over a 24-hour period in the rat (about 4 μg or 100 nmol/L), less than 5% is not bound to CBG (that is, free and biologically available).

Second, the enzyme 11β-HSD type 2 converts cortisol and corticosterone to their inactive 11-dehydro metabolites in mineralocorticoid target tissues, which presumably also occur in periventricular regions. Conversely, the 11β-HSD type 1 isoform that is often colocalized with GR can catalyze the reverse reaction and generate cortisol from cortisone within a target cell. This reaction takes place in the liver and may also be relevant for certain areas in the brain [4].

A third determinant of access, which particularly pertains to exogenous steroids, is the mdr1a P-glycoprotein. This protein is expressed in the apical membranes of endothelial cells of the blood–brain barrier. Mdr1a P-glycoprotein functions as an energy-dependent pump, which limits access to the brain of xenobiotic agents, including the synthetic steroids. Accordingly, the rodent brain (but not the pituitary) is resistant to penetration of moderate amounts of dexamethasone, a not naturally occurring steroid in rats and mice [5].

Corticosteroid receptor diversity

Although GRs and MRs are both high-affinity receptors for corticosterone, they differ in their affinities for several ligands. In rats, MR has an approximately tenfold higher affinity than GR for corticosterone [6]. The important consequence of this is that GR and MR are differentially occupied during the day and during stress responses. MR is already extensively occupied under basal trough conditions, while saturation of GR requires hormone levels that occur after stress or after the circadian peak. Because of its high, almost tonic occupation, it has been hypothesized that the bioactivity of the receptor protein is an important level of regulation for MR, while the GR signal primarily depends on ligand concentration. Synthetic glucocorticoids have higher affinity for GR than for MR, but their access to brain GR is hampered by the mdr1a gene-encoded P-glycoprotein.

Mineralocorticoid receptor/glucocorticoid receptor distribution

The GR is expressed ubiquitously in many different tissues and cell types. In tissues such as liver, lung, and adrenal medulla, GR are crucial for appropriate development. MR has a much more limited distribution, and as receptors for corticosterone (as opposed to mineralocorticoids), they have been characterized in brain and some lymphoid tissues mainly. The pituitary, outside the blood–brain barrier, contains GR as well as MR, although no specific function for MR has been described for any of its cell types.

Throughout the brain, immunocytochemical and in situ hybridization procedures have shown a widespread distribution of GR in neurons and glial cells. Particularly high GR concentrations are found in the limbic system (hippocampus—with relatively low concentrations in the CA3 region—septum, and amygdala), in the parvocellular neurons of the paraventricular nucleus of the hypothalamus (PVN), and in the supraoptic nucleus. In the PVN, the biosynthesis and release of parvocellular vasopressin, corticotrophin-releasing hormone (CRH), and other neuropeptides are under glucocorticoid control. GRs are also present in relatively high concentrations in the ascending monoaminergic neurons of the brain stem. Moderate GR levels are found in many thalamic nuclei and in patch-like distribution in the striatal areas, as well as throughout the cortical hemispheres.

In the brain, MR has a more restricted topography than GR. High MR densities have been found in the neurons of the hippocampal formation, lateral septum, medial and central amygdala, olfactory nucleus, layer II of the cortex, and brain stem sensory and motor neurons. This distribution of MR is essentially the same as discovered in 1968 by McEwen with cell nuclear retention of radioligand after the administration of tracer doses of ^{3}H-corticosterone to adrenalectomized rats. Aldosterone-preferring MR involved in salt homeostasis is localized in the anterior hypothalamus and circumventricular organs, such as the chorioid plexus.

The subcellular localization of MR and GR was studied in hippocampal neurons by dual-labeling immunocytochemistry and confocal microscopy [7]. It was observed that MR and GR are nonhomogeneously distributed over the nucleus. Both receptors are concentrated in about 1000 clusters scattered throughout the nucleoplasm. Many clusters exclusively contain either MRs or GRs, although a significant number of domains were found to contain both receptor types. The latter clusters are candidate sites where the two receptors could inter-

act to establish a coordinated regulation of gene expression. This would imply that GR and MR homodimers, as well as the possible MR/GR heterodimers, are associated with distinct nuclear domains.

Mineralocorticoid receptors/glucocorticoid receptors: Differential regulation gene of transcription

Glucocorticoid receptors and MRs contain a nearly identical DNA-binding domain that recognizes specific DNA elements in the regulatory regions of genes: glucocorticoid response elements (GREs; consensus sequence: GGTACAnnnTGTt/cCT). The steroid receptors bind as homodimers and perhaps also as heterodimers to GREs to stimulate transcription. In general, GRs are more potent activators of transcription than MRs are, at least in in vitro conditions. Heterodimers of MR and GR have been shown in cell systems to have, at times, characteristics that are different from either type of homodimer. The strong synergizing effect of GR-activated transcription on multiple GREs is not observed with MR activation, probably because of the limited homology of the N-terminal sequences. The tyrosine amino transferase (TAT) and phenylethanolamine-N-methyl transferase (PNMT) genes are examples of genes that are regulated via GREs.

Glucocorticoid receptors (and possibly MRs) can also repress gene transcription by binding to DNA. The DNA elements that are involved are known as "negative GREs" (nGREs). The sequence of nGRE can be highly variable and differs from the consensus sequence for positively acting GREs. The mechanism by which transcription is repressed also differs between cases. One mechanism involves binding of GR to the nGRE to occlude adjacent or overlapping binding sites on the DNA for positively acting transcription factors. An nGRE has been described for the human POMC gene.

The mode of action generally referred to as transrepression involves repression by GR of gene transcription activated by other transcription factors such as activated protein-1 (AP-1), nuclear factor-κB (NF-κB), and cAMP-responsive element binding protein (CREB). GRs interfere with these other factors via protein–protein interactions. This may happen independently of binding of the GR to the DNA, and dimerization of GR is not required. The target genes lack GREs.

Corticosteroid receptors may also activate genes in synergy with other, nonreceptor, transcription factors. On elements known as composite GREs, GRs bind to the DNA in close proximity to another transcription factor and may either repress or enhance the effect of this other factor. In case of the proliferin "cGRE," the GR greatly enhances the effect of the adjacently bound transcription factor AP-1 if the latter consists of c-jun/c-jun homodimers. In contrast, GR binding leads to repression of the action of c-jun/c-fos heterodimers. Interactions with other transcription factors depend, by definition, on the presence of these factors, which can be regulated by extracellular signals other than steroid hormones. This demonstrates that the effects of corticosterone vary widely and are context dependent.

Dissociation between MR- and GR-mediated events may arise through these "cross-talk" mechanisms, since it has been shown that GR suppresses AP-1 activity under conditions in which MR is ineffective. It is probable than the unique N-terminal regions of the GR and the MR account for the different properties with respect to transrepression [8].

MINERALOCORTICOID RECEPTORS AND GLUCOCORTICOID RECEPTORS IN BRAIN

Our strategy to examine corticosterone action on centrally regulated functions is based on removal of adrenals and dose-dependent corticosterone replacement for gradual and sequential activation of both receptor populations. A second approach employs the administration of receptor antagonists in minute amounts in the brain. Central administration is required because the synthetic steroids gain poor access to the brain. Finally, a third approach is based on genetic disruption of either MRs and GRs. Through pioneering research by a group in Heidelberg, these mice have become available in a collaborative program [9–12]. The experimental designs also take into account that the putative genomic B effects require at least several minutes to develop and will last for several hours.

Using this strategy, we have reported findings on the cellular, physiological, and behavioral level of analysis, which demonstrate that MR- and GR-mediated actions exerted in hippocampus are distinct in time domain and mechanism and proceed in a coordinate fashion. The effects are "conditional," which implies that the context in which these actions occur is a critical determinant. For instance, in the behavioral realm, corticosterone action "out of context" disrupts information processing and switches behavior to a more opportune response.

Dose–response curves of corticosterone often display a U shape. Low doses of corticosterone predominantly activate MR and activate GR to a lesser extent. MR antagonists can block the MR-mediated effects. These include synthetic compounds such as RU 28318 and spironolactone, but presumably also naturally occurring progesterone and 11β-OH-progesterone, which also display a high affinity to MRs. High doses of corticosterone activate both MRs and GRs; the synthetic glucocorticoid antagonist RU486 can often block the latter effect exerted by corticosterone. Interestingly, blockade of the high corticosterone effect by the MR antagonist also appears to be effective (discussed later in this article). This observation is counterintuitive since the binding

Table 1. Function of brain corticosteroid receptors

Corticosterone condition	Occupied receptor	Function
Hippocampal MR and GR		
Basal	MR	Stabilization of excitability Sensitivity stress response system Pro-active mode of control Selection of behavioral response
Stress	MR + GR	Suppression increased excitability Recovery from stress Re-active mode of control Facilitation memory storage
Periventricular regions: aldosterone-selective MR		
Aldosterone	MR	Salt appetite Volume regulation Sympathetic outflow

Abbreviations are: MR, mineralocorticoid receptor; GR, glucocorticoid receptor.

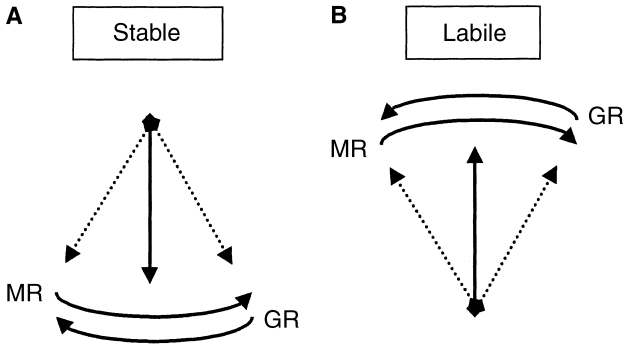

Fig. 1. The mineralocorticoid receptor/glucocorticoid receptor (MR/GR) balance hypothesis. We hypothesize that shifts in the balance of MR-/GR-mediated actions alter the set point of stress system activity. Once an imbalance in MR/GR has occurred, the individual loses its ability to maintain homeostasis, if challenged by an adverse event. This leads to a condition of neuroendocrine disregulation and an impaired behavioral adaptation, which when surpassing a certain threshold, may enhance vulnerability and trigger the onset of a stress-related neurological or psychiatric disorder to which the individual is genetically predisposed [3]. The cartoon shows MR- and GR-mediated actions in either stable of labile equilibrium.

studies suggest saturation of MR at low corticosterone concentrations. Apparently, the MR antagonist also blocks the interaction of MRs and GRs.

Table 1 summarizes our data on the function of MR and GR in centrally regulated processes. Low corticosterone, resulting in a predominant MR activation, maintains (stabilizes) neuroneal activity [13], is of relevance for the threshold or sensitivity of the neuroendocrine stress response system, and contributes to control of behavioral reactivity and response selection (discussed later in this article). This "stabilizing" function predominantly operating via MR by low corticosterone contrasts to the effect of high corticosterone in "recovery" of disturbed homeostasis requiring MR + GR occupancy. Thus, high corticosterone operating via a coordinate MR + GR activation restores excitability transiently raised by excitatory stimuli [13], facilitates termination of the stress-induced neuroendocrine response, and promotes storage of information on stress-provoking events. Based on these observations, a model for coordinate MR- and GR-mediated action in hippocampus was proposed. Figure 1 shows the antagonistic effects of progressive MR and GR activation by increasing corticosterone concentrations. The MR-/GR-mediated actions are aimed to maintain homeostasis, either in stable or labile (continuously adjusting to change) equilibrium.

In previous reports, we have stated that the extensive occupancy of hippocampal MR already at low levels of circulating corticosterone suggests that this receptor mediates a tonic influence on hippocampus function. In addition, the occupancy data obtained with radioligand binding suggest that MRs operate only in the low range of corticosterone concentrations. This hypothesis will be tested by experiments that are described in the next sections. Experiment 1 examines hippocampal MR function at high levels of exogenous corticosterone. Experiment 2 is designed to study MR function during conditions of hyperthermia and stress, which supposedly enhance the action of endogenous hormones via MR [14].

CENTRAL MINERALOCORTICOID RECEPTOR FUNCTION AND BEHAVIOR

The hippocampus is critical for learning and memory processes, particularly regarding spatial orientation. This can be assessed in the Morris maze test, which includes that rats learn the location of a spatially fixed underwater platform with the help of distant cues during several training sessions. The time and swimming distance required for the rats to find the platform serve as criterion for acquisition, consolidation, and retrieval of spatial orientation. Oitzl et al observed corticosteroid modulation of behavioral performance of male Wistar rats in the Morris maze [15]. The effects of the corticosteroid hormones on behavioral performance in this test could be distinguished in distinct MR- and GR-mediated effects. Intracerebral administration of the GR antagonist in amounts as low as 10 ng before and after the first training session resulted in impaired performance 24 hours later. Thus, blockade of GRs, and not of MRs, interfered with the learning process by disrupting consolidation of spatial information. Acquisition was not affected and neither was the retrieval of learned information, since administration prior to the second training session did not alter performance [15].

Once the rats have learned the location of the platform, the search pattern displayed by the rats in trials without platform is extremely sensitive to disruption of

hippocampal functioning. Blockade of central MR results in an altered behavioral search pattern, suggesting implication of MR function in the choice of the behavioral response. Performance of spatial navigation of adrenalectomized rats showed a deficiency in both MR and GR function: These rats showed impaired place navigation learning, as well as altered search strategies [15].

The hippocampus also plays a key role in the response to novelty. Disturbances of hippocampal functioning reduced the animals' tendency to explore flexibly its environment resulting in perseverance of acquired behavior. This is not a matter of stimulus detection, but of a different reactivity to stimuli. Since MR is involved in the process of response selection, as demonstrated by the altered search strategy in the water maze, we proposed a particular involvement of MR in the structure of the behavioral response to a novel environment. Therefore, a task was designed allowing the animal to distribute its exploratory activity between an object in the center and the periphery of an open field [16].

We found a U-shaped relationship between the exploration pattern and the circulating level of corticosterone and consequent receptor occupancy. Tested one day after adrenalectomy, rats explored significantly more the center area and its object compared with sham-operated and intact rats. Treatment of adrenalectomized rats with a low dose of corticosterone, that is, preferential occupancy of MR one hour before the test, reduced exploration of the center area and resulted in an exploration pattern similar to sham-operated and intact rats. Adrenalectomized and intact rats injected with a high dose of corticosterone, that is, complete occupancy of MR and GR, showed more exploration of the center. Blockade of central MR by 100 ng RU 28318 prevented the high corticosterone-induced increase in exploration of the center area, while the administration of the GR antagonist had no effect. The total locomotor activity did not differ between the groups.

In conclusion, corticosterone controls the behavioral response of an animal to novelty in a U-shaped manner over a concentration range from below 25 nmol/L up to stress levels of 1000 nmol/L corticosterone. Minimal reactivity toward the novel object in the center is observed at about 100 nmol/L of total corticosterone, which is consistent with predominant MR and little GR occupancy. At any concentration of corticosterone, its effect can be blocked by pretreatment with MR antagonist given intracerebroventricularly (icv). This finding suggests a critical role for hippocampal MR in the control of the animals' response to novelty, even under conditions of high corticosterone.

CENTRAL MINERALOCORTICOID RECEPTORS AND AUTONOMOUS FUNCTION

The pioneering studies of Brody et al have demonstrated that mineralocorticoid-induced changes in blood pressure are coordinated by centrally regulated functions [17]. These functions include central control of sodium homeostasis and of sympathetic nervous activity, which are influenced by the mineralocorticoids and by the neuropeptides, angiotensin II, and natriuretic peptide, acting in coordination in the anteroventral part of the periventricular hypothalamus (AV3V).

Van den Berg et al showed that in conscious, normotensive Wistar rats, a single (icv) injection of a few nanograms of aldosterone induced an increase in systolic blood pressure at eight hours after administration, whereas an icv injection of the MR antagonist RU28318 caused a long-lasting decrease [18–20]. Other researchers showed that icv infusion of RU28318 abolished the development of deoxycorticosterone acetate-salt hypertension and blocked the centrally evoked aldosterone-induced hypertension [21].

Our observations on the central effect of the mineralocorticoids were made with the indirect tail cuff method to measure blood pressure. This procedure involves—for reasons of habituation to the experimental procedure—a training period of 14 days to the conditions of the blood pressure measurement. Animals are exposed for 30 minutes daily to a warm lamp, resulting in an elevated ambient temperature (32°C) and elevated core temperature (38.5°C), followed by placing the animal into a small cage for one minute to allow application of the tail cuff.

When arterial pressure was directly measured in conscious freely moving cannulated rats or in rats implanted with biotelemetry, the icv administered MR agonists and antagonists were ineffective (Van Acker and Sibug, unpublished observation). Also, exposure of the rats to the condition of chronic discontinuous heat did not alter the arterial pressure. However, the subsequent brief restraint stress evoked a pressor response. Pretreatment with the MR antagonist icv suppressed this stress-induced pressor response, but only if the rats had been trained for two weeks to the condition of chronic discontinuous heat and restrained stress. The effect of the MR antagonist developed slowly and was significant after seven hours (Fig. 2).

During the seven hours after the icv injection of the antagonist, the rats also showed increased diuresis and urinary electrolyte excretion [22], which was abolished in bilaterally denervated kidneys. Systolic blood pressure in such denervated rats was also diminished. These results demonstrate that brain MRs are involved in blood pressure regulation and homeostasis of kidney function. These brain MRs are likely localized in the anterior hypothalamus and the periventricular brain regions.

HIPPOCAMPAL MINERALOCORTICOID RECEPTORS AND NEUROENDOCRINE REGULATION

We have based our analysis of hippocampal function on the central administration of selective receptor antag-

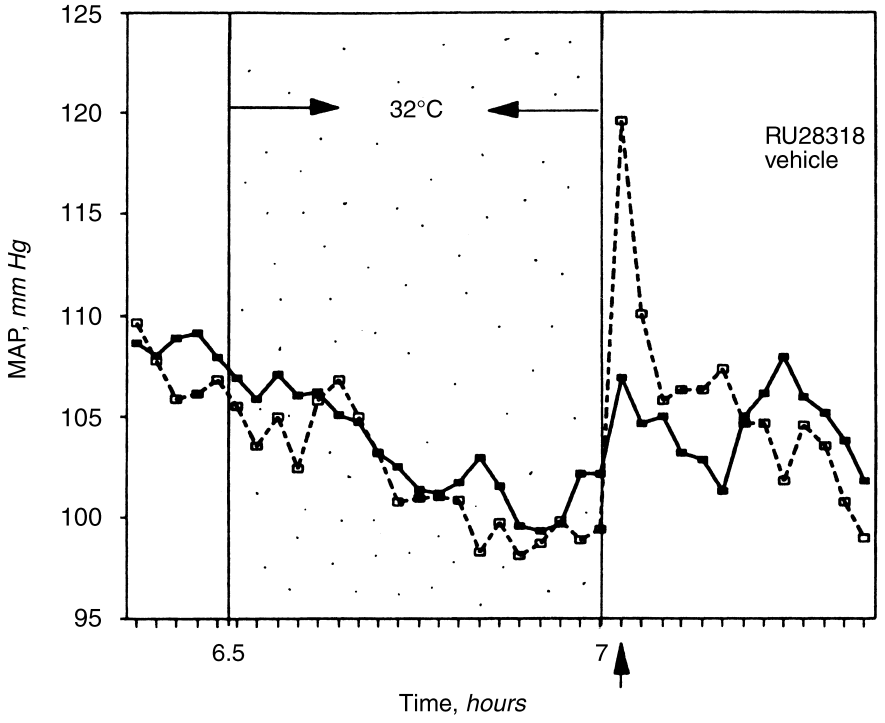

Fig. 2. Effect of MR antagonist intracerebroventricularly (icv) on blood pressure response to stress. The effect of mineralocorticoid antagonist on the mean arterial blood pressure of rats exposed to an ambient temperature of 32°C for 30 minutes during 14 days is shown. The dotted area indicates the warmest period. The arrow refers to the time point of 1.5 minutes of restraint stress. Symbols are: (□) vehicle-treated rats; (■) RU 28318-treated rats. Data are from van den Berg et al [19], and are reprinted with permission from the American Physiological Society.

onists in adrenally intact animals, allowing us to study the role of endogenous corticosterone in the presence of adrenal medullary hormones, which have potent actions on brain CRH expression and adrenal sensitivity to acrenocorticotropic hormone (ACTH). In these studies, ACTH and (free) corticosterone levels were measured in sequential blood samples obtained via indwelling intravenous cannulas from freely moving animals. Intravenous administration of MR antagonist elevated basal (a.m.) trough levels of plasma corticosterone and exposure of the rats treated with the antimineralocorticoid to a novel situation resulted in enhanced adrenocortical responses [23]. In the p.m. phase, MR antagonists (100 g icv) also elevated basal ACTH and corticosterone levels, as did a tenfold lower dose injected bilaterally into the hippocampus [24]. Consistent with the MR specificity of the response, a corticosterone implant in the dorsal hippocampus suppressed adrenalectomy-induced elevations in ACTH levels, while dexamethasone implants were ineffective. Finally, systemic administration of spironolactone increased basal hypothalamus-pituitary-adrenal (HPA) activity in humans, although this response was not noted in all studies. Thus, hippocampal MRs appear to mediate the effect of corticosterone in maintaining the tone of basal HPA activity [3].

A number of other studies also attest to the importance of hippocampal MR in controlling HPA tone. First, the cyclic increase of HPA activity in female rats on the evening of proestrus occurs when the high estrogen and progesterone levels impair MR function; estrogens lower hippocampal MR mRNA levels and binding capacity, while progesterone causes a profound decrease in MR binding affinity [25]. Second, rat strains with high levels of hippocampal MR expression (for example, Lewis rats) show lower basal and stress-induced HPA activity, but elevated free corticosterone levels compared with Wistar rats from which they are derived [24]. Third, aged rats generally have reduced MR (and GR) expression and an increased basal HPA activity and prolonged stress-induced ACTH release [26]. Fourth, tricyclic antidepressants increase expression of hippocampal MR and decrease basal and stress-induced HPA activity, also in humans [27]. Finally, icv administered endotoxin impairs MR function and causes a chronically elevated basal HPA activity [3, 28].

Hippocampal MRs are important in terms of the control of inhibitory tone over the HPA axis. This effect of corticosterone via MRs is modulated by GRs, which become progressively occupied after stress and during the circadian rise in glucocorticoid, which also negatively feed back on the PVN. We have found that icv administration of the antiglucocorticoid RU 38486 (100 ng) to intact rats has no effect on basal (a.m.) trough levels of plasma corticosterone, probably because at that time, the low levels of corticosterone produce negligible GR occupation. If the antagonist is administered icv during the pm phase, basal HPA activity increases, as seen after a local administration of 5 ng RU486 near the PVN. In

contrast, an administration of the same dose of antagonist directly into the hippocampus decreased basal ACTH levels in the p.m. phase. We interpret these apparent paradoxical data after icv and intrahippocampal administration as follows. First, if solely hippocampal GRs are blocked, their attenuating effect on MR-mediated action is eliminated, resulting in an enhanced MR-mediated inhibitory tone. Second, if RU486 is given icv, the effect of blockade at the level of the PVN appears to override that of GR antagonism in the hippocampus. It would be of interest to test this interpretation at the cellular and circuit level [29, 30].

Thus, intrahippocampal antiglucocorticoids suppress ACTH levels under conditions in which antimineralocorticoids enhance the release of ACTH. Such opposite effects correlate well with the electrophysiological data previously discussed, since MRs and GRs mediate opposite effects on excitability and excitatory outflow. The nature of the HPA regulation via hippocampal MRs and GRs is also consistent with the cellular actions they evoke in the hippocampus: Predominant MR activation (comparable with local antiglucocorticoid application) maintains hippocampal excitability [30] and through transsynaptic inhibitory projections to the PVN basal HPA activity. Conversely, with rising glucocorticoid concentration, GR activation suppresses the hippocampal output, resulting in a disinhibition of PVN neurons. The functions mediated by both receptor types are linked. A deficiency in MR is predicted to allow more readily a corticosterone response, thus leading to more pronounced GR-mediated effects. These data illustrate the importance of balance in MR- and GR-mediated effects involved in HPA regulation.

CONCLUSIONS

The following conclusions can be drawn on brain mineralocorticoid function.

1. Brain (presumably periventricular) MRs mediate aldosterone-selective effects on salt homeostasis, diuresis, and blood pressor responses to stress.
2. Hippocampal MRs are substantially occupied at low corticosterone concentrations, but this does not exclude that the receptors also mediate the effects of high corticosterone concentrations in a dynamic fashion.
3. Mineralocorticoid receptor-mediated corticosterone effects maintain excitability, determine the sensitivity of the stress response system, and facilitate selection of the appropriate behavioral response to cope with stress.
4. The hippocampal MR-mediated effects occur in a coordinate manner with those mediated by the colocalized lower affinity GR.
5. These coordinate effects in hippocampus result in a U-shaped dose responsiveness after rising corticosterone concentrations, demonstrating opposing roles of MRs and GRs in the maintenance of cellular homeostasis.
6. The U-shaped dose responses also occur in solely MR-mediated effects (salt appetite and behavioral reactivity).
7. The context in which MR and GR activation occurs is a critical determinant for the steroid effects.
8. Corticosteroid actions become disruptive when MR/GR activation occurs out of context and/or the actions via the two receptor sites are imbalanced for a prolonged period of time.

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