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Brain Corticosteroid Receptor Balance in Health and Disease*

E. RONALD DE KLOET, ERNO VREUGDENHIL, MELLY S. OITZL, AND MARIAN JOËLS

Division of Medical Pharmacology (E.R.D.K., E.V., M.S.O.), Leiden/Amsterdam Center for Drug Research, University of Leiden, 2300 RA Leiden, The Netherlands; and Institute for Neurobiology (M.J.), University of Amsterdam, 1098 SM Amsterdam, The Netherlands

Address reprint requests to: E. R. de Kloet, Ph.D., Division of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research, P.O. Box 9503, 2300 RA Leiden, The Netherlands. E-mail: e.kloet@lacdr.LeidenUniv.nl.

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This review is dedicated to Dr. Margaret (Mags) Carey and Dr. Bernd Schöbitz whose untimely deaths are a great loss to us all.

I. Introduction

EVERY disturbance in the body, either real or imagined, evokes a stress response, which serves to restore homeostasis and to facilitate adaptation. Essential to the stress response are neurons in the paraventricular nucleus (PVN) of the hypothalamus, which express CRH with its cosecretagogue vasopressin (VP), and other neuropeptides that drive the activity of the sympatho-adrenomedullary and the hypothalamic-pituitary-adrenal (HPA) systems. These two systems are not separate entities but exert control over each other's activity. Of the two, the HPA system involving corticosteroid hormone secreted by the adrenals (cortisol in man or corticosterone in rat) is slower and more persistent in its actions (Fig. 1). This review addresses mainly the action of corticosterone in the rat brain.

In concert with other components of the stress response system, the action of corticosterone displays two modes of operation. In the first, "proactive" mode, corticosterone maintains basal activity of the HPA system and controls the sensitivity or threshold of the system's response to stress. The hormone promotes coordination of circadian events, such as the sleep/wake cycle and food intake and is involved in processes underlying selective attention, integration of sensory information, and response selection. In the second, "reactive" mode, corticosterone feedback helps to terminate stress-induced HPA activation. The steroid facilitates an animal's ability to cope with, adapt to, and recover from stress; corticosterone promotes learning and memory processes.

A brief period of controllable stress may be experienced with excitement and can be beneficial to emotion and health. In contrast, lack of control and uncertainty can produce a chronic state of distress, which is believed to enhance vulnerability to disease. Selye (1) noted the antagonistic actions exerted by mineralocorticoids and glucocorticoids in host defense and formulated the "pendulum hypothesis" to explain the switch from good to bad effects of stress. This hypothesis stated that "excess mineralocorticoids predispose the body to inflammation, while excess glucocorticoids augment the danger of infection." Ever since, corticosterone has been tightly linked to stress and adaptation. Corticosterone restrains defense reactions to stress, which would themselves become damaging if left uncontrolled (2–4), and redirects metabolism to meet the energy demands during stress (5).

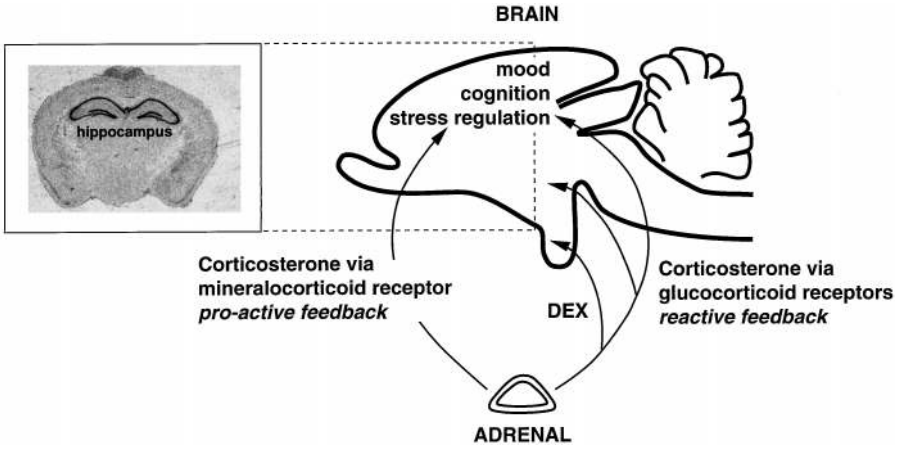

FIG. 1. HPA axis: proactive and reactive corticosteroid feedback mode. HPA activity driven by CRH, VP, and other peptides released by PVN neurons into the portal vessels, in a pulsatile fashion (317). The secretagogues are released in various compositions as a "neuroendocrine signature" identifying basal conditions as well as various modalities of the stress response (265). The secretagogues coordinately control the genesis of pituitary corticotropes as well as the synthesis and the release of pituitary ACTH, one of the end products of POMC processing (41, 429). Adrenal corticosteroid secretion usually reaches maximal levels within 15 min after HPA activation; the adrenal response to ACTH is modulated by locally produced factors and sympathetic nervous activity (430). Corticosteroid hormones feed back in two modes of operation: a proactive MR mode maintaining basal HPA activity and a reactive GR mode facilitating recovery from stress-induced activation. DEX, Dexamethasone acting predominantly on the pituitary level in the blockade of stress-induced HPA activity.

Since Selye's report, the mineralocorticoid hormone (aldosterone) has rarely been connected with the stress response, since control of the sodium balance through actions in kidney and hypothalamus was considered its unique homeostatic function (6). This situation changed when it appeared that the receptors for mineralocorticoids showed high affinity for corticosterone as well as for aldosterone (7–9).

Corticosterone actions in the brain are mediated by glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) (10, 11). GRs occur everywhere in the brain but are most abundant in hypothalamic CRH neurons and pituitary corticotropes. Aldosterone-selective MRs resembling those in the kidney are expressed at hypothalamic sites involved in the regulation of salt appetite and autonomic outflow (12–17), but these effects are beyond the scope of the present review. By far, the highest MR expression is found, however, outside the hypothalamus, *i.e.*, in the hippocampus, a brain structure involved in learning and memory processes. Importantly, in the hippocampus the aldosterone selectivity of MR is lost. Since these apparently "nonselective" MRs bind corticosterone with high affinity, approximately 10-fold higher than colocalized GRs, hippocampal MRs will respond strongly to corticosterone (7, 8, 18, 19). Thus, in the hippocampus, one compound, corticosterone, serves to activate two signaling pathways via MR and GR (9).

The findings on corticosteroid receptor diversity led to our working hypothesis that "tonic influences of corticosterone are exerted via hippocampal MRs, while the additional occupancy of GRs with higher levels of corticosterone mediates feedback actions aimed to restore disturbances in homeostasis" (20). The progressive activation of MRs with a low concentration of corticosterone and additional GR activation when steroid levels rise can cause profound changes in neuronal integrity (21–23) and neuronal function (24) associated with changes in neuroendocrine regulation (25, 26) and behavior (27). These findings led us to postulate that a "balance in MR- and GR-mediated effects" exerted by corticosterone is critical for homeostatic control (11, 28–30). This proposal provides a receptor-based version of Selye's classical pendulum hypothesis on opposing effects of mineralocorticoids and glucocorticoids in host defense.

In the present review, we will focus on the function of the various types of brain corticosteroid receptors. Valuable information has been gleaned from a number of recent reviews and books (25, 26, 31–45). Here we will highlight the determinants of brain corticosteroid receptor activity and examine the various levels at which their function may change. The molecular and cellular responses mediated by, in particular, hippocampal corticosteroid receptors will be considered in the context of HPA regulation and associated behavioral responses. The thesis is pursued that MRs are involved in maintenance of stress system activity, while GRs (in coordination with MRs) mediate steroid control of recovery from stress. Also, new findings on the MR-GR interplay are discussed that either challenge or support the original thesis. Next, we will argue that (early) life events superimposed on genotype program the stress system for the rest of one's life and contribute to individual differences in vulnerability to stress-related psychopathology. Further understanding of the role of corticosteroids in gene-environment interactions may help to answer a fundamental question in the endocrinology of stress and disease: when do corticosteroid hormone actions cease to be beneficial to health and, instead, become damaging?

II. Corticosteroid Receptor Properties

When corticosteroid hormones enter the brain compartment, they bind to intracellular receptors. The corticosteroid receptors are part of a cytoplasmic multiprotein complex, which consists of one receptor molecule and several heat shock proteins (hsp) [*i.e.*, two molecules of hsp90, one hsp70, one hsp 56, and an immunophilin (for review see Refs. 46–

48)]. Binding of glucocorticoids leads to a rapid chain of events consisting of dissociation of the hsp and immunophilin, multiple phosphorylation steps, and increased affinity of the ligand-activated receptor for nuclear domains (49, 50).

Molecular and biochemical studies have demonstrated two receptor subtypes, MR and GR, in brain tissue. If colocalized, they mediate the corticosteroid signal in synergism or antagonism, depending on cellular context. Several determinants for the receptor-mediated steroid response have been recognized. First of all, the access of (synthetic) corticosteroids to the brain receptors is determined by a variety of factors, such as corticosteroid-binding globulin (CBG), steroid-metabolizing enzymes, and the mdr1A P-glycoprotein. Second, the responsiveness to corticosteroids is governed by the cellular expression of MR, GR, and their variants. Generation of such variants may be disease-specific, a notion that can now be directly tested in mutant mice carrying a genetic defect in MR or GR. Third, the cellular context and physiological conditions can determine whether the steroid receptor complex either enhances or represses gene transcription. The response mode depends on the cross-talk between the steroid receptors and various affiliated nuclear factors, such as activating protein 1 (AP-1), cAMP-response element-binding protein (CREB), or nuclear factor-κB (NFκB), activated by other agents (*e.g.*, neurotransmitters, other hormones). Finally, there may be a higher order control of receptor interaction with the genome, relating to the spatial organization of the cell nucleus during cellular differentiation and growth (51–54); the latter, however, is beyond the scope of the present review.

TABLE 1. Two intracellular corticosteroid receptor types in the brain

1. Mineralocorticoid receptor (MR)
High affinity for corticosterone ($K_D \approx 0.5$ nM)
In limbic brain structures
Agonist: aldosterone
Antagonist RU 26752, spironolactone
2. Glucocorticoid receptor (GR)
Lower affinity for corticosterone ($K_D \approx 5.0$ nM)
Ubiquitous
Agonist: dexamethasone, RU 28362
Antagonist: RU 38486

A. Corticosteroid receptor diversity in brain and pituitary

Thirty years ago McEwen and co-workers (18) demonstrated that a [^{3}H]corticosterone tracer administered to adrenalectomized (ADX) rats is retained in high amounts in the hippocampus several hours later: autoradiography showed abundant [^{3}H]corticosterone-labeled cell nuclei in the dentate gyrus and pyramidal cells of the hippocampus as well as in other regions of the limbic forebrain, *e.g.*, lateral septum and amygdala (55). This retention pattern in limbic brain has subsequently been found in widely divergent species such as birds, dogs, and monkeys that secrete either corticosterone (birds, rodents) or cortisol (dogs, primates) as the naturally occurring glucocorticoid. This suggests that the retention of corticosteroids, particularly in the hippocampus, is a trait that is conserved in evolution (10).

The early studies with tracer amounts of corticosterone had, in fact, identified MRs rather than GRs in hippocampus, since the tracer dose of corticosterone was too low to detect GR (9, 56). This became apparent when binding properties of MRs and GRs were studied in cytosol, using selective GR ligands (RU 28362) that allowed discrimination between the two receptor types (57) (Table 1). It was found that MRs bind corticosterone with an affinity 10-fold higher [dissociation constant (K_d~) 0.5 nM, 4 C] than GRs. MR and GR are both present in hippocampal dentate gyrus neurons and CA1 cells; the CA3 area mainly expresses MR. Subsequently, it was shown that low basal corticosterone levels predominantly occupy MR. GR can be activated additionally to MR only when corticosterone levels are high, *i.e.*, at the circadian peak and during stress (9, 11, 20, 58). With autoradiography of selectively labeled MR and GR (59), immunocytochemistry (60–65), and *in situ* hybridization (66–69), the spatial distribution of the two receptor types in brain tissue was studied. In agreement with [^{3}H]corticosterone labeling, MRs prevail in limbic brain areas, while GRs are widely distributed in neurons and glial cells. Table 2 summarizes in chronological order the highlights in the discovery of brain corticosteroid receptor diversity.

The subcellular localization of MR and GR was studied in hippocampal neurons by dual labeling immunocytochemistry and confocal microscopy (70). It was observed that MR

TABLE 2. Milestones in brain corticosteroid receptor research

Year	Milestone
1968	First report on selective retention of [^{3}H]corticosterone in hippocampus (18)
1972	Corticosterone receptors in pyramidal neurons of hippocampus (432)
1975	Low retention [^{3}H]dexamethasone in hippocampus; high in pituitary corticotropes (19)
1980	Selective GR agonists discriminate between MR and GR (57)
1982	*In vitro* hippocampus and kidney cytosol contain MR and GR (7, 8)
1985	MR and not GR retains [^{3}H]corticosterone in neuronal nuclei of hippocampus (9)
1985	Cloning of GR and splice variants (95)
1985	First brain map of immunoreactive GR neurons (60)
1987	Cloning of MR (103)
1988	MR and GR mRNA are expressed in hippocampal neurons (66)
1988	11-HSD confers aldosterone selectivity to MR (79, 80)
1991	First brain map of immunoreactive MR neurons (64)
1993	Identification of MR mRNA splice variants (104)
1994	*In vitro* demonstration of MR/GR heterodimerization (117)
1995	mdr1A Pgp in blood-brain barrier prevents brain penetration of dexamethasone (90–92)
1996	Colocalized immunoreactive MR/GR clusters in hippocampal neuronal nuclei (70)
1996	11-HSD regenerates *in vitro* bioactive corticosterone in hippocampus (87)

and GR are nonhomogeneously distributed over the nucleus. Both receptors are concentrated in about 1000 clusters scattered throughout the nucleoplasm. It was found that many clusters exclusively contain either MR or GR, although a significant number of domains was found to contain both receptor types (Fig. 2). The latter clusters are obvious candidate sites at which the two receptors could interact to establish a coordinated regulation of gene expression. This implies that GR and MR homodimers, as well as the possible MR/GR heterodimers, are associated with distinct nuclear domains. However, we also observed that the distribution of GR clusters in nuclei of human bladder carcinoma cells is not related to transcription initiation sites, suggesting that most of the detected clustered receptor molecules are not directly involved in gene transcription (71, 72).

B. Access of corticosteroids to brain receptors

Access of natural and synthetic corticosteroids to brain steroid receptors is controlled by many factors, three of which will be discussed below.

The first determinant of corticosterone access to brain is CBG. Circulating corticosterone is bound to CBG (K_d ~50 nM, 4 C) and with a much lower affinity to serum albumin. Of the average corticosterone concentration circulating over a 24-h period, less than 5% is not bound to CBG, *i.e.*, is free and biologically available (73). This amount is in the range of the K_d for the corticosteroid receptors, measured *in vitro* in cytosol. CBG levels are regulated by numerous signals. Particularly potent inducers of CBG synthesis are the estrogens; this accounts for the much higher level of total circulating corticosterone in females compared with males (74). Glucocorticoids and stress down-regulate CBG (75). CBG is a static regulator of the biological availability of corticosterone. The binding protein is also expressed intracellularly in the pituitary. Here, CBG may compete with the steroid receptor for intracellular corticosterone, as was also found in the liver, kidney, and lung. In the pituitary, uptake of corticosterone in nuclei of corticotropes is very low, whereas the potent synthetic glucocorticoid dexamethasone does not bind to CBG and is retained in high amounts (19, 76). Furthermore, CBG belongs to the SERPIN (serine protease inhibitor) superfamily. Accordingly, CBG is a substrate for neutrophil elastase, which cleaves CBG so that delivery of corticosterone to inflammation targets may be locally enhanced (77). Although CBG is not present in the healthy brain, the latter process may play a role in disease.

The second determinant of corticosterone access to the brain discussed here is a dynamic regulator. It is involved in the local metabolic conversion of corticosterone and is the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD; Ref. 78). There are two isoforms of 11β-HSD. 11β-HSD type 2 is an NAD-dependent high-affinity enzyme, which acts as an exclusive dehydrogenase and functions to exclude corticosterone or cortisol from MR-containing targets such as epithelial cells in the kidney (79–82). In the brain, 11β-HSD2 is

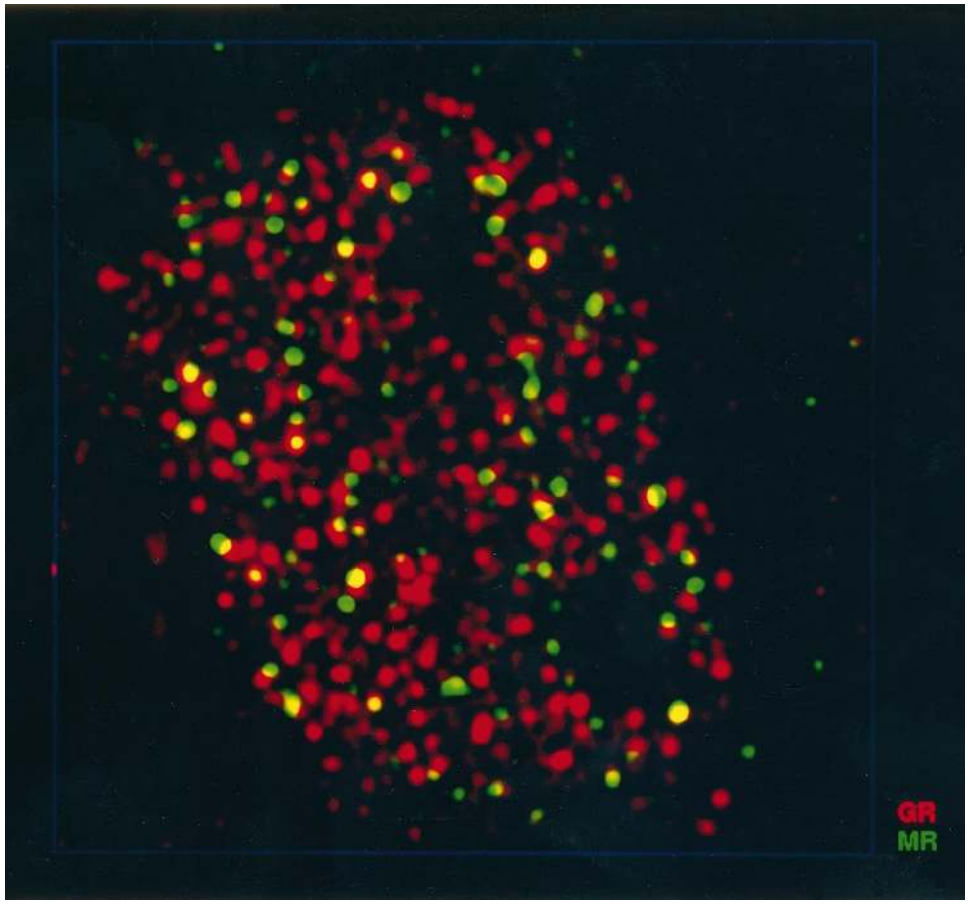

FIG. 2. Colocalization of MR and GR in nuclear domains of hippocampus. Representative confocal microscopy image (restored) of the distribution of corticosteroid receptor types in the cell nucleus of a rat hippocampal CA1 neuron. ADX animals were injected sc with 300 μg corticosterone/100 g body weight. After 1 h, brain tissue was fixed by cardiac perfusion with 4% formaldehyde. Brain slices (30 μm) were dually labeled with antibodies against the MR (*green*) and GR (*red*). Each cluster is about 10 receptor molecules. *Yellow* indicates colocalized MR and GR. Single optical sections of three-dimensional images are shown (70). [Reproduced with permission from Dr. B. van Steensel.]

confined to the anterior hypothalamus and circumventricular organs (83, 84) involved in salt appetite, volume regulation, and autonomous outflow (12, 13, 15–17). No detectable amounts of 11β-HSD2 are found in the hippocampus, but it does contain the reversible NADP(H)-dependent 11β-HSD type 1 isoform (85). The 11β-HSD1 isoform has a much higher Michaelis-Menten constant (K_m) value than 11β-HSD2 and is often colocalized with GR.

The reports on 11β-HSD activity in hippocampal tissue, which appeared at the beginning of the 1990s have created much confusion with regard to its physiological significance. *In vitro*, in hippocampal homogenates, predominantly oxidase activity has been demonstrated, leading several groups to argue in favor of a protective role of this enzyme against corticosteroid overexposure. In agreement with this line of reasoning, 11β-HSD inhibitors (carbenoxolone or glycerrhetinic acid) increased cell nuclear uptake of [^{3}H]corticosterone in hippocampal tissue slices (86). In another study using hippocampal cell cultures, it was argued that 11β-HSD reductase activity regenerates corticosterone from 11-dehydrocorticosterone, as it does in most tissues containing the 11β-HSD1 isoform (87). It is possible that *in vitro* the direction of the oxidoreductase activity relates to the ratio of $NADP^+$ and NADPH.

We tested the significance of hippocampal 11β-HSD1 activity *in vivo*. Using autoradiography it was observed that intracerebroventricularly (icv) administered carbenoxolone (ED_{50} 30 μg), effective in 11β-HSD blockade, did not affect the retention of [^{3}H]corticosterone by MRs in neuronal nuclei of the hippocampus (86). This finding suggests that 11β-HSD1 does not interfere with or enhance the access of corticosterone to hippocampal tissue under conditions of low, basal corticosterone levels. However, it cannot be excluded that 11β-HSD1 plays a role in modulating the access of high amounts of corticosterone as has been suggested for the regeneration of the steroid in hippocampal neurons (87).

A third determinant of access, which particularly pertains to synthetic corticosteroids, is the mdr1a P-glycoprotein (88). This protein is expressed in the apical membranes of endothelial cells of the blood-brain barrier (89). Mdr1a P-glycoprotein functions as an energy-dependent pump that limits access to the brain of xenobiotic agents including the synthetic steroids. Mutant mice with a genetic disruption of the mdr1a gene show increased accumulation of [^{3}H]dexamethasone in the brain (90). This uptake was found to be further enhanced in GR-containing brain targets for glucocorticoids using autoradiography of brain sections obtained from ADX mutant mice treated with tracer amounts of dexamethasone. In the hippocampus and PVN of mutant mice, an increase in cell nuclear retention of up to 10-fold was observed, compared with wild-type controls, reaching levels observed in the pituitary (91, 92). Accordingly, the brain is resistant to penetration of moderate amounts of dexamethasone because of mdr1a P-glycoprotein activity (Fig. 3). Since the synthetic steroids are substrates for the P-glycoprotein extrusion pump, they could potentially induce expression of the mdr1a gene and, thereby, enhance their own resistance.

C. Expression of MR, GR, and receptor variants

The human GR is localized on chromosome 5 whereas the MR is localized on chromosome 4, indicating an early duplication of their common ancestor during evolution. Despite this early divergence, their genomic organization is very similar, notwithstanding differences at the 5′- and 3′-ends (93, 94).

Alternative splicing of the 3′-end of the human GR (hGR) pre-mRNA creates an hGRβ variant in addition to the common hGRα (93, 95) (Fig. 4). However, note that rat GR pre-mRNA lacks this splice site (96). Translation of GRα and GRβ produces two proteins that are identical in the first 727 N-terminal amino acids containing the transactivation and DNA-binding domains. They differ in their carboxy termini, which implies that GRα binds cortisol while GRβ does not (97). However, GRβ is capable of binding to glucocorticoid-responsive elements (GREs; Ref. 98) and forms homodimers as well as heterodimers with GRα (99) *in vitro*. Accordingly, GRβ has been shown to block GR-mediated transactivation, although it does not seem to interfere with transrepression (33). In the human brain, GRβ mRNA is found in the hypothalamus and the hippocampus (98), but the abundance is only 1% relative to GRα (97). Since inhibition of GRα function requires a 5-fold excess of GRβ, an unlikely 500-fold induction of GRβ expression is required to protect GRα *in vivo*, *e.g.*, from chronic overexposure of glucocorticoids. However, partial protection may exist, as indicated by the preferential

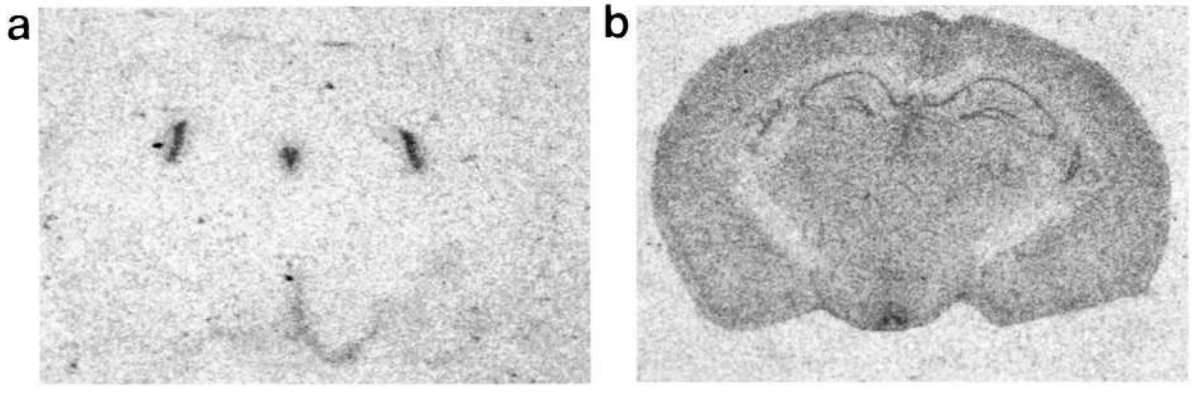

FIG. 3. Mdr1a-P-glycoprotein and dexamethasone uptake in brain. Representative autoradiograms of 10-μm brain sections of wild-type mice (a) and of mice with a targeted disruption of the mdr1a P-glycoprotein. Penetration of [^{3}H]dexamethasone was measured at 1 h after administration to these mice, which were adrenalectomized the day before (91, 92).

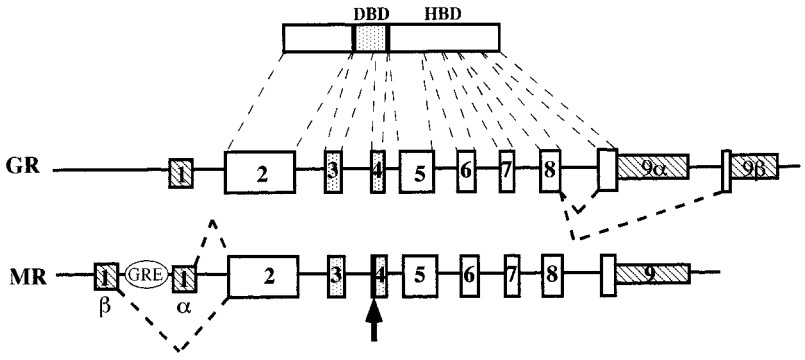

FIG. 4. Genomic organization and splice products of the MR and GR genes. Exons are *numbered and indicated in boxes*. The 5′- and 3′-untranslated domains are represented by *smaller* and *striped boxes*. A glucocorticoid responsive element (GRE) is present in the MR gene as well as the MR splice variant containing 12 additional nucleotides (see *arrow*). *Dotted exons* 3 and 4 correspond to the DNA-binding domain. Alternative splice events resulting in GRα and GRβ, and of MRα and MRβ, are indicated with a *dashed line*.

induction of the GRβ variant over GRα observed after exposure to cytokines (100). Recent experiments show heterodimerization of GRβ with MR resulting in repression of MR activity (101). However, in other studies a role of hGRβ as a proposed dominant negative inhibitor of hGRα could not be demonstrated, although the presence of the GR isoform in human tissue was also found (102).

Expression of the human MR gene may result in the formation of at least four transcripts, which are derived from two different promoters (94, 103, 104). The two main transcripts, MRα and MRβ, differ only in the 5′-untranslated exon 1 and thus are translated into the same 985-amino acid MR protein (Fig. 4). In rat, an MRγ transcript derived from exon 1 is detectable in very low amounts. Recently, another intriguing splice variant has been described (105): the use of an alternative splice site between exon 3 and 4 creates a 12-bp insertion which, after translation, corresponds to four additional amino acids in the amino acid sequence bridging the two zinc finger domains of the DNA-binding domain. A low proportion of this splice variant has been found in the human and rat (105) hippocampus (1:20 relative to MRα; E. Vreugdenhil, unpublished results). Given the involvement of the DNA-binding domain in translocation of MRs to the nucleus, dimerization, and interaction with other transcription factors, it is very likely that this splice variant will exhibit aberrant functional properties.

The MRα, -β, and -γ variants are all expressed in the brain. In the rat hippocampus, MRα mRNA is highly expressed in CA2 and the dentate gyrus, whereas MRβ and -γ mRNA are evenly distributed in the pyramidal layer. In general, MRα mRNA and MRβ mRNA are expressed in equal amounts. Interestingly, MRα, but not MRβ, mRNA is up-regulated after adrenalectomy, an effect that is reversed by administration of steroids. In agreement, the MRα-, but not the -β, promoter was found to contain a GRE-like element (104). As the different splice variants result in the same MR protein, the biological significance of their presence is unclear. Possibly, the presence of different 5′-untranslated regions may lead to different translation efficiencies and/or different stabilities of the transcripts (94, 104).

Receptor variants may play an important role in the disease state. Thus, individuals with familial glucocorticoid resistance may express a GR variant, and as a consequence have deficient GR function and impaired glucocorticoid feedback resulting in hypercorticoidism. However, they lack symptoms of Cushing's syndrome as ACTH and cortisol levels are also at a higher set point, and GRs are in general less sensitive to glucocorticoid activation (30, 106). The symptomatology of familial glucocorticoid resistance is usually related to overproduction of adrenal mineralocorticoids and androgens in response to ACTH (107). Although in man these severe inherited deficits in GRs resulting in asymptomatic hypercorticoidism are rare disorders, there are also pronounced species differences in GR, *c.f.*, guinea pigs, prairie voles, and new world monkeys. These animals display a normal circadian rhythm in HPA activity, but ACTH and cortisol are circulating at a much higher level. Apparently, the elevated set point in HPA regulation is an adequate adaptation.

D. Regulation of transcriptional activity

Ligand-activated GR and MR can contribute to the regulation of gene transcription in at least three different ways (Fig. 5). For a detailed overview, see the recent article by Beato and Sanchez-Pacheco (54).

The first mode involves activation or repression of gene expression through binding of steroid receptors to single, multiple, or composite GREs that are present in the promoter region of glucocorticoid-responsive genes (108). In addition to positive GREs, negative GREs, causing an inhibition of the target gene, have also been reported (109). Transcription-initiation by RNA polymerase II also requires interaction of the receptors with docking proteins and with other transcription factors (110). Since the DNA-binding domains of the GR and MR are nearly identical, they also have near-equivalent transcriptional activity at GREs. However, the synergizing effect of multiple GREs with GR-activated transcription is not observed with MR activation, probably due to the limited homology of the N-terminal sequences (111, 112).

The second mode refers to repression by GR of gene transcription activated by other transcription factors such as AP-1, NFκB, and CREB (113–115). This involves protein-protein interactions, and dimerization of GRs may not be required (116). The target genes involved lack of GREs. Dissociation between MR- and GR-mediated events may arise through this mechanism, since it has been shown that GR suppresses AP-1 activity under conditions in which MR is ineffective (111).

The third type of interaction concerns the formation of heterodimers between different nuclear receptors. One example recently described is the transcriptional activity of MR/GR heterodimers. Using a reporter construction under

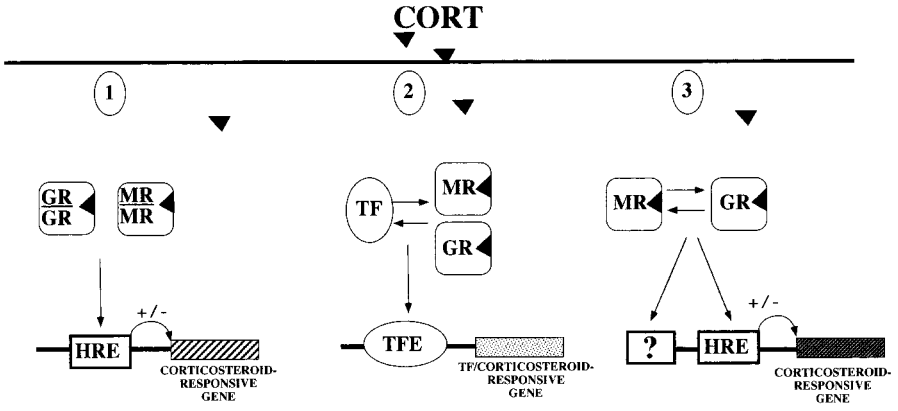

FIG. 5. Molecular mechanism of corticosteroid action on gene expression. 1. *Homodimerization/transactivation*. Corticosteroids (cort) bind to the GR or MR, which are translocated to the nucleus as dimers. After homodimerization of the GR or MR, the receptors will bind to specific DNA elements, the hormone-responsive elements (HRE) in promoter regions thereby affecting the transcription rate of corticosteroid-responsive genes. 2. *Transrepression*. Activated GRs may block the activity of other transcription factors (TF) such as AP-1, NFκ-B by direct protein-protein interaction. GR-blocked TFs can no longer bind to their TF elements (TFE) which will result in down-regulation of TF/corticosteroid-responsive genes. 3. *Heterodimerization.* Activated GR and MR may dimerize and bind to GREs or as yet unknown DNA elements (indicated by ?) thereby affecting the transcription rate of corticosteroid-responsive genes. Conserved amino acid motifs in the DNA-binding domain of the MR and GR are involved in heterodimerization. As these motifs are also present in other nuclear receptors, heterodimerization may not be restricted to MR and GR.

the control of multiple GREs, experimental evidence was provided for the existence of an MR/GR heterodimer configuration *in vitro* with distinct properties in terms of transcription activation (117, 118). Along the same lines, several recent papers have reported an inhibitory effect of other nuclear receptors on MR- and GR-mediated action, but the underlying mechanism is still unclear (119).

Aberrant cross-talk between different types of nuclear receptors and/or membrane signaling cascades may contribute to the consequences of steroid resistance or supersensitivity. For example, GRs interact with nonliganded transcription factors (AP-1, CREB, NFκB) that are activated by membrane-signaling pathways in response to inflammatory, immune, and stress mediators (*e.g.*, cytokines, excitatory amino acids, biogenic amines). Normally GRs repress the generally positive effects of AP1, CREB, and NFκB on gene transcription either directly via composite GREs or indirectly by protein-protein interaction. Inadequate repression by GR, which is characteristic of steroid resistance, will alter the functional outcome of such cross-talk. Alternatively, steroid resistance or supersensitivity can also develop when steroid receptor properties change through enzymatic modifications, *e.g.*, phosphorylation in response to peptides and transmitters (120).

E. Conclusion

In the hippocampus, corticosterone binds with a 10-fold higher affinity to MRs than to GRs. The high affinity MRs, even at basal levels of HPA axis activity, are substantially occupied, suggesting that this receptor is implicated in the maintenance of basal activity of the stress system by *proactive* feedback. High concentrations of corticosteroids progressively saturate GRs, implying that the suppression of stress-induced HPA activity occurs, in particular, through GRs by *reactive* feedback in a coordinated manner with MRs. Consequently, the balance in these MR- and GR-mediated effects on the stress system is of critical importance to the set point of HPA activity.

MR and GR activation depends (among other things) on the access of the hormone to its receptors. In binding, CBG competes for the naturally occurring corticosteroids (cortisol, corticosterone), and the steroids are subject to metabolic conversion, notably by the 11β-HSD isoforms. 11β-HSD2 in peri- and circumventricular regions is thought to regulate aldosterone selectivity, but the significance of hippocampal 11β-HSD1 for regeneration of bioactive corticosterone is not yet clear. Access of the synthetic glucocorticoid dexamethasone to central targets is hampered by mdr1a P-glycoprotein, at the level of the endothelial cells of the blood-brain barrier. The (local) generation of MR and GR variants that may interact, and other events in the receptor life cycle, further adds to the modulation of corticosteroid action.

MR- and GR-mediated actions occur through activation or repression of gene transcription. The actions depend on the cellular context, which is determined in part by other agents (*e.g.*, neurotransmitters, hormones, cytokines). Through membrane-signaling cascades, these can activate their own transcription factors, which in turn interact with MR and GR. The multiple interactions at the DNA and the protein-protein level provide an enormous diversity and complexity of transcriptional control by corticosteroid hormones. Resistance or supersensitivity of the receptors may be acquired when the receptor interactions become disproportionate.

III. Molecular and Cellular Effects of Corticosteroids in Hippocampus

Activation of intracellular corticosteroid receptors in neurons may induce a variety of cellular responses, influencing diverse processes such as cellular structure, energy metabolism, or signal transduction. Changes in cellular structure usually develop over the course of several days, whereas

effects on energy metabolism or signal transduction may become apparent within hours (10). Although the delayed onset of the observed effects, as opposed to the rapidly induced effects by neurosteroids (121–124), favors a gene-mediated effect via MR and GR, the molecular mechanism has, in many cases, not been resolved.

The cellular effects of steroids will have consequences for functional processes involving the hippocampus, *e.g.*, its regulatory role in neuroendocrine activity and behavioral adaptation. Steroid effects on cell function can develop with fluctuations of the steroid level within the physiological range, as may occur after acute stress. The nature of these actions may alter when animals are chronically exposed to aberrant corticosteroid levels, *e.g.*, in pathophysiological situations.

A. Intrinsic cell properties

A conspicious feature of corticosteroid actions on cellular activity in the hippocampus is the apparent lack of effect when neurons are studied under basal conditions: resting membrane potential and membrane resistance do not show steroid dependence (125–128). Only when neurons are shifted from their basal condition, *e.g.*, by the action of neurotransmitters, do corticosteroid effects become visible. This indicates that as for peripheral actions of corticosteroids, their cellular effects in the brain are also aimed at restoring homeostasis.

The conductances that are a potential target for steroids can be subdivided into two categories (Fig. 6). First, the voltage-gated and ion-sensitive ionic conductances, which are in many cases only indirectly altered by neurotransmitters. The second category involves the ion conductances, which are directly affected by neurotransmitter actions, either because the channels are an intrinsic part of the transmitter receptors or because the channels are modulated via receptor-activated G proteins. Steroid effects on these two targets will be discussed briefly.

It has been shown that the predominant occupation of MRs in CA1 hippocampal neurons is associated with small, voltage-gated Ca currents (Fig. 7 and Ref. 129). Recent experiments with mice lacking the GR protein through a genetic defect suggest that the presence of at least some functional GRs is required for the MR-mediated reduction in Ca currents to develop (130). When GRs are activated to a large extent, Ca current amplitude increases considerably (129, 131). The GR-mediated increase in Ca influx depends on *de novo* protein synthesis (131). Not only voltage-gated Ca influx is affected by corticosteroid receptor occupation: both basal and stimulus-induced intracellular Ca levels were found to be increased by substantial GR activation, which may be explained by steroid effects on Ca buffering or extrusion mechanisms (132–134).

Steroid modulation of Ca homeostasis will have consequences for Ca-dependent phenomena in hippocampal neurons, *e.g.*, the activation of a slow Ca-dependent K-conductance (135). This current hyperpolarizes neurons when they receive a prolonged excitatory input, resulting in a reduction of firing (accommodation). Since deactivation of the current is very slow, a lingering afterhyperpolarization (AHP) can be seen at the end of the depolarization, which also serves to suppress transmission of excitatory input. In accordance with the steroid effects on Ca influx through voltage-gated channels, both the accommodation and AHP amplitude were found to be small with predominant MR activation (Ref. 136; see Fig. 7). Additional occupation of GRs led to an increased accommodation and AHP amplitude (125, 126, 136). This corticosteroid modulation of the AHP characteristics depends on *de novo* protein synthesis (137). For a steady excitatory input to the hippocampal CA1 area, this steroid modulation means that the CA1 hippocampal output is effectively transmitted with predominant MR activation and reduced when GRs are concomitantly activated.

Other K conductances were found to be far less sensitive to central corticosteroid effects (138), with only the inwardly rectifying Q current being sensitive to corticosteroid exposure, in a similar way as the Ca currents. The functional

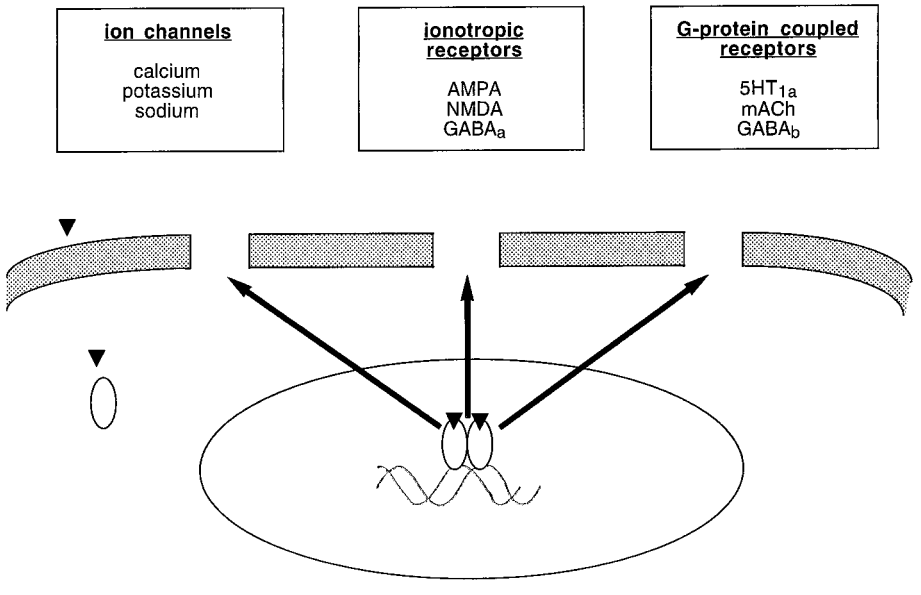

FIG. 6. Gene-mediated steroid effects on membrane properties. Changes in transcriptional activity induced by steroid receptor dimers can affect many conductances in neuronal membranes. Targets that are discussed in the text comprise the voltage-gated ion channels, ionotropic receptors, and channels that are regulated via G protein-coupled receptors.

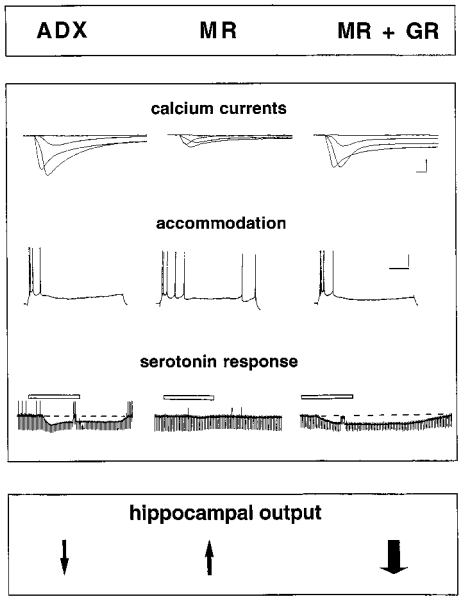

FIG. 7. Corticosteroids and neuronal excitability: implication of U-shaped dose response for hippocampal output. Properties that determine the cellular excitability in hippocampal cells are differently affected by specific corticosteroid receptor activation. The *upper traces* show calcium currents evoked in hippocampal CA1 neurons by depolarization of the membrane. The *middle traces* illustrate the number of action potentials induced in a hippocampal CA1 neuron during a steady depolarizing input. Due to activation of a calcium-dependent potassium conductance, neurons cease firing after an initial burst of action potentials (accommodation). The *lower traces* show the hyperpolarization of the membrane after activation of serotonin-1a receptors (application during *horizontal bar*). Calcium currents, accommodation, and serotonin responses are large both in the absence of corticosteroids (ADX) and when MRs and GRs are concomittantly activated. By contrast, these cell properties are small with a predominant MR activation, pointing to a U-shaped dose dependency. Due to these effects on CA1 excitability, hippocampal output is expected to be *maintained* at a relatively high tone with the predominant MR activation and *reduced* when GRs in addition to MRs are activated.

significance of this may be that GR activation counteracts profound perturbations of the membrane potential in the hyperpolarizing direction, *i.e.*, the voltage range in which the Q current is active. Similar to the K conductances, voltage-dependent Na conductances were also little affected by steroid receptor occupation (139). Only small shifts in voltage dependency and kinetic properties were observed after adrenalectomy and subsequent steroid receptor occupation. Still, these small shifts may contribute to an MR-mediated increase in the amplitude and duration of the action potential in CA1 neurons (128) and to an enhanced threshold for the generation of action potentials with concomitant GR activation (127). Although K and Na conductances are thus much less of a target for steroid modulation, MR-mediated effects on these conductances will still promote maintenance of excitatory hippocampal output to other brain regions, while additional GR effects will reduce the hippocampal output.

B. Amino acid transmission

The predominant signaling molecule in the hippocampal CA1 area is the excitatory amino acid glutamate (140). In addition, local γ-aminobutyric acid (GABA)-ergic networks provide feed-forward and feedback inhibition (141). Several studies have demonstrated modulatory effects of corticosteroids on the amino acid-mediated synaptic transmission. When synaptic responses are recorded extracellularly, predominant MR activation is associated with a stable excitatory transmission at a high tone (142–145). Occupation of GRs resulted, usually within 20 min, in depression of the glutamatergic transmission (143–146), particularly with high extracellular Ca concentrations (147). Intracellularly, similar effects were found on excitatory postsynaptic potentials (148).

Fast inhibitory postsynaptic potentials are mediated via $GABA_a$ receptors (140). These potentials are not greatly affected by changes in MR/GR occupation (148), although very high corticosterone concentrations result in depressed inhibitory responses (127). Slow inhibitory postsynaptic potentials, mediated via $GABA_b$ receptors, are more susceptible to steroid effects (148). These slow inhibitory potentials remain very stable when mainly MRs are occupied, and with additional GR activation they are largely suppressed.

The overall picture is that both excitatory and inhibitory information is maintained at a stable level when MRs are predominantly activated, *i.e.*, with low corticosteroid levels. When corticosteroid levels rise and GRs become occupied additionally, excitatory transmission, and thus CA1 hippocampal output, is reduced; at very high steroid levels, inhibitory networks are also impaired.

It should be noted that the onset of corticosteroid modulation of amino acid-mediated transmission is usually rapid (within 20 min) and is reversible within 1 h (146, 148) The molecular mechanism is unclear and, in fact, it has not been established that these effects require gene transcription and/or protein synthesis of components in the amino acid neurotransmission pathway. Instead, there is some evidence that the GR effects may involve impairment of energy metabolism (145, 149, 150), which, through failure of electrogenic pumps, could result in a gradual rundown of synaptic responsiveness. Molecular studies have indeed supplied evidence that GRs affect the expression of metabolic enzymes and other proteins involved in neuronal energy metabolism, *e.g.*, glutamine synthetase (151, 152).

The high efficiency of amino acid transmission with predominant MR activation is also reflected in long-term plastic changes involving this hippocampal network, *i.e.*, with long-term synaptic potentiation. In this paradigm, brief tetanic stimulation of glutamatergic afferents to the CA1 area results in enhanced synaptic responses for at least 1 h (153). The prolonged enhancement of synaptic strength is considered to be a neuronal substrate for learning and memory formation. It appeared in both corticosterone-replaced ADX animals and intact rats that synaptic potentiation is most pronounced with moderate corticosterone levels, so that most of the MRs and only part of the GRs are activated (154, 155); when corticosterone levels are either reduced or enhanced synaptic potentiation is far less effective (155–158). Similar steroid dependency was observed for synaptic potentiation in other parts of the hippocampal formation, *i.e.*, in the dentate gyrus (159–161). Long-term depression of synaptic responses, which is induced by lower frequency stimulation of gluta-

matergic afferents, was found to display a similar steroid receptor dependency (162).

The observed steroid receptor dependency will have consequences for the efficacy of synaptic potentiation during acute stress. Thus, it has been shown that exposure to a novelty stress always blocks long-term potentiation (163, 164). This was also observed after subjecting rats to an inescapable shock, but here stress-induced factors other than corticosterone seem to be involved (165–167).

C. Aminergic transmission

In addition to amino acid input, hippocampal neurons also receive considerable input mediated by biogenic amines such as acetylcholine, noradrenaline, and serotonin. Noradrenaline blocks the slow Ca-dependent K conductance via a β-adrenergic receptor, resulting in increased excitability of the CA1 hippocampal area (168). This β-adrenergic effect, which is mediated by cAMP, is reduced after administration of high corticosterone levels occupying GRs (125). Selective MR activation has not yet been studied.

Serotonin (5-hydroxytryptamine, 5HT) evokes many different effects in CA1 hippocampal neurons, of which $5HT_{1A}$-receptor-mediated hyperpolarization of the membrane is most prominent (169). This hyperpolarization is small in amplitude with predominant (but not exclusive) MR occupation (Refs. 130, and 170–172; see Fig. 7); additional GR activation increased 5HT responses, with a delay of ~2 h (171). This was seen when corticosterone was applied exogenously and after acute stress (173). The strong inhibitory effect of 5HT with GR activation was shown to result in a marked suppression of the excitatory transmission in the CA1 area (174).

MR-mediated reduction of the 5HT response requires *de novo* protein synthesis (137). Although under comparable conditions, $5HT_{1A}$ receptor mRNA expression and binding capacity in CA1 and dentate cells was also reduced (175), it has not been established that the functional impairment is indeed caused by a reduced binding capacity. The observation that high corticosterone levels largely suppress $5HT_{1A}$ receptor mRNA expression, while responses to 5HT are relatively large, in fact suggests that the changes in mRNA expression may not correlate with the altered responses after steroid treatment.

Acetylcholine affects hippocampal cell properties in many different ways (176). Postsynaptically (among others) depolarization of the membrane due to blockade of at least two K conductances can be observed. Presynaptically, a large reduction of neurotransmitter release is evoked. It was observed that the postsynaptic depolarization induced by the metabolically stable cholinergic analog carbachol (CCh) is small with predominant MR activation (177). Additional GR activation by exogenous corticosterone application, but not after acute stress, resulted in large CCh responses (178). The relevance of this modulation for the CA1 hippocampal excitability is, however, probably rather limited: the consequence of the CCh-evoked depolarization seems to be entirely overriden by the large, steroid-insensitive depression of synaptic responses due to presynaptic cholinergic actions (174).

D. Chronic absence of corticosterone

Structural changes of hippocampal neurons were observed both with chronic absence and chronic overexposure to corticosteroids (37), indicating that steroid-dependent expression of genes is of crucial importance for hippocampal integrity. Removal of the adrenal glands results, within 3 days, in apoptotic-like degeneration of mature, granule cells in the rat dentatus gyrus, but not in other hippocampal fields. Dentate cells showed chromatin condensation, cell nuclear pyknosis, DNA fragmentation, and cytoplasmic shrinkage (179, 180). The loss of functional neurons is likely to affect neurotransmission in this and connected regions. In agreement, it was recently observed that particularly glutamate-dependent features of the synaptic field responses are reduced in animals showing signs of apoptosis (181).

The degeneration and associated loss of synaptic function could be prevented by treatment with MR ligands (179, 181, 182). Some, but not all (183, 184), papers describe a lack of effect of the synthetic glucocorticoid dexamethasone on adrenalectomy-induced apoptosis (185, 186), suggesting a controversial role for GRs. In fact, dexamethasone was found rather to induce apoptosis (186, 187) because it depletes the brain of corticosterone, creating a condition of chemical adrenalectomy. A different regulation may take place in the neonatal rat (188), when MR and GR are still developing and conditions, such as maternal separation, actually induce glucocorticoid resistance (189) and apoptosis in the developing hippocampus (190). Several studies have addressed the process underlying the apoptotic-like degeneration after adrenalectomy. Of paramount importance for one line of investigation is the fact that the dentate gyrus, in contrast to most brain regions, shows neurogenesis even during adulthood (191, 192), which can be blocked by chronic stress and adrenal steroids (23, 193). It was argued that MR activation maintains the balance between cell birth and cell death in the dentate gyrus, by enhancing the excitatory input to this region (194). Adrenalectomy results in increased cell birth and cell death, which is suppressed by corticosterone replacement. However, newborn neurons in the dentate gyrus do not express corticosteroid receptors, suggesting that the steroid effects on neurogenesis are indirect and possibly involve modulation of excitatory transmission (23, 194) and neurotrophins (195, 196).

Immediate early genes and cell cycle-related genes, such as the tumor suppressor p53, have been indicated as markers for the cell death cascade after adrenalectomy (197). *In vitro* experiments show that p53 down-regulates the apoptosis blocker bcl-2 and up-regulates apoptosis enhancer bax by a direct interaction with DNA elements in the promotor region of both genes (198, 199), suggesting that adrenalectomy-induced apoptosis is regulated by members of the bcl-2 family. The expression of a limited number of genes induced by excitatory amino acids was found recently to be enhanced by adrenalectomy (200). One of these genes was identified as the growth-associated immediate early gene Krox-20 (201). Preliminary data indicate increased Krox-20 expression in apoptotic cells in the dentate gyrus, suggesting its implication in control of hippocampal cell viability (201).

Although apoptotic neurons were never encountered in

the CA1 hippocampal region, cellular function in this region was nevertheless affected by chronic absence of corticosteroids. The most prominent effect seems to be that voltage-gated Ca currents display a very large amplitude (129, 202). Interestingly, the Ca-dependent K conductance was rather small in tissue from untreated ADX rats, notwithstanding the large Ca influx (Refs. 125 and 126; see Fig. 7). This shows that control of the Ca-dependent K conductance can take place independently of Ca influx, *e.g.*, at the level of the channel itself (203) or of the energy-dependent extrusion of Ca ions. Consistent with the latter it was shown that adrenalectomy results in an improved energy supply to CA1 hippocampal neurons (204).

Amino acid-mediated transmission in the CA1 hippocampal area was found to be only slightly reduced in tissue from ADX animals (126, 143, 145, 148), although one study reported a large suppression of field responses (205). Synaptic potentiation in the CA1 area was significantly impaired, however, in ADX rats compared with animals with predominant MR occupation (155, 156). Changes in GABA-ergic transmission by adrenalectomy seem to be limited (148). Aminergic responses were all relatively large in tissue from ADX rats. Responses due to activation of β-adrenergic receptors were enhanced in ADX rats (125, 206–208), compared with rats in which MRs and GRs were occupied. Responses to 5HT were enhanced in tissue from untreated ADX rats, compared with animals with predominant MR activation (170, 171, 174). Finally, depolarizing responses to CCh were also larger in tissue from ADX rats than in cells from rats with predominant MR occupation (177, 178).

The data demonstrate that specific parts of the hippocampus, *i.e.*, the dentate gyrus, show neurodegeneration and associated loss of synaptic function after adrenalectomy. Other parts, such as the CA1 area, show little effect on low frequency amino acid-mediated synaptic flow, although long-lasting synaptic changes are also impaired in this region, with profound changes in Ca-conductances and aminergic efficacy. Functional processes in the hippocampus, such as learning and memory formation, for which long-term modulation of amino acid-mediated transmission and cellular viability are important, are thus likely to be influenced by these cellular effects of adrenalectomy.

E. Chronic exposure to high corticosteroid levels

There is now ample evidence that chronic elevation of corticosteroid levels leads to neurodegeneration or suppressed neurogenesis in the hippocampus (22, 23, 209). CA3 pyramidal neurons seem to be particularly vulnerable, although effects in the CA1 and dentate subfield have also been reported (210). Three weeks of restraint stress in rats causes regression of apical dendrites of hippocampal CA3 pyramidal neurons (211, 212). This effect is mimicked by 3 weeks of treatment with a high dose of corticosterone (213, 214) and does not occur when corticosterone secretion is blocked by cyanoketone treatment. The regression occurring after 3 weeks of high levels of corticosteroid is reversible and can be prevented by treatment with the antiepileptic drug, phenytoin (215); an *N*-methyl-D-aspartate antagonist was also protective (212). Changes in nuclear chromatin structure in CA3 neurons were observed in subordinate tree shrews after a prolonged psychosocial conflict (23, 209). These data support the view that an imbalance in the CA3 (and possibly CA1) network favoring excitatory over inhibitory signals, leading indirectly to enhanced Ca influx, contributes to the observed degeneration.

This is partly supported by the cellular and molecular processes seen under these conditions. Indeed, one of the most prominent features seen with temporary elevations in corticosteroid level, and thus GR occupation, is the long-term enhancement of Ca influx in CA1 neurons (129, 131). This effect may persist when animals receive very high corticosterone amounts: chronic treatment of ADX rats with a very high corticosterone dose was associated with elevated mRNA levels for several Ca channel subunits (216). By contrast, chronic supply of low levels of corticosterone led to reduced expression.

Experimental work indicates that altered glutamatergic transmission, possibly in combination with enhanced Ca influx, may play a role in neurodegeneration with chronic exposure to high corticosterone levels (212). In agreement, the gene for glutamine synthetase (GS), an ATP-requiring enzyme catalyzing the formation of glutamine from glutamate and ammonia, has been shown to contain a GRE. With chronic elevation of corticosterone levels, the GS gene is markedly activated (151, 152), resulting in a depletion of glutamate necessary to maintain or induce synaptic transmission. Moreover, chronic steroid-mediated overinduction of GS and other ATP-requiring enzymes, such as glycerolphosphate dehydrogenase (152), may deplete ATP stores. ATP depletion would negatively affect the many ATP-demanding processes that include enzymatic processing, *e.g.*, maintenance of membrane potentials by ATP-dependent membrane pumps and ATP-dependent energy transport, such as glucose uptake. It should be noted, however, that basal responses in the CA1 area to synaptic glutamatergic input were largely unaffected in chronically stressed middle-aged rats (217). Nevertheless, a clear reduction of synaptic potentiation due to tetanic stimuli was observed after repeated (217) or chronic (68) exposure to stress.

Lack of neurotrophic capacity may also contribute to enhanced neuronal vulnerability. Indeed, chronic stress or administration of glucocorticoids decreased steady-state levels of the brain-derived neurotrophic factor mRNA (218–220) in the dentate gyrus and CA3 layer. Tyrosine kinase B expression also seems to be down-regulated via GR (218, 221), while MR activation results rather in an up-regulation of tyrosine kinase B (220). In addition to brain-derived neurotrophic factor, nerve growth factor, basal fibroblast growth factor, and transforming growth factor expression in the hippocampus are also affected by glucocorticoids (152, 222, 223). GR activation also facilitates synthesis of glycoprotein neural cell adhesion molecules, which are thought to be necessary to achieve synaptic connectivity underlying storage of information (224).

A critical duration of overexposure to steroids is essential for the neurodegenerative effects to develop: temporary high levels of the hormone decrease responsiveness to excitatory amino acids and reduce excitability by activation of Ca-dependent K conductances. Local depolarization is sustained

and breakdown of inhibitory networks occurs due to chronically enhanced corticosteroid exposure. Hippocampal neurons will subsequently be subjected to a substantial GR-dependent rise in intracellular Ca levels. After this line of reasoning, beneficial effects exerted by phasic activation of GRs are turned into damaging actions when GRs are chronically activated. The experiments of Krugers *et al.* (225) support this; when the chronic suppression of the HPA axis with exogenous glucocorticoids is discontinued, the ensuing low circulating corticosterone level occupies mainly MR and apparently protects against seizures and hippocampal damage evoked by hypoxia/ischemia.

Although neurodegenerative processes are an important feature of chronic overexposure to steroids in the hippocampus, this is by no means the only effect on local signal transduction. It was observed recently that 5HT-evoked responses in CA1 hippocampal cells, which showed no signs of degeneration, were modulated by chronic overexposure to corticosteroids in a manner that was completely different from the modulation observed with acute rises in corticosterone level (128, 172). This may signify that the susceptibility of neurotransmitter systems to the actions of corticosterone is altered after long-term treatment with the hormones, or even that chronically elevated steroid levels affect transmitter responsiveness via an entirely different mechanism of action than seen with brief exposure.

F. Conclusion

Studies at the cellular level have supplied ample evidence that shifts in corticosteroid receptor occupation, such as occur after an acute stress or due to circadian variations in steroid level, exert a *delayed and long-lasting control* over excitability in limbic brain regions. They do so in a *context-dependent* manner, *i.e.*, when neurons are shifted from their basal condition through actions of neurotransmitters. The interdependency of steroid and neurotransmitter actions fits very well with a molecular mechanism depending on protein-protein interactions rather than one acting via steroid receptor dimers binding to a hormone-responsive element. Clearly, validation of this idea awaits further electrophysiological studies in animals with genetically modified steroid receptors, such that only one of these molecular mechanisms of action can develop.

The general picture emerging is that conditions of predominant MR activation, *i.e.*, at the circadian trough at rest, are associated with the *maintenance* of excitability so that steady excitatory inputs to the hippocampal CA1 area result in considerable excitatory hippocampal output. In contrast, additional GR activation, *e.g.*, after acute stress, generally *depresses* the CA1 hippocampal output (148, 226). A similar effect is seen after adrenalectomy, indicating a *U-shaped dose-response dependency* of these cellular responses to corticosteroids.

In many cases, the molecular mechanism underlying these cellular effects is not known. For some transmitters the actions seem to involve at least the capacity of the receptor (175). In other cases, second messenger systems may be regulated (227, 228), similar to the corticosteroid action observed in pituitary cells (229). In addition to these postsynaptic effects, brief changes in neurotransmitter release may also contribute to the observed depressed activity with acute stress.

The MR- and GR-mediated effects at the cellular and network level will have consequences for functional processes in which the hippocampal formation plays an essential role, *e.g.*, learning and memory. However, the steroid actions on hippocampal output will also affect, via transsynaptic inhibitory connections with the PVN, neuroendocrine regulation. Based on the generalization outlined above, predominant hippocampal MR activation will inhibit PVN function, while additional GR activation in these same hippocampal cells is expected to disinhibit feedback function in the PVN.

Chronically aberrant corticosteroid levels will not only affect hippocampal cell responses but, in fact, compromise the viability of the cells, particularly when the neuroendocrine dysfunction is associated with additional challenges to the network (29, 35, 37, 230, 231). Disturbed Ca homeostasis and altered glutamatergic transmission may underlie the observed increased vulnerability. This implies that when corticosteroid levels are chronically too low *or* too high, hippocampal transmission is impaired and therefore hippocampal outflow is reduced. This will result in disinhibition of CRH-producing neurons in the PVN. It is not known when and how the corticosteroid hormones cease to be beneficial and begin instead to enhance vulnerability to damage.

IV. Role of Corticosteroid Receptors in the Central Stress Response

Changes in network function of higher brain areas through molecular and cellular effects of corticosteroids will, via trans-synaptic pathways, result in an altered drive to the hypothalamic CRH-producing neurons. Moreover, the steroid-induced influences on information processing of the hippocampus may also result in adaptation of behavioral patterns, which indirectly affects the state of the HPA system. These corticosteroid-mediated effects on hippocampus function and their role in the central stress response will be the focus of this section. As a preamble, regulation by corticosteroid hormones of the stress response directly at the level of the PVN will be briefly summarized. The final part of the section will focus on dysregulation of the HPA system when converging inputs on the CRH neurons either fail to restrain the neuronal activation by stress or prevent it from responding adequately.

A. Corticosteroid receptors and HPA control

The role of MR and GR in the HPA control has been the subject of many studies over the past decade. Pituitary corticotropes and PVN contain the primary feedback sites for stress levels of the naturally occurring glucocorticoid. At low concentrations of circulating corticosterone, the brain is the primary target (232–236), as access of corticosterone to the pituitary POMC gene is hampered by competitive binding to intracellular CBG-like molecules (19, 76, 235). While corticosterone readily enters the brain, the exogenous synthetic glucocorticoids penetrate the brain poorly, reflecting the mdr1a P-glycoprotein barrier (90–92). Steroids such as dexa-

methasone, therefore, predominantly block stress-induced HPA activity at the pituitary level (19, 92, 236, 237) and deplete the brain of exogenous corticosterone. Three experimental approaches, which have been used to explore the brain feedback sites of corticosteroids, will now be reviewed: 1) replacement of ADX rats with receptor agonists, 2) pharmacological inhibition of individual receptor types in adrenally intact animals using more or less selective antagonists, and 3) correlative evidence between receptor properties and HPA dynamics. In the latter approach, receptor levels were often manipulated with subsequent measurement of the effect on HPA regulation.

Adrenalectomy leads to an increase in CRH and particularly VP mRNA and peptide levels in the PVN and in the external layer of the median eminence (238). Basal ACTH levels are dramatically elevated, while circadian changes and stress responses of the hormone show a large amplitude in excursions (239). Levels of 150–300 nM corticosterone, occupying both receptor types and achieved with subcutaneous corticosterone implants, efficiently suppress VP and CRH expression and release into portal blood (240–242). Implants of naturally occurring and synthetic glucocorticoids near the PVN act similarly (243–245), while local application of the antagonist RU 38486 has the opposite effect (246).

The rise in basal trough levels of ACTH after adrenalectomy is prevented by chronic replacement with very low amounts of exogenous corticosterone; under these conditions, corticosterone also suppresses the adrenalectomy-induced synthesis of VP, while CRH is not affected by either treatment (234). The IC_{50} of corticosterone suppression is about 0.5 nM in terms of circulating free corticosterone, in the range of the MR K_d value. Accordingly, MR mediates the *proactive* feedback mode of corticosterone involved in *maintenance* of basal HPA activity. At the circadian peak, much higher levels of exogenous corticosteroids are required, and half-maximal suppression is achieved by a free concentration of about 5 nM, close to the K_d of GRs (9). However, exclusive activation of GRs is insufficient to suppress the circadian peak, and MR activation appears to be indispensable (234). The corticosteroid concentration does not need to be continuously high, in that an episodic rise in glucocorticoid levels by injection or ingestion via the normal evening drink is sufficient to occupy both receptor types and to maintain ACTH levels with small amplitude changes over the 24-h period (247).

These GR-mediated effects observed after exogenous glucocorticoids thus are also involved in maintenance of HPA activity. An interesting paradox is that exogenous corticosteroids suppress subsequent stress-induced ACTH levels whereas similar levels of the steroid attained after a first stress do not (26). Apparently, stress evokes in the PVN a local transient condition of steroid resistance; the elevated corticosterone facilitates the termination of the HPA response to stress, and various temporal (fast and slow feedback) domains have been distinguished (26). These GR-mediated effects triggered in response to stress represent the *reactive* mode of feedback operation.

Observations on HPA regulation have often been made without consideration of the steroid effects on higher brain functions involved in arousal and processing of information.

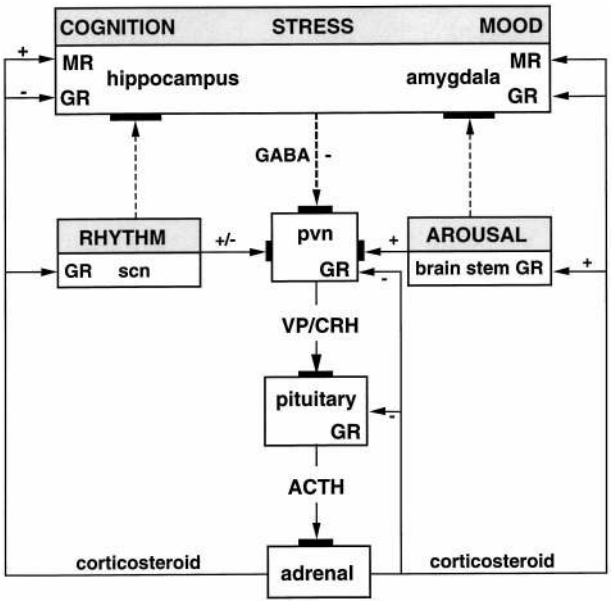

FIG. 8. Neuronal afferents, corticosteroid receptors, and HPA control. The diagram shows the organization of the HPA axis and in simplified form, some of its major neuronal afferents. Neural activation of PVN neurons in response to visceral stimuli occurs via monosynaptic catecholaminergic projections arising from brain stem nuclei (248). Projections of the suprachiasmatic nucleus transfer excitatory as well as inhibitory information to ensure circadian rhythmicity of the HPA axis (250). In hypothalamus, preoptic area, and bed nucleus of the stria terminalis (BNST) a γ-aminobutyric acid (GABA) network conveys an inhibitory input to the PVN neurons. This inhibitory GABA-ergic tone is enhanced by excitatory hippocampal output. GABA-ergic inhibitory tone is inhibited (and thus becomes excitatory) through a GABA input from the central amygdala (40, 254, 255, 431). In addition, peptidergic pathways such as neurotensin (253), neuropeptide Y, opioids and substance P, as well as cytokines, modulate CRH activity (39). Most of these transmitter and peptide projections are transsynaptic, providing ample opportunity for modification of information transfer to the PVN (254). MRs mediate potentiation of hippocampal output, and thus enhance neural inhibition of HPA axis, while via GRs corticosteroids dampen hippocampal output, which thus leads to HPA disinhibition. GRs also mediate the activation of excitatory input (NE, E, 5HT) to PVN from brain stem. GRs in PVN and pituitary mediate the blockade of stress-induced HPA activation.

GR-mediated effects in brain areas projecting to the PVN have profound and long-lasting consequences for feedback regulation. First of all, ascending aminergic neurons via direct, monosynaptic inputs excite the PVN, an action potentiated by stress and corticosteroids (60, 248, 249). Second, the suprachiasmatic nucleus (SCN) conveys excitatory and inhibitory circadian pacemaker activity to the PVN and other hypothalamic nuclei, an activity that is modulated by corticosteroids. One such SCN output regulates, via spinal projections, pronounced daily shifts in adrenal sensitivity and corticosterone secretion (232, 250). Third, GABA-ergic neurons in the hypothalamus and preoptic area directly influence the PVN. Corticosteroids have been reported to enhance GABA turnover in the hypothalamus, suggesting that an enhanced GABA-ergic tone may govern inhibitory control over the PVN (40, 251, 252). These systems with inputs to the PVN generally express GRs and contain numerous colocalized neuropeptides, which also regulate PVN activity in their own right (253–255).

Limbic inputs impinging on the PVN and the hypothalamic GABA-ergic neurons also express high levels of MR in addition to GR (40, 254, 255), suggesting dual regulation of these inputs by corticosteroids (Fig. 8). Moreover, these inputs can be either excitatory from hippocampus, enhancing GABA-ergic tone, or inhibitory (*e.g.*, from amygdala) and reducing GABA-ergic tone (40, 256). This implies that with enhanced hippocampal input, the HPA axis is relatively more suppressed and that enhanced amygdaloid input would lead to disinhibition of GABA-ergic input to the PVN and enhanced HPA activity. Roles for the amygdala in fear, anxiety, and activation of HPA axis are well-documented (257–260). The amygdala expresses CRH, part of an extrahypothalamic CRH network mediating the behavioral expressions of stress, fear, and anxiety (261). Corticosteroids enhance the expression of CRH in this extrahypothalamic network, suggesting a positive feedback as opposed to the negative feedback role in the hypothalamic PVN. In contrast, the significance of MR and GR in regulation of CRH expression and function in the amygdaloid nuclei has not been well established.

The activation of a particular afferent neuronal network innervating the PVN area is stressor specific and depends on the nature of the stimulus (262–265). If it constitutes a direct threat to survival through physical stressors (*e.g.*, respiratory distress, hemorrhage, inflammation, infection, trauma), the ascending aminergic pathways promptly activate the autonomic and neuroendocrine centers in the hypothalamus. If sensory stimuli are subject to appraisal and interpretation processing in higher brain regions is required, this may subsequently lead to modulation of GABA-ergic tone and change in synthesis of CRH, VP, and other neuropeptides of the PVN secretagogue cocktail. Activation of brain stem and limbic circuitry is not separated but, in fact, mutually interactive and stress-induced corticosteroids readily enter the brain and feed back on all components of the neural stress circuitry, but in a context-dependent manner.

B. Role of hippocampus in HPA regulation

Lesioning and electrical stimulation studies suggest an overall inhibitory influence of the hippocampus on HPA activity (25). Dorsal hippocampectomy or transection of the fornix elevates the basal HPA activity at the circadian trough in particular, and CRH mRNA and VP mRNA expression in the morning (266). The effect of hippocampal manipulation on the HPA axis is "state-dependent," varying both during the day and after stress, suggesting a modulatory role for corticosteroids (11, 25, 267).

We have based our analysis of hippocampal function on the central administration of selective receptor antagonists 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 ACTH. In these studies ACTH and (free) corticosterone levels were measured in sequential blood samples obtained via indwelling intravenous cannulae from freely moving animals. Intraventricular (icv) administration of MR antagonist elevated basal (morning) trough levels of plasma corticosterone (268), and exposure of the rats treated with the antimineralocorticoid to a novel situation resulted in enhanced adrenocortical responses. In the afternoon phase, MR antagonists (100 ng icv) also elevated basal ACTH and corticosterone levels (269), as did a 10-fold lower dose injected bilaterally into the hippocampus (270). 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 (271). Finally, systemic administration of spironolactone increased basal HPA activity in man (272, 273), although this response was not noted in all studies (274). Thus, hippocampal MRs appear to mediate the effect of corticosterone in maintaining the tone of basal HPA activity.

A number of other studies also attest to the importance of hippocampal MR in controlling HPA tone. First, the cyclical 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 (275). Second, rat strains with high levels of hippocampal MR expression (*e.g.*, Lewis rats) show lower basal and stress-induced HPA activity, but elevated free corticosterone levels compared with Wistar rats from which they are derived (269). Third, aged rats generally have reduced MR (and GR) expression and an increased basal HPA activity, and prolonged stress-induced ACTH release (276–279). Fourth, tricyclic antidepressants increase expression of hippocampal MRs and decrease basal and stress-induced HPA activity (32, 280–283), also in man (284). Finally, icv administered endotoxin impairs MR function and causes a chronically elevated basal HPA activity (285).

Hippocampal MRs are important in terms of control of inhibitory tone over the HPA axis. This effect of corticosterone via MRs is modulated by GRs that 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 (morning) trough levels of plasma corticosterone, probably because at that time the low levels of corticosterone produce negligible GR occupation (86, 268). If the antagonist is administered icv during the afternoon phase, basal HPA activity increases, as seen after local administration of 5 ng RU486 near the PVN. In contrast, administration of the same dose of antagonist directly into the hippocampus *decreased* basal ACTH levels in the afternoon phase (270). 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.

Thus, intrahippocampal antiglucocorticoids suppress ACTH levels under conditions in which antimineralocorticoids enhance the release of ACTH (Fig. 8). Such opposite effects correlate well with the electrophysiological data pre-

viously discussed, since MRs and GRs mediate opposite effects on excitability and excitatory outflow (24, 28). 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, and through transsynaptic inhibitory projections to the PVN basal HPA activity. Conversely, with rising glucocorticoid concentrations, 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.

C. Behavioral effects involving hippocampal MR and GR

While the action of corticosteroid in hippocampus is thus involved in HPA regulation, further fine tuning of the HPA response to stress occurs by its behavioral effect. The hormone does not necessarily cause a behavioral change, but rather influences information processing and thereby affects the likelihood that a particular stimulus elicits an appropriate behavioral response. Moreover, through coordinate MR- and GR-mediated actions in higher brain areas, *e.g.*, neocortical regions, and limbic areas such as hippocampus, septum, and amygdala, the corticosteroid hormone affects learning and memory processes. Accordingly, when the effect of corticosteroid on information processing and cognitive function facilitates behavioral adaptation (coping) to stress, the associated HPA response is more readily extinguished. Therefore, when one studies the modulation of behavioral responses by corticosteroids, the time and duration of the hormone action, as well as its context, need to be considered.

It is generally accepted that hippocampal formation plays a key role in animals' reactivity to novelty and provides an essential contribution to learning and memory (286–288). Stress hormones, including corticosterone, are released during learning and are necessary for establishment of an enduring memory. In this context the role of corticosteroid hormones on acquisition, consolidation, and retrieval of information has been studied for more than four decades. For this purpose, simple associative learning tasks (*i.e.*, active and passive avoidance, fear conditioning) were used as well as tasks requiring the association of more complex stimulus configurations (*i.e.*, spatial learning in the water maze). All these tests revealed that administration of exogenous corticosterone in the appropriate temporal context, *i.e.*, in close relation to training, potentiated memory in a dose-related fashion (10, 289–292). Recently, Sandi and co-workers (293) showed that corticosterone facilitates spatial memory if given immediately after the task in amounts comparable to those elicited by stress. If, however, an acute stressor is introduced into a training sequence, giving rise to additional hormonal stress responses, spatial learning is impaired (294). These findings emphasize that corticosterone modulates information processing in a time- and context-dependent way. Furthermore, corticosterone administered after training facilitates extinction of passive and active avoidance responses. This implies that in addition to facilitation of learning and memory processes, the steroid also promotes the elimination of behavior that is of no more relevance (291). We now know that these effects of corticosteroids require GR activation.

Adrenalectomy impairs behavioral performance, and replacement with corticosteroids allows identification of not only GR-, but also MR-, mediated responses. A few studies have found a stringent specificity for corticosterone, while dexamethasone and aldosterone were not active. This was the case with specific features of exploratory behavior (295) and in the so-called "forced extinction" paradigm. In the latter test, a complete extinction of an avoidance response is achieved after rats are allowed, shortly after the learning trial, to explore the compartment where they had previously experienced punishment. The response was impaired after adrenalectomy, but maintained exclusively by replacement with corticosterone (296). An interaction of corticosterone with adrenaline was reported by Borrell *et al.* (297); pretreatment with corticosterone reduced the efficacy of adrenaline to restore passive avoidance responses at least 1000-fold. In all instances, low amounts of corticosterone were given that would lead to predominant occupation of MR. Moreover, treatment with MR antagonists revealed a change in behavioral reactivity (298), and this finding further supports the role of MR in processes of selective attention and sensory integration.

The importance of the balanced activation of MR- and GR-mediated effects by glucocorticoids on cognitive processes was demonstrated by the use of receptor-specific antagonists (Fig. 9). Memory in spatial and avoidance tasks is impaired in the absence of appropriate GR activation after the learning task (27, 246, 299–301). Moreover, direct injec-

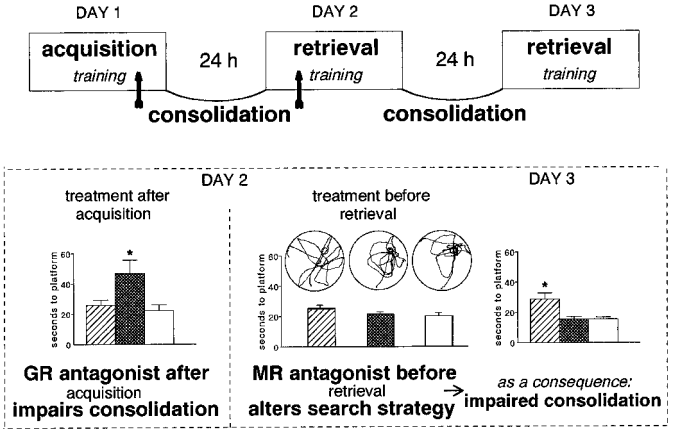

FIG. 9. Effect of MR or GR antagonists on spatial learning of rats in the Morris water maze. Corticosteroid binding to MR and GR affects different components of spatial learning and memory. Rats were trained (four trials per day) to find a submerged platform in a fixed position in a water maze. Effects of treatment (*arrow*; icv injection) with GR antagonist (*dark bars*), MR antagonist (*hatched bars*), and vehicle (*open bars*) were related to time and context. GR antagonist after training primarily influences consolidation, resulting in an impaired performance 24 h later. MR antagonist before retrieval does not affect latency to platform, but alters the search strategy (*swimming paths above bars*). The secondary effect is impaired performance on day 3. Therefore, impaired performance might be due to MR and GR dysfunction. [Derived from M. S. Oitzl and E. R. De Kloet (27).]

tion of a GR antagonist or GR antisense into the hippocampus prevented the retention of immobility in the Porsolt model (246, 300). In contrast to GRs, MRs modulate ongoing behavioral activity, as demonstrated by blockade of MRs during, but not after, the training session (27, 298, 299, 302). These effects mediated by MR regulate sensory integration underlying evaluation of environmental information and response selection and thus have the capacity to subsequently alter memory storage for spatial and avoidance behavior. Interestingly, recent behavioral studies in homozygous GR-deficient mice demonstrated that the MR-mediated effects on spatial behavior require interaction with functional GRs (303).

The reports of cognitive impairment in relation to chronically increased corticosteroid levels are somewhat contradictory. In older animals treated for months with high doses of corticosterone, or subjected to continuous social stress, dramatic behavioral deficits were observed (210, 304–306). Young animals, however, either showed marginal cognitive impairment with long-lasting (exogenous) elevation of corticosterone or improved their performance (305, 307–309); however, when chronically elevated steroid levels were combined with neurotoxic agents, behavior was impaired (310). Unfortunately, the specific contribution of brain MR and GR to these cognitive deficits has not been established. The correlation of cognitive decline with possible neuronal damage associated with prolonged stress or old age and corticosteroid receptor changes (23, 37, 210, 211, 283, 304, 311) remains a matter of debate.

In conclusion, two features of the behavioral effects of corticosteroids are relevant to the neuroendocrine focus of this review. First, MR- and GR-mediated effects on behavior can be discriminated. Hippocampal MRs mediate effects of corticosterone on appraisal of information and response selection, whereas GR function does not modify these aspects of sensory integration but rather promotes processes underlying consolidation of acquired information. Second, MR- and GR-mediated effects on information processing faciliate behavioral adaptation, which promotes the inhibitory control exerted by higher brain circuits over HPA activity.

D. Glucocorticoid feedback resistance and supersensitivity

Glucocorticoid resistance becomes manifest if stress-induced activation of CRH neurons is no longer restrained. The principal feature of glucocorticoid resistance in CRH neurons is the disturbed balance between GR function, on the one hand, and drive by excitatory signals on the other (34). One way in which this balance can be disturbed is under conditions of a local GR deficit. This can be congenital, as in the recent transgenic mouse line with brain-selective reduced expression of GR. Such mice display hypercorticoidism, cognitive impairment, and metabolic disturbances, which in many ways resemble the symptoms of Cushing's syndrome (32, 312). Feedback resistance can also be acquired, as in administration of the antiglucocorticoid RU 38486 (313, 314). If RU 38486 is infused continuously (100 ng/day) into the cerebral ventricles of rats, within 4 days elevated corticosteroid levels are observed during the circadian peak and in response to stress. Hypothalamic CRH mRNA, ACTH, and basal trough corticosterone levels are not changed after the 4-day treatment, but the adrenocortical sensitivity to stress and ACTH is increased (314). Chronic icv MR antagonist or MR antisense led to an enhanced ACTH response to stress and changes in adrenocortical sensitivity to ACTH (315). Another way in which the balance between excitatory and inhibitory signals in the PVN can be changed is through impairment of adrenocortical function; if rats are treated with cyanoketone, an inhibitor of steroid synthesis, their corticosterone response to stress is facilitated (26, 31, 316). The latter observation demonstrates that the excitatory and inhibitory neural control of ACTH can be modulated by corticosteroids in a dose- (and thus MR-/GR-) dependent manner.

Reset of feedback sensitivity occurs when the input from multiple sensory signaling pathways converging on CRH neurons becomes disproportionate. This occurs, for example, when chronic physical stressors activate brain stem aminergic neurons and thus stimulate CRH and VP synthesis directly through α1-adrenergic receptors (317). Disproportionate input to CRH neurons can also be due to environmental changes, emotion, arousal, or cognitive stimuli, which may become particularly potent chronic stressors under conditions of uncertainty, lack of control, or poor predictability of upcoming events. Such conditions can be created in models of psychosocial stress in rats housed in mixed-sex groups in a complex environment, which results in a sustained HPA activation in subordinates (318). The elevated glucocorticoid levels caused by such chronic physical and psychological stressors produce tolerance to elevated glucocorticoids through down-regulation of GRs in the CRH/VP neurons (263, 319). The lower GR number then transduces reduced magnitude of signal relative to the glucocorticoid elevation, leading to further dysregulation of the HPA axis (304, 320, 321).

Resistance to glucocorticoid feedback in CRH neurons causes increased HPA activity and produces hypercorticoidism. As an unfortunate consequence, the rest of the body, including the brain and its neural stress response circuitry, suffer from glucocorticoid overexposure. Importantly, glucocorticoid elevation synergizes with stress-induced activation of serotonergic, dopaminergic, and noradrenergic neurons in the brain stem and thus increases the sensitivity of limbic-forebrain areas to aminergic inputs (249, 322–325). These include direct aminergic input to the CRH/VP neurons as well as indirect afferent inputs to these CRH neurons via the hippocampus. Moreover, the amygdaloid CRH system involved in stress-related behaviors is also activated by chronic stress and corticosterone (326). By these mechanisms, the feedback resistance at the level of the CRH neurons is increasingly reinforced.

The reverse occurs in situations where feedback inhibition of corticosteroids is enhanced, so that the organism suffers from hypocorticoidism that is centrally regulated. How such enhanced feedback inhibition at the level of the PVN is achieved is not known. It may be through synergy of GRs with intracellular signaling mechanisms in the PVN, or via MR-enhanced, neurally mediated, tonic inhibitory input from the hippocampus on HPA activity. Alternatively, reduced adrenocortical output may also be caused by a deficit

in the CRH drive (327) or by altered sympathetic outflow diminishing adrenal sensitivity to ACTH (250). Interestingly, in group-housed rats, a subgroup of chronically stressed subordinate animals displays a reduced corticosterone response to restraint stress (318, 328). Using this type of psychosocial stressor, future studies may reveal how chronic stress results in pathology characteristic of stress-related disorders.

E. GR knockouts

Recently, mice were generated with a targeted disruption of exon 2 of the GR gene (329, 330). Most GR-deficient mice died shortly after birth from lung atelectasis, but about 10% of the mice survived for as yet unknown reasons. The survivors displayed hypertrophy and hyperplasia of the adrenal glands, with corticosterone production enhanced 3-fold, and ACTH levels showing a 10-fold rise. The adrenal medulla was almost nonexistent and unable to produce adrenaline, leaving only a few noradrenaline-producing chromaffin cells. In the liver, marked defects in activation of glucose-6 phosphatase and tyrosine aminotransaminase were observed (329, 330).

Further studies with the GR knock-outs showed that GRs are not involved in the control of $5HT_{1A}$ receptor expression in the hippocampus (331). Electrophysiological studies with the GR knockouts showed that responses to 5HT and CCh were indistinguishable from responses in ADX mice, suggesting that functional GRs are necessary for the development of MR-induced suppression of neurotransmitter responses in hippocampal CA1 neurons (174). The GR deficit was also observed in behavioral studies; the homozygous mutants were impaired with regard to processing spatial information and did not display the search behavior of wild-type controls, again suggesting a dysfunction of MRs in the absence of GRs. Experiments using the Morris water maze showed that long-term memory of spatial information was also impaired in the homozygous mutants. However, as soon as the knock-out mice had localized the quadrant with the platform, they could identify its exact location (*i.e.*, being there is knowing where) (303). The coming years will be marked by numerous studies using tissue-selective mutations in the GR gene.

F. Conclusion

The pituitary is the principal site of action of moderate amounts of administered dexamethasone in the blockade of stress-induced HPA activation. Dexamethasone treatment lowers systemic levels of endogenous corticosteroid and fails to replace these steroids in the brain, reflecting its extrusion by mdr1a P-glycoprotein. Corticosterone preferentially targets the brain and exerts its primary feedback through GRs in the parvocellular PVN.

Hippocampal MRs are involved in the maintenance of basal HPA activity throughout the circadian cycle by corticosterone. The underlying mechanism probably involves steady MR-controlled hippocampal excitatory output, which regulates GABA-ergic inhibitory tone on PVN neurons. In the hippocampus corticosterone activation of GR inhibits MR-mediated inhibitory input into the HPA axis. GRs also facilitate HPA activation through ascending aminergic pathways and a peptidergic limbic (amygdaloid) network involved in stress-related behavior. Corticosterone modulation via MR and GRs of other inhibitory and excitatory neural influences impinging on the PVN (*e.g.*, from amygdala, frontal cortex, SCN) have not been widely studied. Such future studies must consider the finding that corticosteroid feedback is context-dependent in those circuits that have been activated in a stressor-specific fashion.

The actions mediated by MR are proactive in the maintenance of basal HPA activity and in regulation of the HPA response to the processes underlying selective attention, sensory integration, and response selection. Impairments of MR function will have general consequences for subsequent GR-mediated processes that depend on the rise of corticosterone as well as the temporal and contextual features of information processing in which they operate. GR located in the PVN mediates reactive feedback inhibition aimed to terminate the HPA response to stress. Paradoxically, GR-mediated influences of corticosterone on the stress circuitry innervating the PVN generally facilitate disinhibition. In their own right, as tested with selective agonists and antagonists, the acute physiological GR-mediated effects in the hippocampus facilitate memory processes depending on context (Table 3).

When behavioral adaptation to stress, modulated by steroid effects on higher brain functions, is successful, then negative feedback action via the PVN and neural inhibitory circuits overrides the excitatory extrahypothalamic influences on the HPA axis. If coping with stress fails, an imbalance between drive and feedback develops at the level of the PVN, resulting in altered expression of CRH, VP, and other ACTH secretagogues, with the extent of the alterations being dependent on the nature and context of the stress (265). How the imbalance between excitatory and inhibitory signals develops is not known, although evidence is accumulating for an excitatory ascending aminergic and amygdaloid CRH system *vs.* inhibitory influences arising from hippocampus and frontal cortex (39). Whatever the cause, ultimately, after adaptation of the HPA axis, the imbalance leads at the adrenal level to altered sensitivity to ACTH.

V. Implications for Age- and Stress-Related Brain Disorders

Imbalance in drive and feedback can develop under various conditions at different stages in life. Within a population, some individuals are more likely to develop a deficit in

TABLE 3. Function of brain corticosteroid receptors

Corticosterone condition	Occupied receptor	Function
Basal	MR	Stabilization of excitability Sensitivity stress response system *Proactive* feedback Selection of behavioral response
Stress	MR + GR	Suppression increased excitability Recovery from stress-induced activation *Reactive* feedback Facilitation memory storage

HPA regulation than others, differences that are presumably linked to their genotype. Environmental and experience-related factors, some originating in early life, can also add to HPA imbalance, as can psychosocial conditions (*e.g.*, dominant *vs.* subordinate). Once manifest, HPA dysfunction constitutes an added risk factor for many disorders associated with chronic stress, aging, and neurodegeneration, and/or with disturbances in cognition, mood, and affect.

A. Role of genotype

A fundamental question in stress research is why some individuals suffer from stress-related brain pathology, while others are healthy under seemingly similar conditions. Of great significance for this question are the seminal observations by Henry and Stephen (332), which indicate that individuals with extreme differences in terms of stress reaction coexist in a normal population with the extremes displaying either an active fight/flight or a passive conservation/withdrawal response to a psychosocial challenge. Also, in humans, pronounced individual differences in HPA activity were found (333). Active animals rely on stable living conditions, show impaired adaptation to a changing environment, and flee after a defeat. Their behavioral features (249) resemble the sensation-seeking trait in humans, which is defined as "the need for varied, novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experiences" (334).

In past decades, strain differences and genetic selection of rat and mouse lines have been used to discriminate between the individual differences in the behavioral and endocrine response pattern to stress (335–337). In rats, Cools *et al.* (338) have been able to breed these two types of individuals on the basis of extreme differences in susceptibility to the dopaminergic agonist apomorphine, *i.e.*, the apomorphine-susceptible (apo-sus) and apomorphine-nonsusceptible (apo-non-sus) Wistar rats. The apo-sus rat line has a higher expression of tyrosine hydroxylase mRNA and D_2 receptors in brain dopamine pathways (339), which explains why PRL release responds poorly to stress in these animals (340). Apo-sus rats display a high sympathetic tone, which is in line with their "fight/flight" identity.

These rat lines also show profound differences in their HPA system. Apo-sus rats have elevated hypothalamic CRH mRNA; their levels of ACTH and free corticosterone remain markedly elevated in response to novelty exposure (340, 341). This inability to turn off stress-induced ACTH release indicates resistance to glucocorticoid feedback. The apo-sus rats have a higher number of hippocampal MR and frontal cortex GR, which might potentially enhance corticosteroid feedback signaling, but appears not to (340, 342); apparently glucocorticoid feedback does not overcome enhanced central aminergic drive. Apo-sus animals require much larger amounts of ACTH than their apo-non-sus counterparts to achieve the same corticosterone output in response to stress (340), possibly a manifestation of reduced adrenal sensitivity to ACTH due to the altered sympathetic outflow in these animals. Collectively, these data show that containment of stress-induced HPA activation is reduced in apo-sus animals.

Immune responses and disease susceptibility are also dramatically different between the two lines. Immune responses in the apo-sus rats are directed toward the production of antiinflammatory rather than proinflammatory cytokines, in line with their elevated free corticosterone levels and higher sympathetic tone. Accordingly, apo-sus rats display enhanced susceptibility to infection with the nematode, *Trichinella spiralis,* whereas their apo-non-sus counterparts are prone to experimental autoimmune encephalomyelitis (343).

In developing apo-sus rats, the divergence in the stress response system precedes the appearance of differences in dopamine phenotype, raising the issue of the role of early life experience in the programming of phenotypes associated with the stress response. In adult rats deprived as pups from mother rearing, dopamine responsiveness and tyrosine hydroxylase mRNA are increased, resembling to some extent the apo-sus rat line (344, 345). Genotype and early life experience thus appear to interact in programming individual variation in emotional and adrenocortical reactivity in later life.

B. Impact of early life experience

There is now convincing evidence that early life experience can cause changes in the stress response system and in emotionality that persist into adulthood (346, 347). One procedure to program the stress system is "handling," a brief daily separation of mother and pup; adult animals handled as pups show reduced emotionality and reduced adrenocortical reactivity (348). They also have increased GR expression in the brain, a lower stress-induced corticosterone level, and improved cognitive function in terms of spatial learning (349). However, the opposite effects on the stress-induced HPA activation, brain GRs, and cognition were found when the mother-pup separation was increased to 3 h per day, with pups at the age of 2 months showing hypercorticoidism and poor performance in spatial learning tests (350).

Wistar rats that were maternally deprived for a single period of 24 h at postnatal day 3 also showed hypercorticoidism and altered brain corticosteroid receptor profiles as adults. In male rats the procedure resulted in reduced GR expression in the anterior pituitary, PVN, and hippocampus, consistent with the feedback resistance observed in these animals (345). In contrast, female rats showed increased hippocampal GR number after deprivation (351), and a similar sex difference in GR expression was found in endotoxin-treated rat pups (352). Moreover, the 24-h separation at day 3 enhanced ACTH release at day 20, but ACTH release at this time was suppressed after separation at day 11. Collectively, these data show that the effects of maternal deprivation on HPA activity and receptor profile in adult life depends on the duration, frequency, and age of the pup at the time of separation, and that there are pronounced sex differences.

At old age, Wistar rats handled during development have higher levels of brain GR expression and more effective glucocorticoid feedback compared with nonhandled controls, which usually show hypercorticism at senescence (353, 354). Moreover, handled animals have lesser deficits in cognitive performance and reduced neuronal loss (353, 354). In con-

trast, aged Brown Norway rats show generally reduced adrenocortical sensitivity under conditions in which albino rat strains display hypercorticism (276, 277, 335). We have studied the effect of maternal deprivation in Brown Norway rats, which are known for their long and healthy life span. Half the litter was deprived from the mother for 24 h at postnatal day 3, their siblings, nondeprived littermates, served as controls. At the age of 30 months, the individual performance within each group was strikingly different. In the deprived group, animals were either good or poor learners, and a few animals displayed an intermediate performance. The mother-reared group showed a normal distribution: several good, a few impaired, and a large group of intermediate performers (355). This study with Brown Norway rats demonstrates that maternal deprivation has no general impairing effect on mental function at an older age, since about half of the animals had excellent spatial and memory abilities. Thus, susceptibility to maternal deprivation shows profound individual and strain differences, and the positive and negative aspects of mental abilities become amplified during the aging process.

The mechanism underlying the effect of maternal deprivation on the brain is still poorly understood. Days 4–14 of neonatal rat life are considered to be the stress-hyporesponsive period, with the implication that secretion of corticosterone can be constant (and very low) because of the presence of the mother. Stressors that cause pronounced adrenocortical activation in the adult are unable to do so in the pup (356) except when the pup is exposed to extremely potent stimuli, such as an endotoxin or interleukin 1 treatment (352, 357). However, whereas the mother-reared pups fail to respond to a mild stress, maternally deprived pups show a robust response. The adrenal becomes sensitized to ACTH stimulation and in response to stress starts to secrete corticosterone (358). This effect of maternal deprivation is more profound at day 12 than at day 3 (359–361).

Thus, maternal deprivation causes a profound immediate activation of the HPA axis, while other mild psychological and physical stressors do not at that time. How is this possible? In extensive collaborative studies with S. Levine and colleagues, certain factors were identified that might be implicated. It was found that maternal deprivation caused profound responses in the stress circuitry such as the expression of CRH- and cFos mRNA in the PVN, and of MR- and GR mRNA in hippocampus (189, 362). The enhanced expression of these central stress markers can be completely prevented in the 24-h deprived pup by stroking only three times for only 45 sec. ACTH was also restored by stroking, but feeding was additionally required for suppression of the adrenocortical response (189, 363). Feeding, therefore, did not appear to be a crucial element producing the changes in the brain; rather, the tactile contact between mother and infants was the primary factor. Interestingly, brief separation of mother and pup (handling) evokes enhanced sensory stimulation after reunion (347, 358) providing a clue to why the handling of pups has such profound effects on the programming of the HPA axis during development. Also, the prevention of hypercorticoidism in the offspring of stressed pregnant dams after adoption of the pups by a nonstressed foster mother may be explained by enhanced sensory stimulation (364).

The elevated corticosterone did not mediate the central effects of maternal deprivation, since these effects were not affected by dexamethasone blockade of HPA activity (189). Moreover, reactive feedback mediated by GR was deficient and further impaired after maternal deprivation. In line with this finding is the poor GR functioning in the neonatal brain, which is also further suppressed by maternal deprivation (365, 366). In contrast, MR already has adult-like levels in the brain (367–369), and proactive feedback is intact in the neonate, suggesting that these MRs participate in the maintenance of the low basal HPA activity during the stress hyporesponsive period (356, 370).

C. Corticosteroids and affective disorders

Disturbances in mood, cognition, and behavior and abnormal levels of corticosteroids often coincide. About 50% of patients suffering from depression have a hyperactive HPA system resulting in hypercorticosolism (371). In these patients CRH and VP expression in PVN is enhanced (372), the adrenals show hypertrophy, and basal corticosteroid levels are elevated. In response to stress their HPA activation is both sluggish and persistent. These patients, when challenged with cortisol (373), dexamethasone, CRH, or the combined dexamethasone-CRH (374) test, show feedback resistance at the level of the PVN and pituitary (32). Alternatively, about 50% of the Cushing patients suffer from depression. After correction of hypercortisolism, overall psychopathology decreased significantly. However, of the remaining psychopathology, atypical depression continued to be the prevailing diagnosis (375).

Preliminary evidence suggests that feedback resistance and mild hypercortisolism are already present in healthy subjects at genetic risk for depression (376). Although ultimate proof of a causal relationship must await the actual manifestation of depression in these individuals, the resistance suggests an imbalance in drive and feedback inhibition preceding the manifestation of clinical symptoms. It is possible that such individuals at risk have mild deficits in cortisol signaling related to the expression of receptor variants, or defects in receptor-associated transcription factors, GREs, or regulatory regions of GR target genes. Such receptor variants could induce a degree of imbalance that only becomes harmful during conditions of chronic stress. Alternatively, this genetic influence could render the individuals more susceptible to stressful events. The same investigators have created a transgenic animal model displaying mild hypercorticoidism and feedback resistance that may allow verification of this hypothesis (32).

The studies aimed at establishing a causal relationship between hypercorticoidism and vulnerability to depression have pointed to early life experience (*Section V.B*). Maternal deprivation may be such a vulnerability factor for later life in view of its long-term effects on the set point of HPA regulation, cognitive function, and emotional reactivity. In mature rats long-term effects of psychosocial distress can be demonstrated after a decisive defeat (377) or after exposure to a single session of inescapable footshock (378). After such

single traumatic events, feedback resistance slowly evolves over a period of several weeks. Human studies with neuroendocrine measures point to life events, chronic difficulties at work or in marital relationships, and childhood abuse as vulnerability factors for depression, while social support is, in contrast, protective (371, 379, 380).

The similarities between behavioral disturbances in animals after chronic stress and during depression in man may be of considerable assistance in understanding the underlying pathogenic mechanisms. Animal studies in this regard have invariably shown that beneficial effects are obtained after application of antiglucocorticoids into a specific area of the hippocampus, the dentate gyrus (246, 381). These effects include improved cognition, a decrease in basal cortisol levels, and an antidepressant-like behavioral change. Other studies have shown that in this region of the hippocampus, 5HT transmission becomes dysregulated during chronic stress. Under physiological conditions, low levels of corticosterone lower 5HT synthesis rate and turnover (382, 383), 5HT release (384), 5HT1A receptor expression (385–389), and the 5HT1A hyperpolarization response in the hippocampus (Refs. 170 and 173; see *Section III. C*); during the stress response, GRs stimulate all these features of 5HT transmission (175). In mice genetically selected for dominance characterized by low corticosterone levels, 5HT1A receptor expression is enhanced (390). However, during chronic psychosocial stress and hypercorticoidism, 5HT transmission is again impaired and noradrenergic transmission in the hippocampus is suppressed, a similar series of events as seen during depression (391).

Since corticosteroid signaling in brain is causally involved in enhancing vulnerability to depression, the implications for treatment are obvious. Preliminary attempts to eliminate excess cortisol through treatment with the cortisol synthesis inhibitor metyrapone have had some therapeutic effects (392). Paradoxically, dexamethasone treatment was reported to be effective (393), perhaps because it reduces levels of brain exposure to cortisol. Second, at the brain level, corticosteroid antagonists should be effective, as already indicated by the previously cited animal experiments (394). Although new approaches for targeting antiglucocorticoids to the hippocampus are required. The mdr1a P-glycoprotein barrier may limit access; blockade of GRs in pituitary, PVN, and other brain areas outside the hippocampus may override the therapeutic effect of the antagonist in the hippocampus.

Imbalance of MR/GR expression or function may also be an important factor in the etiology of depression. In this context, it is extremely interesting that the tricyclic antidepressants not only restore 5HT and noradrenergic transmission in brain, but also increase the expression of brain corticosteroid receptors, particularly MRs, in parallel with normalization of HPA tone (280–282). Consistent with an important role for MRs in vulnerability to depression, systemic administration of antimineralocorticoids was found to impair the therapeutic efficacy of antidepressants (395).

Finally, increased HPA axis drive, feedback resistance, and adrenal hypertrophy are associated with depression; the reverse conditions of reduced CRH function, feedback supersensitivity, and adrenal deficit may also be vulnerability factors for brain disease (Table 4). Posttraumatic stress disorder is characterized by enhanced feedback, perhaps through hippocampal MRs, which results in a lower setpoint of HPA activity and reduced production of cortisol over a 24-h period (396). Chronic fatigue syndrome (397, 398) and fibromyalgia (399–401) also show features of secondary adrenocortical deficiency of central origin, but perhaps for different reasons. Reduced adrenocortical output in chronic fatigue syndrome seems to be associated with deficient central CRH function (397), whereas in fibromyalgia reduced adrenocortical sensitivity and feedback resistance appear to be the hallmark (399, 400).

TABLE 4. Corticosteroids and stress-related disorders

DHPA dysregulation	
Enhanced feedback	Feedback resistance
Reduced CRH/VP function	Enhanced CRH/VP function
Reduced adrenocortical sensitivity	Enhanced adrenocortical sensitivity
Vulnerability to disease	
Posttraumatic stress syndrome	Depression
Chronic fatigue syndrome	
Fibromyalgia	
Susceptibility to inflammation	Susceptibility to infection

D. Aging, neurodegeneration, and age-related diseases

Aging is characterized by a reduced ability to maintain homeostasis (402), and the lability of the HPA axis is increased, with ACTH responses to stress enhanced and prolonged as compared with young animals. In response to stress, however, the ACTH, corticosterone, or both may be relatively increased (403). Moreover, there is a consistent finding across strains, and individuals of reduced MR and GR number in hippocampus and PVN, associated with feedback resistance. Prolonged hypersecretion of corticosteroids observed in aged rats has received much attention, since it is considered to facilitate an age-dependent neurodegenerative cascade of effects in the hippocampus. These effects include atrophy of dendritic processes, enhanced vulnerability to noxious stimuli, and cell death (Fig. 10). The underlying mechanism is thought to involve energy deprivation (230, 304), excitotoxicity (35, 230), and disturbed Ca homeostasis (28, 230, 320); in addition, neuronal defense mechanisms and repair by neurotrophins are impaired by corticosteroids (230).

A key element of the hypothesis is that hippocampal GRs were thought to promote escape from negative feedback via down-regulation (304). We now know, rather, that it is the balance of MR- and GR-mediated activities in hippocampal circuits that determine excitability, stress responsiveness, and behavioral reactivity (11, 24, 27). Elevated corticosteroid input via hippocampal GR increasingly counteracts MR-mediated effects, leading to destabilization and disinhibition from negative feedback in much the same way as age-induced reduction of MRs produces. These actions, mediated by MRs and GRs, are of course context-dependent on the

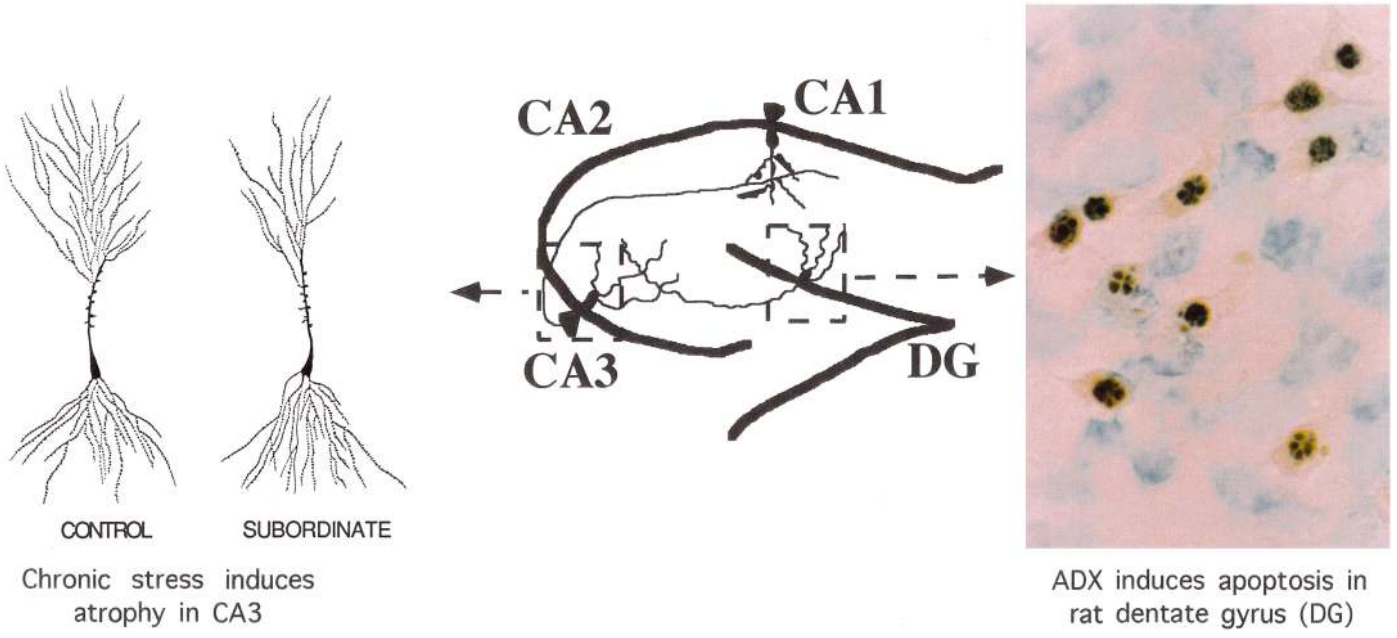

FIG. 10. Corticosteroids and neuronal morphology in hippocampus. High corticosteroid levels during chronic stress and lack of corticosteroids have deleterious consequences for the hippocampal trisynaptic circuit. *Left*, Atrophy of apical dendrites of hippocampal CA3 neurons of a subordinate tree shrew after chronic psychosocial stress, a condition leading to chronically elevated corticosteroids (Ref. 209, courtesy of professor E. Fuchs). *Right*, apoptosis of hippocampal dentate gyrus neurons after adrenalectomy. Photograph shows *in situ* end labeling of highly condensed pyknotic cells representing all morphological features of apoptosis (courtesy of Dr. P.J. Lucassen).

cellular and circuit level and in terms of physiology, environment, and behavior.

Since hippocampal MRs appear to be important determinants for stability of the stress system at old age, would treatments aimed to restore MR function be beneficial? One approach would be to chronically administer the GR blocker RU486, which would favor MR-mediated effects. Indeed chronic RU 486 reduces age-related changes in the hippocampus (404). We found increased MR number after administration of the neurotrophic ACTH-(4–9) analog (ORG 2766) to aged rats (405, 406). ORG 2766 administration from midlife onward was previously found to retard the morphological and functional markers of hippocampal aging (407) and also improved learning and social behavior in rats, an effect blocked by antimineralocorticoids (298). On the other hand, antidepressants known to enhance brain corticosteroid receptor expression and cognitive function in young animals are not effective in the aged (283).

Does the destabilization of the stress system in old age imply enhanced vulnerability to neurodegenerative disorders? There is indeed evidence that corticosteroids enhance vulnerability to Alzheimer's disease; in affected individuals, increased cortisol levels correlate with mental deterioration and decreased hippocampal volume (408). Experimental studies have shown that MR and GR mRNA levels are not altered in hippocampal neurons (409, 410), although GR expression is increased in the surrounding glial cells (409). In contrast, neurodegeneration in the brains of Alzheimer's disease patients may reflect an immunological reaction from microglial cells to deposits of β-amyloid (411), which is consistent with rheumatoid arthritis patients receiving antiinflammatory drugs having a reduced incidence of Alzheimer's disease. Accordingly, it appears that during the development of Alzheimer's disease the containment of immunological defense reactions by endogenous corticosteroids is reduced (412, 413), and that resistance to corticosteroids facilitates the proinflammatory response and thus enhances disease susceptibility.

Thus, there is evidence from animal experiments (321, 414) and in humans (415) that a dysregulated HPA axis, corticosteroid receptor deficits, and aberrant corticosteroid levels during stress are associated with age-related disease and vulnerability to age-related neurodegeneration. As pointed out in *Section III*, animal studies show that both chronic absence or elevation of corticosteroid levels results in region- and cell-specific atrophy, degeneration, and cell death in the hippocampus (Fig. 10). There has been some confusion about the effects of chronic treatment with synthetic glucocorticoids, although we now know that such treatment produces symptoms of central nervous system corticosteroid depletion, such as apoptosis in the dentate gyrus (186, 187).

Over the past 10 yr there has been increasing evidence that steroid-induced cognitive dysfunction and atrophy may also occur in the human brain. Elderly individuals who develop hypercorticoidism over a period of 4 yr showed deficits in long-term memory (416). In other studies, impaired cognitive function (performance on verbal recall and declarative memory tests) and reduced volume of the hippocampal formation on magnetic resonance imaging were found to correlate with average plasma cortisol levels in Cushing patients (417, 418). Depressive patients with elevated cortisol levels have smaller hippocampi long after relief of the clinical symptoms (419). These findings led Sapolsky (420) to conclude that glucocorticoid excess is a "likely culprit in causing hip-

pocampal atrophy." Yehuda (421) pointed out that posttraumatic stress disorder patients not showing hypercorticoidism also have a smaller hippocampal volume (422, 423), which Sapolsky in reply ascribed to their presumed prior history of stress and hypercorticoidism.

E. Conclusion

The set point of HPA activity is programmed by genotype and can be reset to other levels by stressful experience. In rats, the most persistent effects are observed after an early life experience in which the mother-pup interaction is involved. Maternal deprivation generally results in enhanced stress system activity, at least in a subgroup of individuals. In contrast, procedures allowing enhanced sensory stimulation by the mother causes reduced adrenocortical and emotional reactivity in later life. In one case (353), this condition has been shown to be associated with increased cognitive performance. If a stressful life event is experienced in adult life, reset of HPA activity evolves slowly and may lead to a vicious cycle of enhanced drive to CRH neurons, feedback resistance, and hypercorticoidism (30). This chain of events is plausible in relation to depression; it is not known why in other cases the opposite, *i.e.*, hypocorticoidism, originates from similar disturbances of centrally regulated functions induced by chronic stress.

In this section the effect of stress and corticosteroids in the hippocampus was considered in terms of MR/GR balance as a factor protective against stress-related brain disorders (Fig. 11). A change in the balance of MR- and GR-mediated events alters the ability to maintain homeostasis and progressively creates a condition of disturbed neuroendocrine regulation and impaired behavioral adaptation. In addition to altered corticosteroid homeostasis, numerous changes in neurotrophins and excitatory transmission were found associated with atrophy of hippocampal regions. This hippocampal atrophy has led to a theory linking the neurochemical and morphological changes to pathogenesis of depression (424, 425). Such a condition is frequently met at senescence and after chronic stress. It follows that restoration of deficient corticosteroid receptor function is a promising route of therapeutic intervention in stress-related brain disorders, once the problem of site-specific targeting of the drugs in brain has been resolved.

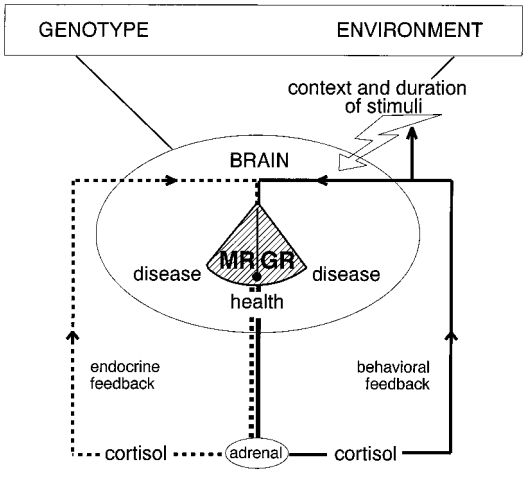

FIG. 11. Gene-environment interaction in control of the stress response system. The MR/GR balance hypothesis. The set point of homeostatic control depends on coordinative antagonistic MR- and GR-mediated effects in the brain exerted by corticosteroids. The hormone operates in proactive and reactive feedback modes on endocrine (HPA) regulation and behavior. The feedback modes maintain homeostasis and faciliate behavioral adaptation to environmental challenge. Aberrant cortisol levels and imbalance of MR/GR-mediated effects increase the vulnerability to disease in genetically predisposed individuals.

The effects of stress and corticosteroids in brain, and their relationship to health and disease, have been the subject of excellent reviews and books (1, 32, 35, 38, 39, 42, 43, 256, 426). Here we will only mention three features that deserve extra attention.

First is the concept that neural and neuroendocrine mediators communicate between various effectors of the stress response in the brain, immune system, cardiovascular system, adipose tissue, and muscles. Dysregulation in any of these mediators may have a disease outcome; depending on the site of dysregulation in genetically predisposed individuals, enhanced vulnerability may develop to either depression, autoimmune or inflammatory disorders, cardiovascular diseases, obesity, diabetes, or hypertension. Corticosteroids and their receptors are critical, since these hormones have the ablility to control the expression of "candidate vulnerability genes" underlying these diseases (201). Using differential display, serial analysis of gene expression, and DNA expression grid technology, these genes will soon be identified and functionally characterized.

Second, dysregulation of mediators may develop as a *consequence* of the magnitude and duration of responses to stressful experiences. In particular, conditions of uncertainty, lack of control, and anxiety are potent chronic stressors. In this context the concept of "allostasis" has been introduced (427), referring to an energy-demanding condition of "labile equilibrium or stability through change" in an attempt to cope with stressors. This condition is the antipode of "stable equilibrium," which depends on homeostatic regulations and is beneficial for the organism. Allostasis has strong driving and anticipatory components, which metaphorically have been indicated as allostatic load (256, 428). The cost of maintaining allostasis is thought to be enhanced vulnerability to pathogenic challenge in organs and systems. The opposing actions mediated by colocalized MRs and GRs in key centers in stress regulation have been recognized as rate-limiting steps in the mechanisms underlying homeostatic and allostatic control.

Third, corticosteroids acting through MRs and GRs have a critical role in maintaining homeostasis (and allostasis). These receptors are abundantly colocalized in hippocampus and amygdala as part of the brain involved in processing stressful information. MRs appear to mediate the *proactive* mode of feedback involved in maintenance of basal activity, while GRs mediate corticosterone actions aimed at restoring homeostasis in *reactive* mode. Imbalance in these receptors, either genetically programmed or induced by stressful life experiences, is reflected as a change in drive and feedback, which in turn alters neuronal excitability, stress responsive-

ness, and behavioral adaptation to a condition of enhanced vulnerability to disease.

VI. Summary

In this review, we have described the function of MR and GR in hippocampal neurons. The balance in actions mediated by the two corticosteroid receptor types in these neurons appears critical for neuronal excitability, stress responsiveness, and behavioral adaptation. Dysregulation of this MR/GR balance brings neurons in a vulnerable state with consequences for regulation of the stress response and enhanced vulnerability to disease in genetically predisposed individuals. The following specific inferences can be made on the basis of the currently available facts.

1. Corticosterone binds with high affinity to MRs predominantly localized in limbic brain (hippocampus) and with a 10-fold lower affinity to GRs that are widely distributed in brain. MRs are close to saturated with low basal concentrations of corticosterone, while high corticosterone concentrations during stress occupy both MRs and GRs.

2. The neuronal effects of corticosterone, mediated by MRs and GRs, are long-lasting, site-specific, and conditional. The action depends on cellular context, which is in part determined by other signals that can activate their own transcription factors interacting with MR and GR. These interactions provide an impressive diversity and complexity to corticosteroid modulation of gene expression.

3. Conditions of predominant MR activation, *i.e.*, at the circadian trough at rest, are associated with the maintenance of excitability so that steady excitatory inputs to the hippocampal CA1 area result in considerable excitatory hippocampal output. By contrast, additional GR activation, *e.g.*, after acute stress, generally depresses the CA1 hippocampal output. A similar effect is seen after adrenalectomy, indicating a U-shaped dose-response dependency of these cellular responses after the exposure to corticosterone.

4. Corticosterone through GR blocks the stress-induced HPA activation in hypothalamic CRH neurons and modulates the activity of the excitatory and inhibitory neural inputs to these neurons. Limbic (*e.g.*, hippocampal) MRs mediate the effect of corticosterone on the maintenance of basal HPA activity and are of relevance for the sensitivity or threshold of the central stress response system. How this control occurs is not known, but it probably involves a steady excitatory hippocampal output, which regulates a GABAergic inhibitory tone on PVN neurons. Colocalized hippocampal GRs mediate a counteracting (*i.e.*, disinhibitory) influence. Through GRs in ascending aminergic pathways, corticosterone potentiates the effect of stressors and arousal on HPA activation. The functional interaction between these corticosteroid-responsive inputs at the level of the PVN is probably the key to understanding HPA dysregulation associated with stress-related brain disorders.

5. Fine-tuning of HPA regulation occurs through MR- and GR-mediated effects on the processing of information in higher brain structures. Under healthy conditions, hippocampal MRs are involved in processes underlying integration of sensory information, interpretation of environmental information, and execution of appropriate behavioral reactions. Activation of hippocampal GRs facilitates storage of information and promotes elimination of inadequate behavioral responses. These behavioral effects mediated by MR and GR are linked, but how they influence endocrine regulation is not well understood.

6. Dexamethasone preferentially targets the pituitary in the blockade of stress-induced HPA activation. The brain penetration of this synthetic glucocorticoid is hampered by the mdr1a P-glycoprotein in the blood-brain barrier. Administration of moderate amounts of dexamethasone partially depletes the brain of corticosterone, and this has destabilizing consequences for excitability and information processing.

7. The set points of HPA regulation and MR/GR balance are genetically programmed, but can be reset by early life experiences involving mother-infant interaction.

8. Chronically too low or chronically too high levels of corticosteroid hormones during stress and the resultant MR/GR imbalance impair information processing and enhance vulnerability of specific hippocampal neurons. Well documented animal studies show apoptotic cell death and altered neurogenesis after adrenalectomy in dentate gyrus, while hippocampal pyramidal CA3 neurons show atrophy during episodes of chronic stress. Therefore, it is proposed that the maintenance in corticosteroid homeostasis and the balance in MR/GR-mediated effects limit vulnerability to stress-related diseases in genetically predisposed individuals.

9. Corticosteroids control the expression of "candidate vulnerability genes" in individuals genetically predisposed for stress-related diseases, such as depression.

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Erratum

In the April issue of *Endocrine Reviews* (vol 19: 101–143), the article, Intraadrenal Interactions in the Regulation of Adrenocortical Steroidogenesis, by Monika Ehrhart-Bornstein *et al.*, was incorrectly listed in the Table of Contents as Intrarenal Interactions in the Regulation of Adrenocortical Steroidogenesis. The printer regrets the error.