

ASSOCIATE EDITOR: GLENDA E. GILLIES

# Unraveling the Time Domains of Corticosteroid Hormone Influences on Brain Activity: Rapid, Slow, and Chronic Modes<sup>[S]</sup>

Marian Joëls, R. Angela Sarabdjitsingh, and Henk Karst

*Department of Neuroscience and Pharmacology, Rudolf Magnus Institute, University Medical Center Utrecht, Utrecht, the Netherlands*

Abstract	902
I. Introduction: from stress to changes in neural function	902
A. Stress and its mediators: focus on corticosteroids	902
B. Release of corticosteroid hormones	904
C. Factors determining the availability of corticosteroids in brain	905
D. Corticosteroid hormone receptors in the brain	906
E. Transcriptional regulation	907
F. Nongenomic pathways	908
G. From stressor to multiple functional endpoints	909
II. Rapid effects	909
A. Rapid modulation of neural activity	909
1. Hippocampus	909
2. A new concept in the basolateral amygdala: metaplasticity	912
3. Paraventricular nucleus	913
B. Rapid modulation of synaptic plasticity	913
C. The underlying mechanism	913
D. Behavioral relevance	914
III. Delayed effects	914
A. Slow modulation of neural activity	915
1. Hippocampus	915
2. Basolateral amygdala	918
3. Medial prefrontal cortex	918
4. Ventral tegmental area	918
B. Slow modulation of synaptic plasticity	918
C. Underlying mechanisms and functional consequences	919
IV. Chronic corticosteroid exposure	920
V. Perinatal stress	924
VI. Concluding remarks	927
A. Overarching principles	927
B. The average male white rat neuron	928
C. In search of multiple dimensions	929
D. Disease and targets for treatment	931
Acknowledgments	931
References	931

Address correspondence to: Marian Joëls, Department of Neuroscience and Pharmacology, Rudolf Magnus Institute, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands. E-mail: [m.joels@umcutrecht.nl](mailto:m.joels@umcutrecht.nl)

This article is available online at <http://pharmrev.aspetjournals.org>.

<http://dx.doi.org/10.1124/pr.112.005892>.

[S] The online version of this article (available at <http://pharmrev.aspetjournals.org>) contains supplemental material.

**Abstract**—Brain cells are continuously exposed to corticosteroid hormones, although the levels vary (e.g., after stress). Corticosteroids alter neural activity via two receptor types, mineralocorticoid (MR) and glucocorticoid receptors (GR). These receptors regulate gene transcription but also, as we now know, act nongenomically. Via nongenomic pathways, MRs enhance and GRs suppress neural activity. In the hypothalamus, inhibitory GR effects contribute to negative feedback regulation of the stress axis. Nongenomic MR actions are also important extrahypothalamically and help organisms to immediately select an appropriate response strategy. Via genomic mechanisms, corticosteroid actions in the basolateral amygdala and ventral-most part of the cornu ammonis 1 hippocampal area are generally excitatory, providing an extended window for encoding of emotional aspects of a stressful event. GRs in hippocampal and prefrontal pyramidal cells increase surface expres-

sion of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and strengthen glutamatergic signaling through pathways partly overlapping with those involved in long-term potentiation. This raises the threshold for subsequent induction of synaptic potentiation and promotes long-term depression. Synapses activated during stress are thus presumably strengthened but protected against excitatory inputs reaching the cells later. This restores higher cognitive control and promotes, for example, consolidation of stress-related contextual information. When an organism experiences stress early in life or repeatedly in adulthood, the ability to induce synaptic potentiation is strongly reduced and the likelihood to induce depression enhanced, even under rest. Treatment with antiglucocorticoids can ameliorate cellular effects after chronic stress and thus provide an interesting lead for treatment of stress-related disorders.

## I. Introduction: from Stress to Changes in Neural Function

Potential threats to homeostatic processes (stressors), physical or psychological in nature, are registered in the brain and give rise to a well orchestrated response via activation of the autonomic nervous system and the hypothalamopituitary-adrenal (HPA<sup>1</sup>) axis. The stressors do not have to be present; in anticipation of potentially threatening situations, the same cascade is triggered. The actual or anticipated situations of threat are subjectively experienced as “stress.”

### A. Stress and Its Mediators: Focus on Corticosteroids

Signals caused by physical stressors, such as respiratory distress or pain, are conveyed to the brainstem and from there can activate preganglionic cells in the intermediolateral cell column of the spinal cord (Kvetnansky et al., 2009; Ulrich-Lai and Herman, 2009). This allows an almost immediate response to the stressor via the sympathetic nervous system, of which the release of adrenaline and noradrenaline from the adrenal medulla is one of the most powerful effector tools. The parasympathetic nervous system is also activated to prevent the reaction from overshooting.

<sup>1</sup>Abbreviations: ADX, adrenalectomized; AHP, afterhyperpolarization; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BLA, basolateral amygdala; BSA, bovine serum albumin; CA, cornu ammonis; CBG, corticosteroid-binding globulin; CRH, corticotropin-releasing hormone; DG, dentate gyrus; ER $\alpha$ , estrogen receptor  $\alpha$ ; ERK, extracellular signal-regulated kinase; GluA2, AMPA receptor GluR2 subunit; GR, glucocorticoid receptor; HPA, hypothalamo-pituitary-adrenal; HSD, hydroxysteroid dehydrogenase; IPSC, inhibitory postsynaptic current; LTD, long-term depression; LTP, long-term potentiation; mdr, multidrug resistance; mEPSC, miniature excitatory postsynaptic current; mIPSC, miniature inhibitory postsynaptic current; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; MSK, mitogen- and stress-activated kinase; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; PND, postnatal day; PVN, paraventricular nucleus of the hypothalamus; RU38486, mifepristone; sIPSC, spontaneous inhibitory postsynaptic current.

In most cases, though, a much more extensive network of brain regions becomes activated in response to (potentially) dangerous situations, in which the paraventricular nucleus (PVN) of the hypothalamus plays a key role. Neurons located in the dorso- and ventromedial part of this nucleus can activate preganglionic sympathetic neurons, adding a more central and integrated aspect to activation of the sympathetic nervous system (Sawchenko et al., 2000). Peripheral release of adrenaline can indirectly change noradrenaline levels in the brain, via the vagal nerve and the nucleus tractus solitarius (Williams and McGaugh, 1993). However, the PVN also harbors cells that are essential to activation of another system. Thus, parvocellular neurons in the middle part of the PVN produce corticotrophin-releasing hormone (CRH) and vasopressin, which upon stress are released in high amounts from terminals at the median eminence into the portal vessels. Through these vessels, CRH and vasopressin reach the anterior pituitary, where their synergistic actions lead to optimal secretion of adrenocorticotropin hormone into the circulation (Gillies et al., 1982). In turn, this gives rise to the synthesis and release of hormones from the adrenal cortex, primarily cortisol in humans and corticosterone in rodents (but also aldosterone; see section I.B). These actions together constitute the HPA axis (Fig. 1).

The activity of the HPA axis is under strong control of many limbic regions, so that perceptual aspects, emotional elements, and reference to earlier experiences can be integrated with information from lower brain areas, usually concerning physical aspects (Ulrich-Lai and Herman, 2009). Although some of the limbic projections impinge directly on parvocellular neurons in the PVN, most inputs relay through GABAergic neurons surrounding the PVN or located in the bed nucleus stria terminalis. Excitatory projections from the hippocampus—particularly from the ventral subiculum—and the prelimbic prefrontal cortex thus indirectly inhibit CRH-producing cells. By contrast, neurons in the infralimbic

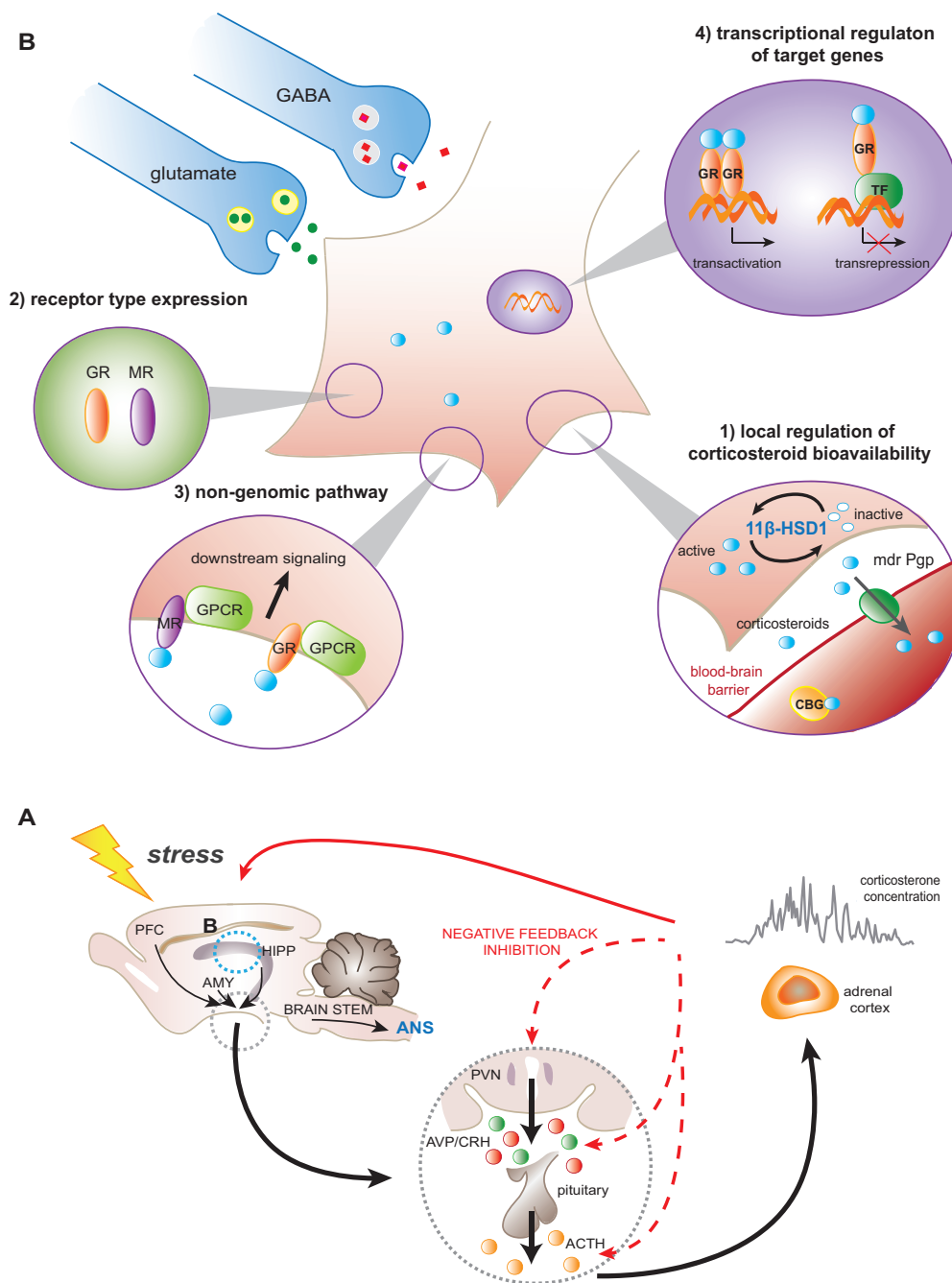


FIG. 1. A, schematic representation of the biological response to stress. Stress provokes the rapid activation of two systems that function together to restore homeostasis. First, the autonomic nervous system (ANS) responds within seconds by increasing circulating (nor)adrenaline levels via sympathetic nervous system innervation. The HPA axis is also triggered, resulting some minutes later in the release of corticosteroids from the adrenal cortex. This occurs via activation of the CRH and vasopressin (AVP) containing neuroendocrine cells in the hypothalamic PVN. These peptides are released from the neurosecretory nerve terminals at the median eminence into the portal blood vessel system, where they induce the release of adrenocorticotropic (ACTH) from the anterior pituitary gland. Adrenocorticotropic is transported in the circulation and acts at the inner adrenal cortex to synthesize and release corticosteroids into the blood; this is a pulsatile pattern under basal conditions. During stress, a surge of corticosteroids is superimposed on the hourly pulses. Corticosteroids in turn act back on different areas in the brain and pituitary via an inhibitory negative feedback loop, thereby controlling the degree and duration of the stress response. B, schematic overview of factors determining the cellular response to corticosteroids. 1) Before corticosteroids can reach and enter neuronal target cells, concentrations are locally regulated via a number of factors including a) binding to plasma proteins such as CBG, b) active transport across the blood-brain barrier via mdr P-glycoproteins, and c) intracellular enzymatic conversion via 11 $\beta$ -HSD1. 2) Once corticosteroids enter the cell, they act via the corticosteroid receptors MR and GR. Alternative splicing and translation of the corresponding genes results in the generation of a wide variety of MR and GR subtypes that are differentially expressed and transcriptionally active. Corticosteroids can affect neuronal cell function 3) rapidly in a nongenomic manner via membrane-bound receptors and 4) slowly via gene-mediated transcriptional regulation.

prefrontal cortex and amygdalar nuclei activate the HPA axis; the latter is explained by the GABAergic nature of the amygdalar efferent projections, causing disinhibition of CRH neurons.

Exposure to stressful situations thus involves release of many neurotransmitters and hormones, including catecholamines, CRH, vasopressin, and corticosteroid hormones, which collectively and in concert help the organ-

ism to adapt to the changing environment. This review will focus on only one element in this complex response (i.e., the effect of corticosteroid hormones on electrical activity of forebrain neurons under nonstressed and stressed conditions).

### B. Release of Corticosteroid Hormones

Upon activation by adrenocorticotropin, the adrenal cortex secretes the glucocorticoids corticosterone and cortisol. The name “glucocorticoid” refers to the important contribution of these hormones to gluconeogenesis in the liver, as opposed to “mineralocorticoids,” another class of adrenal steroids, with a prominent function in maintaining the mineral balance in the body, primarily by acting on the kidney. Aldosterone, a steroid synthesized in the zona glomerulosa of the adrenal cortex, is the main mineralocorticoid hormone. It circulates in a >100-fold lower concentration than corticosterone or cortisol and does not play a major role in limbic areas. Because the referral to glucocorticoid activity gives rise to confusion when discussing the brain – most of the ‘glucocorticoid’ actions in the brain bear no direct relevance to glucose metabolism (see also sections I.C and I.D)– we will in the remainder of the text use the term ‘corticosteroid’ hormones when discussing the actions of corticosterone and/or cortisol in the forebrain.

In mammals, daily corticosteroid release follows a circadian pattern, with hormone levels peaking at the end of the resting phase in anticipation of the increased metabolic demand of the active period (Young et al., 2004). Circadian corticosteroid release is principally controlled by the hypothalamic suprachiasmatic nucleus and is further orchestrated by efferent projections controlling the CRH/vasopressin-containing neuroendocrine cells in the PVN and median eminence (Kalsbeek and Buijs, 2002; Engeland and Arnhold, 2005), and ad-

renal gland sensitivity mediated by the autonomic nervous system (Ulrich-Lai and Herman, 2009).

High resolution blood sampling methods have shown that these circadian fluctuations actually overlay a highly oscillatory ultradian pattern (Fig. 2). Typically, the adrenal gland releases bursts of corticosteroids into the blood with a periodicity of approximately 60 min, with circadian modulation in amplitude. These pulsatile patterns are maintained across the blood-brain-barrier and persist in corticosteroid target regions such as the hippocampus (Droste et al., 2008). Ultradian corticosteroid pulsatility has been described in many species (Weitzman et al., 1971; Tapp et al., 1984; Jasper and Engeland, 1991; Windle et al., 1998b; Cook, 2001). Recent studies demonstrated that corticosterone pulsatility significantly contributes to physiology by maintaining normal GR signaling and HPA axis responsiveness to stress (Lightman and Conway-Campbell, 2010; Sarabdjitsingh et al., 2010a). These results have important implications for experimental studies but also for therapeutic application, because continuous corticosteroid administration is likely to be less effective than pulses. The high efficacy of pulses was already appreciated decades ago in clinical therapy with respect to growth hormones and estrogen replacement therapy (Amato et al., 2000; Shoupe, 2001), but no such administration protocols have yet been designed for corticosteroids. A better understanding of pulsatile glucocorticoid release and the underlying nuclear receptor mechanism may importantly contribute to the prognosis and treatment of (stress-related) diseases.

Until recently, the origin of ultradian corticosterone pulse generation was unknown. Walker et al. (2010) provided elegant biomathematical evidence that systems with a delay between reciprocally connected feed-forward and feedback pathways such as that of the HPA

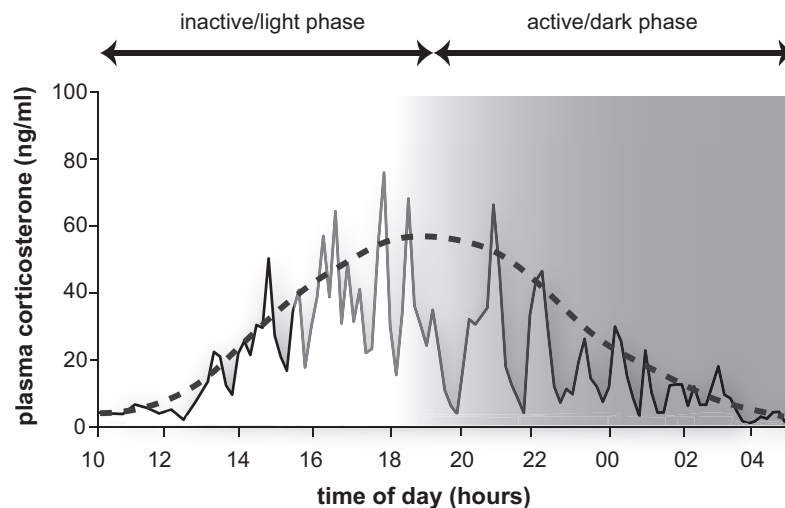


FIG. 2. Ultradian (smooth line) and circadian (dashed line) corticosterone release pattern. Representative individual profile of corticosterone in blood plasma of a male Sprague-Dawley rat collected using automated high-frequency blood sampling under basal conditions. The gray area indicates the dark, active period of the light/dark cycle.

axis, by definition have no other choice than to oscillate. The authors proposed a model describing that rapid feedforward activity via pituitary adrenocorticotropin release and a slightly delayed feedback loop via adrenal corticosterone results in self-sustaining rapid ultradian corticosterone oscillations, even in the absence of hypothalamic input. Augmentation of the pulsatile pattern can occur by alterations in adrenal gland sensitivity and steroidogenesis (Ulrich-Lai et al., 2006; Son et al., 2008; Spiga et al., 2011).

Ultradian corticosteroid amplitude and frequency can be remarkably plastic and vary throughout transitions in the life span (e.g., puberty, lactation, and ageing) (Windle et al., 1997; Lightman et al., 2000; Evuarherhe et al., 2009). Differences in corticosteroid patterns also exist for instance between sexes or strains that differ in their susceptibility to stress (Windle et al., 1998a; Seale et al., 2005). Deregulation in pulse characteristics have been linked to changed neuroendocrine and behavioral responsiveness to stress (Sarabdjitsingh et al., 2010a,c) but also to early-life stress in rodents and to various (stress-related) pathological conditions in humans such as inflammation, depression, and Cushing's syndrome (Young et al., 1994; Shanks et al., 2000; Windle et al., 2001; van Aken et al., 2005). Deviations from the normal physiological pulsatile pattern might enhance vulnerability to (psycho)pathology (Young et al., 2004; Lightman and Conway-Campbell, 2010; Sarabdjitsingh et al., 2012). Collectively, these data illustrate that circulating levels of corticosteroid hormones not only vary as a result of stress exposure but also intrinsically as a result circadian and ultradian processes.

### C. Factors Determining the Availability of Corticosteroids in Brain

The effect of corticosteroid receptor signaling in target tissues such as the brain is largely determined by the local availability of the steroids (Fig. 1). Although corticosteroid secretion is the main regulatory system that determines ligand concentrations, multiple factors "downstream" to the adrenals also influence corticosteroid levels. These include corticosteroid binding to carrier proteins in blood [i.e., corticosteroid-binding globulin (CBG) and albumin] that affect uptake by target tissues and transport across cell membranes, including the blood-brain barrier. Moreover, intracellularly, corticosteroids are prone to enzymatic conversion, which influences receptor signaling more directly.

CBG is a low-capacity, high-affinity plasma protein and functions as the principal carrier for circulating corticosterone and cortisol. Together with albumin, it binds approximately 95% of the corticosteroid pool. The remaining unbound steroid fraction is free to diffuse across target cell membranes and has ready access to receptors. CBG also affects metabolic clearance rates, because only the unbound fraction is subject to degradation by the liver (Hammond, 1990; Rosner, 1990).

Under normal conditions, CBG thus acts as a tissue buffer against the potentially detrimental effects of high corticosteroid levels, by regulating the availability of free steroid access to the brain. Under particular circumstances (e.g., ultradian/circadian peak, stress, disease, enzyme activity, or CBG genetic variance), CBG saturation is exceeded or binding properties and expression levels are affected, increasing the corticosteroid bioavailability (Breuner and Orchinik, 2002; Gagliardi et al., 2010; Henley and Lightman, 2011). CBG is a prime target for specific classes of proteinases (e.g., neutrophil elastase). Elastase cleavage of CBG results in the irreversible loss of steroid binding, thereby presumably elevating steroid concentrations at the sites of inflammation (Klieber et al., 2007).

Before corticosteroids can reach and enter neuronal target cells they have to pass the blood-brain barrier. This highly dynamic, physical, and metabolic barrier involves specialized endothelial cells and maintains brain homeostasis by protecting the brain from compounds in the circulation (Bradbury, 1993). Natural corticosteroids, particularly corticosterone, can readily pass the blood-brain barrier by passive diffusion, because of their small size and lipophilic nature. In accordance, the pulsatile pattern of corticosterone is maintained across the blood-brain barrier, suggesting that neurons are exposed to highly fluctuating corticosterone levels (Droste et al., 2008). This contrasts with the endogenous hormone cortisol (which in rodents circulates in much lower concentrations than corticosterone) and the synthetic steroid dexamethasone, which have hampered penetration because they are a substrate of the multidrug resistance (mdr) 1a P-glycoprotein (Meijer et al., 1998; Karsen et al., 2001). Mdr1a P-glycoprotein is also thought to expel corticosteroids from brain cells (Pariante, 2008). It is noteworthy that this membrane transporter has been proposed as a promising therapeutic target for treatment of depression and the presumed steroid resistance in this disease (Pariante, 2008). For instance, the antidepressant desipramine requires the mdr1a P-glycoprotein to up-regulate GRs in the mouse brain (Yau et al., 2007), potentially normalizing HPA-axis function, which is often aberrant in depressives. Genetic polymorphisms in the mdr1a P-glycoprotein were found to predict clinical response to antidepressants (Pariante, 2008).

After crossing the blood-brain barrier, intracellular levels of corticosteroids are additionally modulated by  $11\beta$ -hydroxysteroid dehydrogenase (HSD) enzymes. These exist in two isoforms and tightly regulate the interconversion of corticosteroids in cells expressing these enzymes (Wyrwoll et al., 2011). Type 2 ( $11\beta$ HSD-2) catalyzes inactivation of glucocorticoids, so that in the kidney, for example, corticosterone and cortisol are no longer available to bind receptors for which they have very high affinity, allowing the less prevalent hormone aldosterone to bind. Type 2, however, is not substantially expressed in most brain regions (with the exception of the nucleus tractus solitarius).

so that corticosterone and cortisol are now the main ligands for the corticosteroid receptors (Wyrwoll et al., 2011). Type 1 is ubiquitously present in multiple tissues, including the brain and pituitary and promotes the reduction of inactive 11-keto-derivatives, such as dehydrocorticosterone and cortisone, into active corticosterone and cortisol, respectively (Seckl and Walker, 2004). These enzymes are essential in determining intracellular corticosteroid levels. The relevance of the enzyme for cognitive function was illustrated by the fact that 11 $\beta$ HSD-1 deficiency protects against cognitive decline during ageing (Wyrwoll et al., 2011).

The conclusions of these studies are 1) that hormone levels in the brain quite accurately follow the fluctuations seen peripherally, albeit with a delay; and 2) that corticosterone and cortisol—rather than aldosterone—are the main ligands for corticosteroid receptors in the brain.

#### D. Corticosteroid Hormone Receptors in the Brain

Once corticosteroid hormones have entered the brain, they can in principle exert their actions on those cells expressing a receptor. Two types of receptors were demonstrated in brain tissue (Reul and de Kloet, 1985): mineralocorticoid receptors (MRs) and glucocorticoid re-

ceptors (GRs). These names refer to the main peripheral processes in which they are involved: mineral balance and gluconeogenesis, respectively. The genes encoding the receptors mediating these peripheral functions are identical to the genes in the brain (Hollenberg et al., 1985; Arriza et al., 1987).

Despite the fact that only two genes encode for these receptors, there are many isoforms known, giving rise to considerable variation in the expression levels and transcriptional activity of corticosteroid receptors in the various brain regions. A wave of corticosteroids reaching the brain may therefore lead to extensive regional differentiation in the transcriptional response, at least with nonsaturating concentrations (for discussion, see section VI.B). More specifically, corticosteroid receptors belong to the superfamily of nuclear receptors, which act as transcription factors. The human *GR* gene consists of nine exons; exons 2 to 9 code for the GR protein (Derijk and de Kloet, 2008; Revollo and Cidlowski, 2009; Turner et al., 2010) (Fig. 3). Exon 1 is liable to alternative splicing, each variant having its own transcriptional start site and promoter region. The variants display regional specificity, which is thought to contribute to differences in GR expression level. Exon 9 can also be alternatively spliced, resulting in the prevalent GR $\alpha$  or

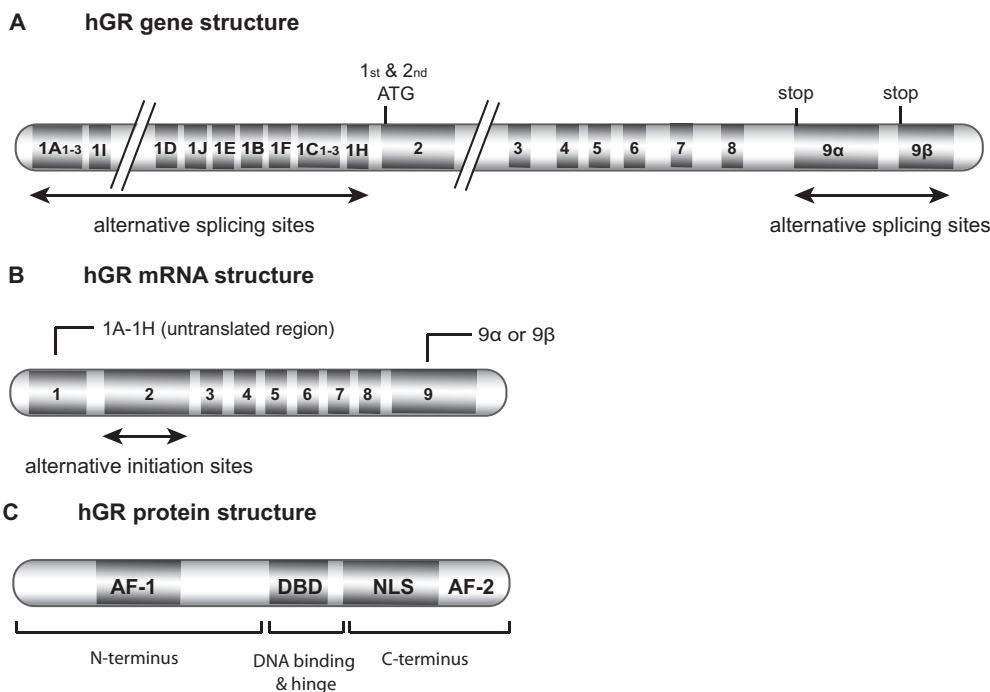


FIG. 3. Structure of the human (h) GR gene. A, the *hGR* gene is located on chromosome 5 (region 5q31p) and contains 9 exons of which exon 2 to 8 are translated. Exon 1 is composed of nine alternatives (1A–1H), each containing its own transcription start sites and promoters. Alternative usage of exon 1 leads to differential mRNA transcripts with region- and tissue-specific expression patterns. Exon 1, however, remains untranslated, because the ATG start codon lies within exon 2. B, alternative splicing can occur in exons 1 and 9, generating various mRNA messages. Alternative splicing of exon 9 produces the two most characterized isoforms of hGR, hGR $\alpha$  and hGR $\beta$ , which are important for the differential expression and regulation of GR. hGR $\alpha$  is the predominant variant of the receptor, whereas hGR $\beta$  is thought to be a dominant-negative regulator of hGR $\alpha$ . Furthermore, alternative initiation sites can give rise to additional isoforms of each mature mRNA message, with progressively shorter N-terminal domains that also have different tissue-expression patterns and transcriptional responsiveness to glucocorticoids. C, the full-length hGR $\alpha$  protein is composed of multiple domains important for GR function. The N-terminal domain contains an activation function (AF), a domain that is necessary to interact with transcription machinery components. The DNA-binding domain is important for DNA interactions via two zinc fingers involved in dimerization. The hinge contains the nuclear localization signal. The C-terminal domain also contains a nuclear localization signal, the ligand binding domain and an AF-2 important for interactions with transcriptional coregulators.

the shorter GR $\beta$  isoform. Both GR $\alpha$  and GR $\beta$  mRNA can give rise to eight translational isoforms, each with its own tissue expression, subcellular localization, and transcriptional activity. Transcriptional activity is further fine-tuned by post-translational modifications. Much less is known about isoforms of the MR, but for this receptor as well, different promoter regions, several splice variants, translational variants, and post-translational modifications have been described previously (Pascual-Le Tallec and Lombès, 2005; Derijk and de Kloet, 2008; Gomez-Sanchez, 2010).

The two receptor types are not uniformly distributed in the brain (Reul and de Kloet, 1985). GRs are quite ubiquitous in their distribution and expressed in neurons and glial cells alike. Nevertheless, there are brain regions with very high expression levels, such as the PVN, the CA1 hippocampal area and dentate gyrus, central and cortical amygdala, lateral septum, and nucleus tractus solitarii. Conversely, MRs are very restricted in their distribution but are, for instance, highly expressed in neurons of all hippocampal subfields and the lateral septum.

The MR and GR proteins consist of several domains that are important for their function (Revollo and Cidlowski, 2009) (see Fig. 3):

1. An N-terminal domain with an activation function motif through which the receptor can interact with the transcriptional machinery;
2. The DNA-binding domain consisting of two zinc-fingers essential for receptor dimerization and binding to recognition elements in the DNA;
3. A hinge that contains a nuclear localization signal; and
4. A C-terminal region that contains 1) a second nuclear localization signal, 2) a motif that is important for protein-protein interactions, and 3) the pocket to which ligands can bind, each with a specific affinity.

MR and GR have different affinities for endogenous corticosteroid hormones, so that variations in hormone concentrations in the brain lead to shifts in the balance between MR and GR activity. The MR has a high affinity for the endogenous hormones aldosterone, corticosterone and cortisol, with a  $K_d$  of approximately 0.5 nM (Reul and de Kloet, 1985). The affinity of the GR for corticosterone and cortisol is approximately 10-fold lower and manyfold lower for aldosterone. Given 1) the very high affinity of MRs for corticosterone, 2) the >100-fold excess of corticosterone over aldosterone, and 3) the fact that most brain cells express high levels of 11 $\beta$ -HSD1 instead of 11 $\beta$ -HSD2, these receptors in brain will almost always be substantially occupied by corticosterone (or cortisol), even with hormone concentrations during the trough of the circadian rhythm and ultradian pulses. By contrast, the affinity of GRs is such that these receptors will be only partly occupied when corticoste-

roid levels are low but gradually become occupied when hormone levels rise (e.g., at the peak of ultradian pulses and the circadian rhythm or after stress). Thus, the expression levels of the receptors determine the range in which neural activity can be affected and the hormone concentration the actual position within this range.

### E. Transcriptional Regulation

In the inactive state, MRs and GRs are located in the cytoplasm and bound to chaperones such as the 90-kDa heat-shock protein. Upon binding of the ligand, this complex dissociates, uncovering nuclear localizations signals, so that the ligand-receptor complex moves to the nucleus. There, they can either bind as homodimers to consensus sequences in the promoter of 1 to 2% of the genes and directly change transcription of these genes or interact with other transcription factors, altering their efficacy (Datson et al., 2008) (see Fig. 1). The former pathway usually promotes gene transcription, whereas the latter can result in suppressive or facilitating effects.

Corticosteroid hormones are fundamental in the regulation of metabolism, development, inflammation as well as several other biological functions. Such a widespread spectrum of biological involvement suggests that a broad array of genes may be regulated by the receptors. Indeed, in clinical therapy, synthetic glucocorticoids are frequently used for the treatment of many pathological conditions. However such generalized glucocorticoid administration often concurs with many adverse side-effects. From a clinical and pharmacological point of view, the classification of (tissue-specific) glucocorticoid target gene-expression profiles into functional categories is necessary information to enhance clinical efficacy while minimizing potential adverse effects.

Functional categories of target genes have been explored for the brain as well. Thus, large-scale gene expression profiling has proved to be a successful strategy in the identification of central target genes underlying corticosteroid-mediated effects in the brain (Datson et al., 2001). The transcriptional response to acute GR activation is highly dynamic (Fig. 4). For instance, hippocampal slices exposed to a 20-min pulse of 100 nM corticosterone were profiled 1, 3, and 5 h after treatment; this dose of corticosterone is assumed to primarily activate GRs in slices prepared from animals killed at the circadian trough and under rest, because the MRs (but not GRs) are already substantially occupied under control conditions (i.e., before corticosterone treatment). Strikingly, the transcriptional profiles seemed to occur in a wave-like pattern, with a shift from strictly down-regulated genes within 1 h to up-regulation of the majority of the genes 3 h after GR activation. After 5 h, the response was back to baseline (Morsink et al., 2006b). Highly similar response profiles of corticosteroid responsive target genes were obtained in cultured cells, displaying kinetically complex transcriptional patterns, frequently with alternating activation and repression

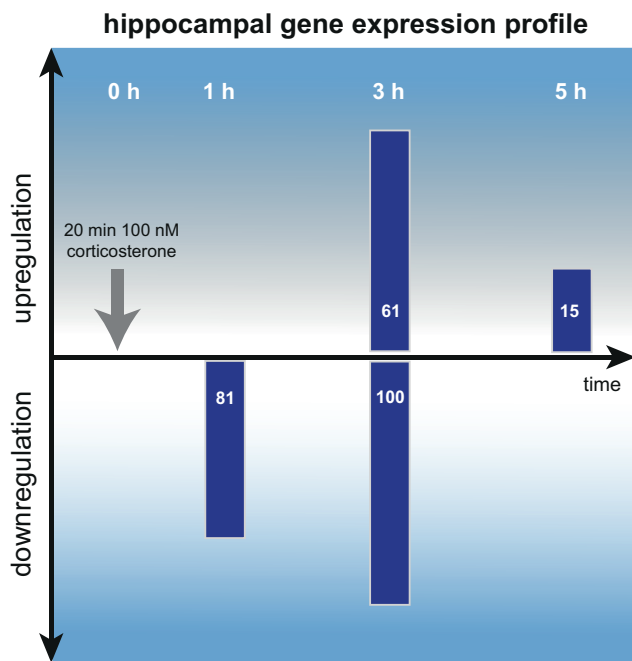


FIG. 4. Time course of gene expression in hippocampal slices in response to corticosterone exposure. DNA microarray profiling was used to measure gene expression responses at 1, 3, and 5 h after a 20-min administration of 100 nM corticosterone to rat hippocampal explant slices. Throughout time, gene expression occurred in a wave-like pattern with strictly down-regulated genes 1 h after corticosterone administration. The numbers in the bars indicate the number of corticosteroid-responsive genes at that particular time point. Based on data from Morsink et al. (2006b).

phases (Morsink et al., 2006a; John et al., 2009). Classification of these corticosteroid target genes into functional categories resulted in clusters of genes that mainly involve energy metabolism, signal transduction, neuronal structure, vesicle dynamics, neuronal catabolism, cell adhesion, and genes involved in regulation of corticosteroid signaling (Datson et al., 2008).

Corticosteroids have regionally different receptor-mediated transcriptional effects, which is important for diversity in physiological effects. These differential corticosteroid-dependent transcriptional responses depend on a number of factors contributing to cell- and even subregion-specific transcriptional responses in the brain, such as the local receptor expression and properties (Kitchener et al., 2004; Turner et al., 2010), differential coregulator recruitment (van der Laan and Meijer, 2008), DNA composition (So et al., 2007; Datson et al., 2011), and chromatin accessibility and remodeling mechanisms (John et al., 2011).

Accumulating evidence shows that GR-mediated transcriptional efficiency is not only governed by stress-induced release of corticosteroids but is also under control of ultradian corticosterone pulsatility (Lightman and Conway-Campbell, 2010; Conway-Campbell et al., 2012). Repetitive corticosterone exposure results in transient cyclic recruitment and exchange of GR at regulatory sites in the genome (Stavreva et al., 2009; Conway-Campbell et al., 2010), whereas MR is retained in

the nucleus (Conway-Campbell et al., 2007). Experimental evidence supports the idea that pulsatile patterns are necessary to safeguard GR sensitivity and downstream signaling in target tissues (Sarabdjitsingh et al., 2010b).

In summary, when a surge of corticosteroids reaches the brain, a transient wave of primary transcriptional events takes place, targeting many genes. This changes the levels of multiple proteins, including those involved in neural activity, in a time window that commences when corticosteroid levels are starting to normalize and that outlasts the hormonal surge by at least several hours. Pulsatile hormone release seems necessary to guarantee optimal transcriptional efficiency.

#### F. Nongenomic Pathways

Despite the overwhelming amount of data showing that corticosteroid hormones via their receptors regulate gene transcription and the detailed knowledge that has been obtained about the signaling pathways, it has been known for decades that corticosteroids can also quickly change neural and brain function, in a time domain that is incompatible with pathways involving transcription and translation (for review, see Borski, 2000; Evanson et al., 2010). For instance, a pioneering study by Pfaff et al. (1971) showed that peripherally administered corticosterone suppresses hippocampal firing within 20 min. Almost instantaneous though prolonged effects of corticosteroids were observed in PVN neurons antidromically identified through their projections to the median eminence (Saphier and Feldman, 1988; Chen et al., 1991); of these cells, nearly three quarters were inhibited by iontophoretically applied corticosterone or hydrocortisone.

Behavioral investigations also supplied evidence for rapid corticosteroid actions in brain. For example, corticosterone was found to inhibit male reproductive behavior as well as medullary firing in newts (Rose et al., 1993), mediated by a corticosteroid receptor in the membrane with a pharmacological profile different from the "classic" nuclear receptor (Orchinik et al., 1991) and linked to G-protein coupled signaling pathways (Orchinik et al., 1992). Such an unexpected pharmacological profile for rapid corticosteroid effects has also been observed in tissues other than the brain (Lösler and Wehling, 2008). A second example of rapid behavioral modulation by corticosterone concerns a mutual rapid positive feedback between HPA axis activation and the brain mechanism controlling aggression: hypothalamic aggression was reported to be rapidly enhanced by corticosterone in adrenalectomized rats, whereas stimulation of the hypothalamus rapidly activated the adrenocortical response, even in the absence of an opponent (Kruk et al., 2004).

The rapid nongenomic corticosteroid actions expand the time window during which these hormones can change neural function. Effectively, their influence stretches from as soon as they enter the brain to many hours later.



### G. From Stressor to Multiple Functional Endpoints

As is evident from the previous sections, once corticosteroids reach a neuron they can exert multiple effects via either genomic or nongenomic signaling (Fig. 1). The nature of the effect firstly depends on the type of receptor that is activated; this in turn is determined by the local receptor availability, the sensitivity of receptors to corticosteroids, as well as the hormone concentration. None of these is a stable factor, though; they are largely modulated by genetic background such as receptor haplotypes, life history of the subject, and even whether or not the organism was exposed to a stressor in recent hours. Most of these aspects will be discussed in the later parts of the review (sections IV and V).

The transcriptome analyses to date underline that corticosteroid hormones target multiple classes of genes, which in some cases (e.g., when corticosteroids target the gene encoding for another transcription factor) regulate a whole array of secondary genes. One surge of corticosteroids can thus change numerous endpoints. These can be studied at many different levels of organization, ranging from changes in gene transcripts, proteins, and biochemical pathways to neurotransmission, structural plasticity, and behavioral endpoints. In this review, we focus particularly on the actions of corticosteroid hormones on neural activity (Fig. 5): How do these steroids affect the properties of ion channels, whole-cell currents, action potentials, firing frequency of cells, and single-cell or field responses to the main excitatory and inhibitory inputs? These endpoints at an intermediate level of integration are highly relevant, because they give insight in functional connectivity between (groups of) neurons. We review the literature for both the rapid nongenomic effects (section II) and slow gene-mediated actions (section III) in the mammalian forebrain. At the end of each of these sections, the relevance of these changes in electrical activity for behavioral adaptation will be discussed.

## II. Rapid Effects

Although several studies over the past 30 years reported corticosteroid-induced changes in neural activity that developed within seconds to minutes—a delay that is incompatible with the classic signaling pathway involving gene transcription and translation—extensive investigation at the single cell level started only approximately a decade ago. Rapid and presumably nongenomic actions have now been observed in several brain areas (Supplemental Table I). We will here discuss only those areas in which the rapid actions of corticosteroids are well documented.

### A. Rapid Modulation of Neural Activity

**1. Hippocampus.** Over the past years it has become increasingly evident that neurons in the ventral-most (20%) part of the hippocampus have electrical proper-

ties, including their response to corticosteroids and stress, different from those of neurons in the rest of the hippocampus (Maggio and Segal, 2010). The data discussed in this review pertain to the latter part (the vast majority of cells), unless stated otherwise.

Rapid effects of corticosteroid hormones on passive and active membrane properties or on specific voltage-dependent ion currents have hardly been investigated in the hippocampus. The former appear not to be affected by corticosterone (Joëls and de Kloet, 1993). An early study reported rapid inhibition of L- and N-type calcium currents in dissociated CA1 pyramidal neurons, but this required very high concentrations of cortisol, whereas corticosterone was not very potent (French-Mullen, 1995). More recently, it was found that the voltage-dependence of activation of a transient  $K^+$  current ( $I_A$ ) in CA1 pyramidal cells is shifted to the right by corticosterone via an MR-dependent postsynaptic mechanism, so that this channel is less activated during small depolarizations (Olijslagers et al., 2008). This will result in a higher likelihood of inducing action potentials with excitatory input.

More information has appeared regarding corticosteroid actions on excitatory and inhibitory inputs to the hippocampus. Rapid excitatory transmission in the brain is primarily mediated by glutamate, acting via AMPA and NMDA receptors. Glutamate release is evoked by the arrival of action potentials and subsequent calcium release in the presynaptic terminal, but to a limited extent glutamate transmission also occurs spontaneously, even in the absence of action potentials. This spontaneous background activity is apparent (Fig. 5) from the postsynaptic response to a spontaneously released synaptic vesicle containing glutamate, a so-called miniature excitatory postsynaptic current (mEPSC). Inhibitory transmission is mostly carried by GABA. Spontaneous release of GABA-containing vesicles is postsynaptically recorded as a spontaneous inhibitory postsynaptic current (sIPSC) or, in case of action potential blockade miniature IPSC (mIPSC).

CA1 hippocampal pyramidal cells were found to respond to corticosterone within minutes with enhanced mEPSC frequency (Karst et al., 2005) (Fig. 6). Other properties of the mEPSCs, such as amplitude, rise time, or decay, were entirely unaffected by the hormone. In a paired-pulse stimulation paradigm, corticosterone diminished the second evoked response relative to the first, indicating that hormone treatment most likely boosts the release probability of glutamate containing vesicles rather than increasing the number of synaptic contacts. Upon washout of corticosterone, the mEPSC frequency rapidly returned to the pretreatment level. A second pulse of corticosterone 1 h later evoked a highly comparable response (Karst et al., 2010). The rapidly reversible response and the fact that corticosterone exerted very similar effects in the presence of a protein synthesis inhibitor support the theory that this effect is

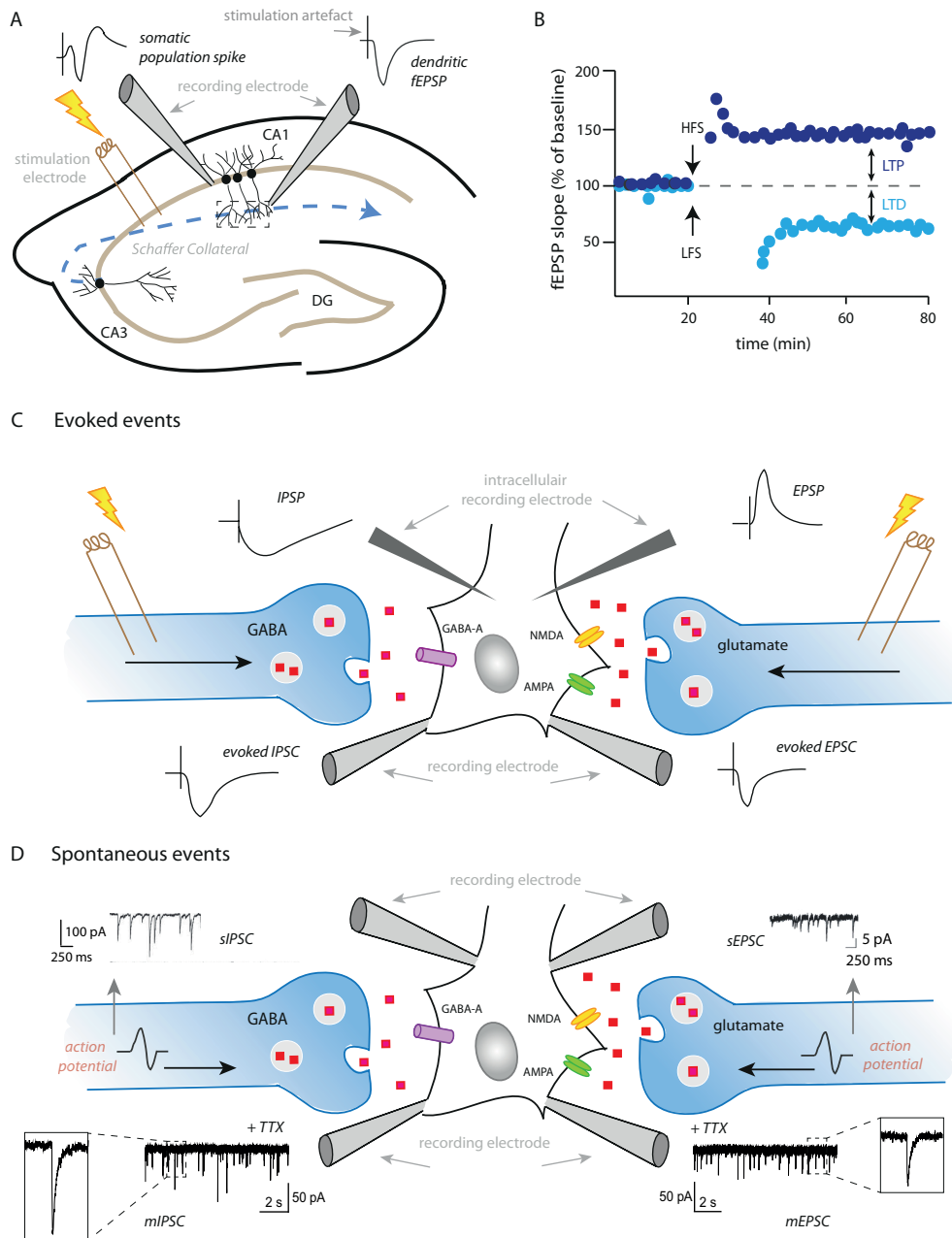


FIG. 5. Overview of all electrophysiological endpoints discussed in this review. A, examples of recording configuration and typical physiologic responses in a hippocampal slice, using stimulation of the Schaffer collaterals. Typical waveforms recorded extracellularly from a population of CA1 neurons through electrodes placed in the pyramidal cell body layer and dendritic stratum radiatum are shown in the insets on top. B, schematic overview of synaptic LTP (dark gray) and LTD (blue) evoked by high-frequency stimulation (HFS) and low-frequency stimulation (LFS) of afferent fibers, respectively. C, synaptic potentials (insets at top) and currents (insets at bottom) evoked by electrical stimulation of afferent projections to a single neuron. Responses mediated by GABA are depicted on the left, and by glutamate on the right. Most studies discussed in this review used patch clamp recording (illustrated at the bottom), but particularly in earlier studies sharp electrodes inserted into the cell were used (shown at the top). D, in the absence of stimulation, GABA- or glutamate-containing vesicles occasionally fuse with the presynaptic membrane spontaneously (top). Postsynaptically this is recorded as an sIPSC (left) or sEPSC (right). Spontaneous release can even occur if arrival of action potentials at the terminal is blocked by addition of tetrodotoxin (TTX), as shown at the bottom. The postsynaptically recorded events are then called mIPSCs or mEPSCs.

accomplished through a nongenomic pathway. Corticosterone conjugated to (membrane-impermeable) bovine serum albumin (BSA) induced very similar effects on mEPSC frequency, whereas intracellular administration was ineffective (Karst et al., 2005; Olijslagers et al., 2008). This suggests that corticosterone binds to a molecule that is accessible from the outside of the cell. Pharmacological and genetic tools supported that this

involves an MR rather than GR. The MR-dependent increase in mEPSC frequency requires expression of limbic system-associated membrane protein, Lsamp (Qiu et al., 2010). A highly similar MR-dependent raise in mEPSC frequency was observed in granule cells of the dentate gyrus (Pasricha et al., 2011).

Follow-up studies in the CA1 area revealed that MRs mediating the rapid effect are probably localized on the

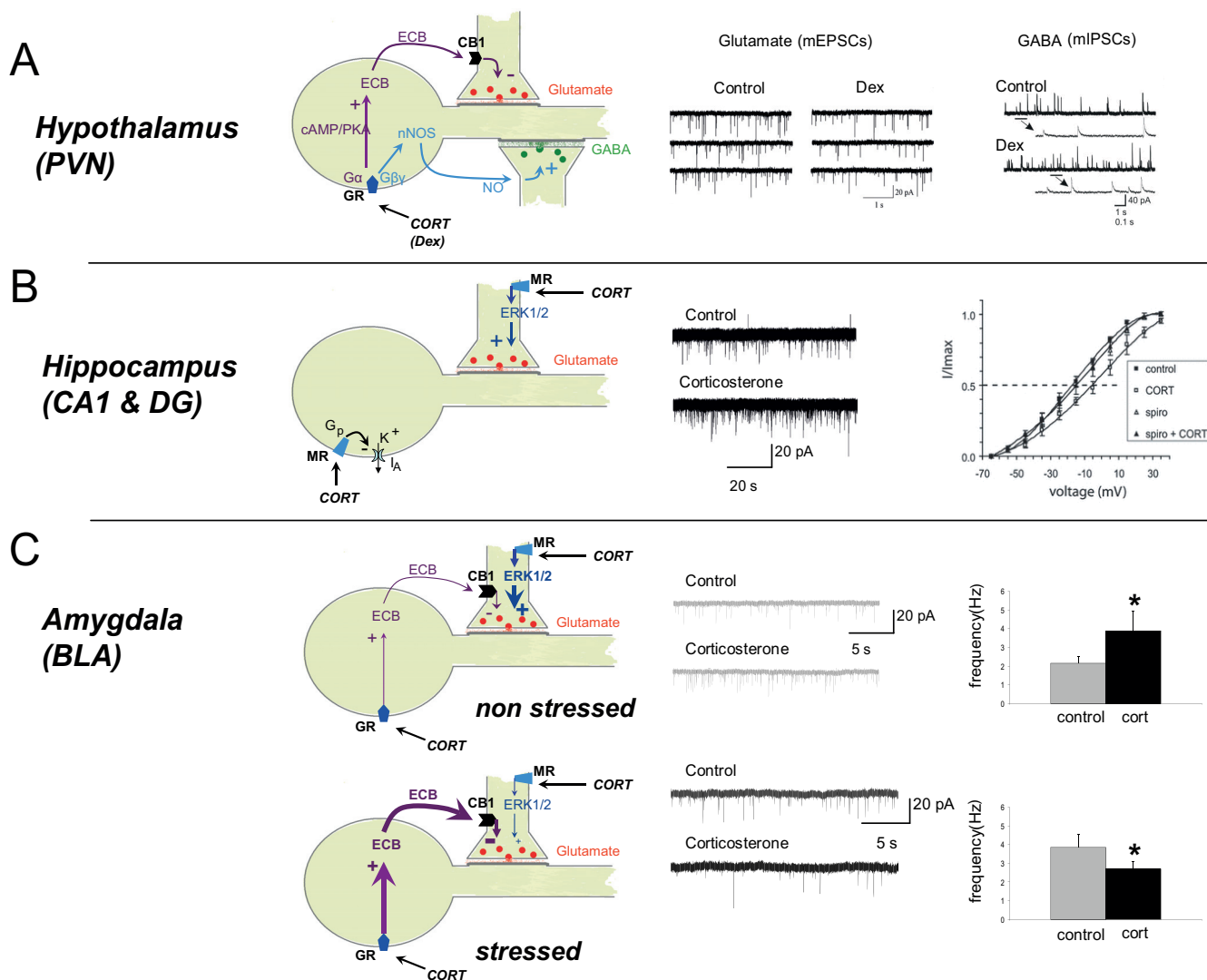


FIG. 6. Rapid effects of corticosterone on electrical activity in the male rodent brain. A, glucocorticoids rapidly suppress glutamatergic mEPSC frequency (middle) and enhance GABAergic mIPSC frequency (right) in the hypothalamic PVN. The former involves retrograde endocannabinoid (ECB) signaling, whereas the latter depends on retrograde signaling via nitric oxide (NO), as represented schematically on the left. [Modified from Di S, Malcher-Lopes R, Halmos KC, and Tasker JG (2003) Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *J Neurosci* **23**:4850–4857. Copyright © 2003 Society for Neuroscience; and Di S, Maxson MM, Franco A, and Tasker JG (2009) Glucocorticoids regulate glutamate and GABA synapse-specific retrograde transmission via divergent nongenomic signaling pathways. *J Neurosci* **29**:393–401. Copyright © 2009 Society for Neuroscience. Both used with permission.] B, in the hippocampus, corticosterone binds to presynaptic mineralocorticoid receptors (MR), which via ERK1/2 signaling, cause a rapid increase in the release probability of glutamate. This is reflected in enhanced frequency of the mEPSCs (middle). In addition, the hormone can bind to postsynaptically located MRs, which are coupled to transient potassium channels (IA) through a G-protein. The hormone causes a rightward shift in the activation curve of this current (right), increasing the likelihood for postsynaptic action potential generation. [Modified from Karst H, Berger S, Turiault M, Tronche F, Schütz G, and Joëls M (2005) Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc Natl Acad Sci USA* **102**:19204–19207. Copyright © 2005 National Academy of Sciences, U.S.A.; and Olijslagers JE, de Kloet ER, Elgersma Y, van Woerden GM, Joëls M, and Karst H (2008) Rapid changes in hippocampal CA1 pyramidal cell function via pre- as well as postsynaptic membrane mineralocorticoid receptors. *Eur J Neurosci* **27**:2542–2550. Copyright © 2008 Federation of European Neuroscience Societies and Blackwell Publishing Ltd. Permission for re-use not required for these articles.] C, principal neurons in the basolateral amygdala (BLA) of unstressed animals show rapid responses to corticosterone similar to those of hippocampal cells (top), increasing the frequency of mEPSCs recorded postsynaptically (middle and right). In BLA cells, this sustained effect changes the properties of these cells such that they respond differently to a second pulse of corticosterone (bottom). In tissue from previously stressed animals, corticosterone activates an endocannabinoid signaling pathway that suppresses mEPSC frequency via a GR-dependent pathway. This is very similar to what has been described for the PVN, depicted in A. [Modified from Karst H, Berger S, Erdmann G, Schütz G, and Joëls M (2010) Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proc Natl Acad Sci USA* **107**:14449–14454. Copyright © 2010 National Academy of Sciences, U.S.A. Permission for re-use not required.]

presynaptic membrane and linked to the ERK1/2 signaling pathway (Olijslagers et al., 2008). It is noteworthy that corticosterone changes glutamate transmission in the CA1 hippocampal area not only by increasing the release probability, a presynaptic property, but also by

other means. In the postsynaptic membrane, GluA2 subunits of the AMPA receptor exhibit increased lateral movement and a higher dwell time in the postsynaptic density (Groc et al., 2008). This effect as well was mediated by MRs, mimicked by corticosterone-BSA, and per-

sisted in the presence of a protein synthesis inhibitor. Both actions on glutamate transmission are expected to increase the (spontaneous) activity of hippocampal CA1 neurons. This would fit with the enhanced population spike amplitude observed extracellularly when treating slices from adrenalectomized rats (devoid of endogenous corticosteroids) with low doses of corticosterone, presumably activating MR (Reiheld et al., 1984).

One study (Tse et al., 2011) reported that CA1 cells also respond more strongly to a slightly later excitatory input (i.e., 20–30 min after the start of corticosterone administration), although the characteristics were somewhat different. When excitatory postsynaptic currents were synaptically evoked (eEPSC), the NMDA/AMPA ratio was increased. No change was observed in paired-pulse responsiveness. This effect seemed to be mediated by GR [i.e., mimicked by dexamethasone and blocked by the GR-antagonist mifepristone (RU38486)] and was not accompanied by AMPA-receptor subunit trafficking. The fact that mifepristone was effective raises the question of whether these effects are truly nongenomic, because this drug is generally ineffective in blocking membrane-receptor-mediated events (for example, see Di et al., 2003; Liu et al., 2007; Zhang et al., 2012). Tse et al. (2011) observed an extracellular increase in the field excitatory postsynaptic potential evoked via NMDA but not AMPA receptors.

With this slightly longer delay, however, several studies reported reduced responses to synaptic input. Spontaneous firing rate of hippocampal cells was reduced by corticosterone peripherally injected 20 min earlier (Pfaff et al., 1971). This fits with more recent data showing that various types of stress impair the stability or reduce the firing rate of hippocampal place cells in this time domain (Kim et al., 2007; Passecker et al., 2011). In vitro-administered corticosterone (at a very high dose) was found to reduce the population spike amplitude in the CA1 area, an effect that reached a plateau 20 to 40 min after beginning corticosterone administration (Vidal et al., 1986). Likewise, the probability of evoking an action potential with synaptic stimulation, as well as the amplitude of the excitatory postsynaptic potential and slow inhibitory postsynaptic potential of CA1 neurons, gradually declined starting 20 min after corticosterone administration (Joëls and de Kloet, 1993). Exposure to a foot shock before preparation of slices reduced the amplitude and frequency of CA1 hippocampal mEPSCs as well as paired-pulse facilitation (Zhang et al., 2005; Gao et al., 2008). The latter may also be linked to the fact that this study involved much younger animals than most other studies. In this respect, it is interesting that corticosterone also reduced NMDA-evoked currents in neonatal cultured hippocampal neurons through a membrane-bound receptor not blocked by classic MR or GR antagonists (Liu et al., 2007; Zhang et al., 2012).

The overall activity of CA1 pyramidal cells will depend on the balance between excitatory and inhibitory transmis-

sion. Exactly how corticosteroids affect GABAergic transmission in the CA1 area is not quite clear. GABAergic inhibitory responses were reduced when recording with sharp electrodes but slightly enhanced with whole-cell recording, indicating that an intracellular molecule is important in mediating the reduced inhibition (Zeise et al., 1992; Teschemacher et al., 1996). Hu et al. (2010) reported—using whole-cell recording—that restraint stress and dexamethasone-BSA increase the frequency and amplitude of sIPSCs, although mIPSCs were unaffected. This effect involved postsynaptic G proteins and retrograde transport by nitric oxide and was not blocked by either MR or GR antagonists.

Although it is not easy to predict how corticosteroid hormones will quickly affect the overall information flow through the CA1 hippocampal area, the balance seems to be tipped toward enhanced spontaneous excitatory activity. Synaptically evoked field potentials, though, are not markedly altered by corticosterone administration (e.g., Wiegert et al., 2006; Pu et al., 2007), but this is a rather indirect signal so that subtle effects may have remained unnoticed. This is also when other transmitters and hormones released by stress are active and determine excitability. For instance, CRH is known to quickly potentiate the population spike in the Schaffer projection to the CA1 hippocampal area (Blank et al., 2002). Overall, enhanced hippocampal activity during this phase directly after stress may prevail. Slightly later (i.e., 20–30 min after corticosterone reaches hippocampal cells), inhibitory actions seem more prevalent. This is an ambiguous time-domain, rather slow for nongenomic actions but probably too rapid for genomic actions.

*2. A New Concept in the Basolateral Amygdala: Metaplasticity.* In the basolateral amygdala (BLA), MRs are expressed at a lower level than the hippocampus (Reul and de Kloet, 1985). Nevertheless, corticosterone rapidly increased mEPSC frequency of principal cells in the BLA via an MR-dependent mechanism (Karst et al., 2010) (Fig. 6), similar to what was observed in the CA1 and dentate neurons. However, in the BLA, the frequency remains at a high level, even after washout of corticosterone. Although the onset is clearly nongenomic, the persistence of the response critically depends on protein synthesis and expression of both corticosteroid receptor types. This (assumed) genomic element changes the properties of BLA cells such that they respond differently to a second pulse of corticosterone, in this case with a diminishment of mEPSC frequency (i.e., exactly the opposite of what is seen upon the first exposure) (Fig. 6). The rapid suppression of mEPSC frequency requires expression of GRs and the cannabinoid receptor-1. It was also seen when animals had been exposed to stress before preparation of the brain slices. This indicates that the rapid response of BLA neurons to corticosterone depends on the recent stress history of the organism, a phenomenon that has been dubbed “meta-

plasticity" (Karst et al., 2010). The shift in responsiveness after a second corticosterone treatment is possibly due to a change in the MR/GR ratio in the membrane (e.g., caused by internalization of MRs after the first pulse of corticosterone).

The extent to which these modulations in mEPSC properties are reflected in the transfer of ongoing excitatory transmission is unclear. At both the single-cell and the field-potential levels, corticosterone did not quickly change AMPA or NMDA receptor-mediated synaptic responses (Liebmann et al., 2009; Pu et al., 2009).

3. *Paraventricular Nucleus.* In parvocellular neurons of the PVN—including those producing CRH—exposure to corticosterone or dexamethasone was reported to consistently decrease the release probability of glutamate-containing vesicles (Di et al., 2003) (Fig. 6). Antagonists of the MR or GR did not prevent this effect of dexamethasone. Although the involvement of a nonspecific corticosteroid receptor was proposed initially, later experiments showed that rapid effect of glucocorticoids are abolished in conditional GR knockout mice (Haam et al., 2010; Tasker and Herman, 2011), suggesting a role for GRs. The suppression in mEPSC frequency involves changes in endocannabinoid levels and retrograde signaling on the cannabinoid receptor-1 (Di et al., 2003) and depends on  $G\alpha_s$  (Di et al., 2009). Similar effects on mEPSC frequency were observed in magnocellular neurons of the PVN, via the same signaling mechanism (Di et al., 2005). It is noteworthy that in these cells corticosteroids also changed spontaneous GABAergic signaling, causing an enhanced GABAergic tone via nitric oxide and  $G\beta\gamma$  (Di et al., 2009). Corticosterone does not affect mIPSC frequency in parvocellular PVN cells (Verkuyl et al., 2005).

As mentioned above, prior stress exposure reveals a cannabinoid receptor-1-dependent suppression of mEPSC frequency in BLA neurons that is not seen under rest. This also may apply to PVN neurons. If so, moderately stressful conditions just before onset of the experiment (e.g., transportation from the animal house to the laboratory) could explain the suppression reported for the PVN. However, the PVN may also be intrinsically different from the BLA with respect to its rapid corticosteroid actions.

### B. Rapid Modulation of Synaptic Plasticity

The frequency of mEPSCs is enhanced during both the early and the late phases of synaptic plasticity (Isaac et al., 1996; Wiegert et al., 2009), and enhanced glutamate release can cause LTP-like strengthening of synapses (reviewed in Nicoll and Schmitz, 2005). Rapid modulation of mEPSC frequency by corticosteroid hormones coinciding with high-frequency input may thus have consequences for synaptic plasticity.

Rapid enhancement of LTP by corticosterone was observed in the CA1 and DG (but Filipini et al., 1991; Wiegert et al., 2006; Pu et al., 2007; Tse et al., 2011), depending on the presence of limbic system-associated membrane protein (Qiu et al., 2010). However, a series

of articles showing that, in particular, exposure to a novel environment prevents induction of LTP, depotentiates earlier induced LTP, and facilitates the induction of LTD, in the CA1 area but also nucleus accumbens (Xu et al., 1997, 1998; Manahan-Vaughan and Braunewell, 1999; Hugues et al., 2003; Yang et al., 2004; Tse et al., 2011). Remarkably, these effects could be blocked by mifepristone (Xu et al., 1998; Tse et al., 2011) and were found to depend on protein synthesis in one study (Xu et al., 1998), although their rapid onset (<10 min) and the fact that they occur independent of increases in corticosteroid level almost precludes a GR-dependent genomic effect.

### C. The Underlying Mechanism

The enhanced mEPSC frequency reported for rapid corticosteroid actions clearly requires MRs (Karst et al., 2005, 2010; Olijslagers et al., 2008; Qiu et al., 2010; Pasricha et al., 2011). The suppression of mEPSC or enhancement of sIPSC frequency, via NO or endocannabinoid, seems to involve GRs (Di et al., 2003, 2005, 2009; Hu et al., 2010; Karst et al., 2010), although mifepristone was usually ineffective, and solid proof for a role of the GR gene was provided only in one study (Karst et al., 2010). The inhibitory effects observed in the CA1 area in a slightly later time window after stress or corticosterone application (i.e., after approximately 20 min) were reported to be blocked by mifepristone, pointing to GR involvement (Xu et al., 1998; Tse et al., 2011), and could be overcome by serotonergic agents (Shakesby et al., 2002). Some care needs to be taken in the interpretation of effects with very high corticosteroid concentrations (e.g., Vidal et al., 1986; Liu et al., 2007), because ethanol (in which corticosterone is dissolved) is also known to acutely reduce NMDA currents (Peoples et al., 1997) and to decrease mEPSC frequency and LTP of evoked EPSCs in hippocampal cells via enhancement of endocannabinoid levels (Basavarajappa et al., 2008).

Whenever tested, steroids conjugated to BSA were as effective in mediating the rapid effects as the native hormone (Di et al., 2003; Karst et al., 2005; Liu et al., 2007; Hu et al., 2010; Pasricha et al., 2011), suggesting that the receptor is located in the membrane. Electron microscopic proof for such membrane location is still scarce (Johnson et al., 2005; Prager et al., 2010), and biochemical isolation of a "membrane receptor," unlike earlier success in amphibian brain (Orchinik et al., 1991, 1992; Rose et al., 1993), has not yet been convincingly demonstrated in mammalian brain tissue. The pharmacological profile of these presumed membrane-located receptors is different from that described for nuclear MR and GR. For example, inhibitory effects purportedly mediated by GRs are not always sensitive to mifepristone (Di et al., 2003; Hu et al., 2010), and the dose of corticosterone required to induce rapid increases in mEPSC frequency of CA1 cells is 10-fold higher than expected for an MR-dependent phenomenon (Karst et al., 2005). These deviations in pharmacological profile

are not unprecedented (Orchinik et al., 1991; for review, see Lösel and Wehling, 2008). They may point to the existence of a different receptor molecule—such as the case for some rapid effects by estrogens (Prossnitz et al., 2008)—but could also be explained by the constraints imposed by the membrane localization and, for example, the inability of chaperones to associate with the receptor.

How can MRs or GRs be translocated to the plasma membrane instead of the nucleus? Very little is known about corticosteroid receptors, in contrast to the mechanisms behind regulation of the membrane associated estrogen receptor  $\alpha$  (ER $\alpha$ ). ER $\alpha$  was shown to be inserted into the membrane via two mechanisms: binding to caveoline-1 and palmitoylation of the receptor (Accoccia et al., 2005; Pedram et al., 2007). The insertion and internalization are very dynamic processes, as was demonstrated by Dominguez and Micevych (2010). Both insertion and internalization peaked within 1 h after estradiol treatment. GR and MR also bind to caveoline-1 (Matthews et al., 2008; Pojoga et al., 2010), although it is presently unclear whether this protein is involved in trafficking of corticosteroid receptors to the plasma membrane of neurons. The GR has a conserved palmitoylation motif, as opposed to the MR (Pedram et al., 2007). For the GR, it is therefore plausible that trafficking to neuronal membranes could take place via a mechanism comparable with that for the ER $\alpha$ , but it is less clear how MRs could be incorporated in the membrane.

#### D. Behavioral Relevance

It has been argued extensively that rapid corticosteroid actions on cellular activity in the PVN contribute to rapid negative feedback regulation of HPA axis activity after stress (Tasker et al., 2006; Tasker and Herman, 2011). In this respect, it seems very likely that the endocannabinoid-dependent suppression of mEPSC frequency in the PVN occurs secondary to activation of the axis, similar to what has been observed in the BLA (Karst et al., 2010); after all, a rapid negative feedback function is meaningful only in the light of earlier activation. The rapid inhibitory effect in the BLA and the excitatory effect in the CA1 region possibly also contribute to this negative feedback, given the stimulatory and suppressive projections, respectively, of these areas to the PVN (Ulrich-Lai and Herman, 2009).

However, rapid corticosteroid actions on electrical activity may also play a role in higher cognitive processes. In the 1990s, MRs were already found to be important for the appraisal of novel situations and selection of response strategies, thus promoting acquisition of important information (Oitzl and de Kloet, 1992; de Kloet et al., 1999); this MR function seems to require the presence of limbic system-associated membrane protein (Qiu et al., 2010). It has been proposed that nongenomic actions via MR favor a shift toward simple learning strategies, which form a good behavioral alternative at

the short term (Schwabe et al., 2007, 2010a,b). MRs are also important for control of emotional arousal and adaptive behaviors, because this is lost in the absence of forebrain MR, so that anxiety-related responses remain augmented (Brinks et al., 2009). In line with this supposed adaptive role of MR, administration of an MR antagonist before training in a contextual fear conditioning paradigm interfered with adequate memory formation (Zhou et al., 2010) (Fig. 7). It is noteworthy that administration of the antagonist immediately after the learning trial was ineffective, indicating that appropriate MR activation during a restricted time window linked to acquisition of the task is important for optimal performance. A highly comparable role of MRs (but not GRs) was observed during reexposure to the aversive environment (Zhou et al., 2011), a situation in which stress hormone levels rise in association with the (earlier) learning context and promote behavioral performance. Re-exposure to a conditioned stressful environment was found to be associated with a higher likelihood to induce LTD (Hugues et al., 2003), which may be due to metaplastic changes in the circuit (see section III).

Administration of stress or corticosteroids out of context before retention of earlier learned information is known to interfere with memory performance through a nongenomic pathway (de Quervain et al., 1998; Sajadi et al., 2006). This effect was shown to involve a nongenomic MR component (Khaksari et al., 2007) (Fig. 7), although interaction with other stress hormones is necessary to accomplish the full effect. The rapid depotentiation of LTP and shift toward LTD reported when animals are exposed to a (stressful) novel environment possibly plays a role in this phenomenon (Xu et al., 1997; Manahan-Vaughan and Braunewell, 1999; Yang et al., 2006; Hirata et al., 2009), although there is evidence that this is GR- rather than MR-dependent (Xu et al., 1998).

Two recent studies give insight into how glucocorticoids may promote consolidation of information in an intermediate time domain (approximately 20 min after stress), through protein-protein interactions. Thus, in the dentate gyrus acute stress starts a cascade in which ERK1/2 is phosphorylated, leading within 15 min to activation of the nuclear kinases MSK (mitogen- and stress-activated kinase)-1 and Elk-1 (Gutiérrez-Mecinas et al., 2011). This in turn results in histone acetylation and induction of the immediate early genes *c-fos* and *Egr-1*. Histone acetylation via nongenomic actions of GR on phosphorylated cAMP response element-binding protein in the insular cortex was found to be important for object recognition, whereas such a process in the hippocampus plays a role in object location memory in the hippocampus (Roosendaal et al., 2010).

### III. Delayed Effects

Although rapid nongenomic corticosteroid actions have been increasingly acknowledged over the past de-

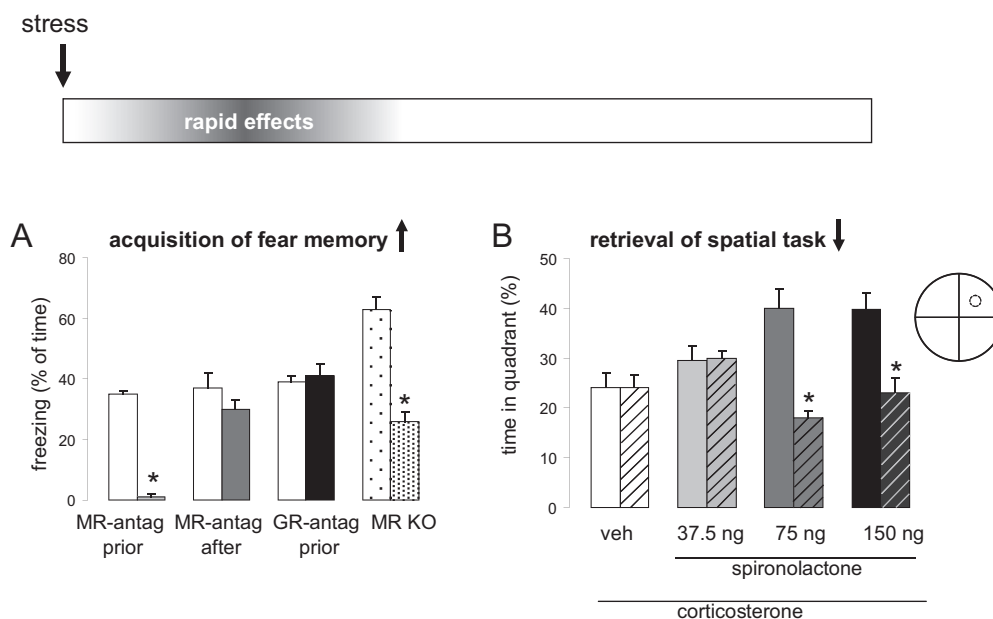


FIG. 7. Rapid effects of corticosteroid hormones on cognitive processing in male rodents. A, administration of the MR antagonist spironolactone 30 min before training in a fear conditioning paradigm reduces freezing behavior of mice tested 3 h later. Injecting spironolactone after the training session is ineffective, indicating that MR activation during training is essential. Administration of a GR-antagonist before training is also ineffective; apparently, these receptors do not play a major role during the learning phase. Forebrain-specific inducible deletion of MR caused less freezing behavior than in wild type; the level of freezing in the latter, however, was higher than in the control animals. Based on data from Zhou et al. (2010). B, during a free-swim trial of rats trained in a Morris water maze paradigm, corticosterone-treated animals (1 mg/kg i.p. 30 min before the test) did not discriminate between the quadrant where the platform was located earlier and the opposite quadrant (hatched bars). Intracerebroventricular pretreatment with spironolactone dose dependently reversed the corticosterone-induced impairment in retrieval. [Modified from Khaksari M, Rashidy-Pour A, and Vafaei AA (2007) Central mineralocorticoid receptors are indispensable for corticosterone-induced impairment of memory retrieval in rats. *Neuroscience* 149:729–738. Copyright © 2007 Elsevier B.V. Used with permission.]

cade, many more studies have revealed hormone actions on neural activity in a much slower time domain, fitting the gene-mediated signaling pathway of nuclear receptors. Areas that have been studied most intensively include the hippocampus, BLA, mPFC, and the ventral tegmental area (Supplemental Table II).

#### A. Slow Modulation of Neural Activity

**1. Hippocampus.** Corticosteroids generally do not change passive or active membrane properties of CA1 pyramidal neurons, such as resting membrane potential, input resistance or characteristics of the action potential, at least not in tissue from ADX animals (e.g., Joëls and de Kloet, 1989; Kerr et al., 1989). One study in ADX animals reported a higher membrane time constant when animals received a low dose of corticosterone (mimicking a condition of predominant MR activation) for several weeks (Beckford et al., 1996). More recently, a clear difference between the ventral-most (20%) and remaining part of the hippocampus was observed with respect to corticosteroid actions (Maggio and Segal, 2009a). In the ventral-most part, corticosterone lowered the threshold for action potential generation, resulting in higher excitability; in the dorsal hippocampus, corticosterone reduced the input resistance and membrane time constant, making cells leakier.

A second category of functional targets concerns the voltage-dependent currents. Sodium and potassium cur-

rents were not much affected by the hormone (Karst et al., 1993; Werkman et al., 1997). However, voltage-dependent calcium currents form a major target for corticosteroid hormones. In particular, the amplitude of sustained high voltage-activated calcium currents was found to be enhanced by glucocorticoid treatment compared with the situation in which predominantly MRs are activated (Kerr et al., 1992; Karst et al., 1994). The enhancement in calcium current amplitude requires protein synthesis and DNA-binding of GR homodimers (Kerr et al., 1992; Karst et al., 2000). Other characteristics of the current, such as voltage dependence or kinetics, were unaltered. The enhanced calcium current amplitude was also observed several hours after stress exposure (Joëls et al., 2003). Through pharmacological isolation of the various current types, it was demonstrated that L- rather than N-type calcium currents are a target for glucocorticoids (Chameau et al., 2007). It is noteworthy that in the absence of corticosteroid hormones (or with reduced levels of GRs), sustained calcium current amplitude was also high (Karst et al., 1994; Hesén et al., 1996), revealing a U-shaped dose dependence (Joëls, 2006). A similar U-shaped dose dependence was also described for CA3 neurons, when correlating circulating corticosteroid levels throughout the day with the calcium current amplitude (Kole et al., 2001). By contrast, dentate granule cells do not show an enhanced calcium current amplitude several hours after they have

been exposed to a pulse of corticosterone (van Gemert et al., 2009), although MR activation was shown to be necessary to restrain calcium influx in ADX animals (Karst and Joëls, 2001).

What happens when hippocampal cells receive amino acid-mediated synaptic input? This has been examined in three ways: 1) by exposing cells to a depolarizing step, to mimic a steady excitatory input; 2) by examining specific glutamatergic pathways; and 3) by studying GABAergic inputs. The results of these experiments are

described below. Corticosteroid actions on other neurotransmitters/modulators, such as noradrenaline, are only briefly addressed in section VI.C.

When CA1 neurons are depolarized, they fire action potentials, but the frequency gradually accommodates during depolarization (Fig. 8). This is caused by activation of a slow calcium-dependent potassium current ( $I_{sAHP}$ ). Upon termination of the depolarization, the  $I_{sAHP}$  is slowly deactivated, which results in a lingering afterhyperpolarization (AHP). Both phenomena (i.e., fir-

## Hippocampus (CA1)

## Amygdala (BLA)

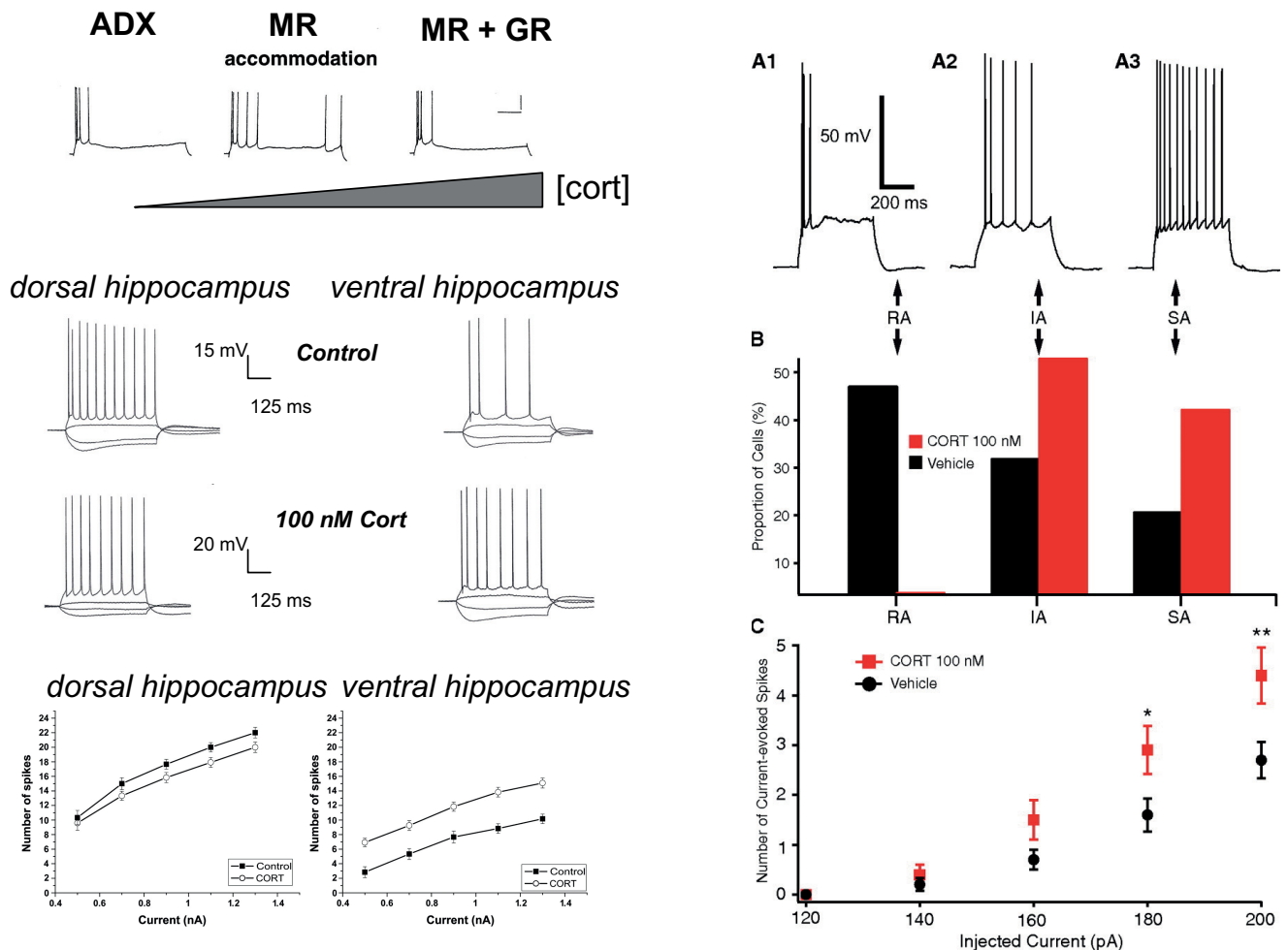


FIG. 8. Gene-mediated effects of glucocorticoids on firing frequency accommodation, which develop with a delay of  $>1$  h. In the hippocampus (left), predominant activation of MR (top) results in more efficient transfer of excitatory information than when corticosterone (cort; Cort; CORT) is absent (adrenalectomy; ADX). When corticosteroid levels rise, GRs become activated in addition to MRs. This causes again a stronger accommodation of the firing frequency, illustrating the U-shaped dose dependence. The opposite effect is seen in the ventral-most part of the hippocampus (bottom), where a high dose of corticosterone (sufficient to activate GRs as well as MRs) increases the number of spikes during a brief depolarization. The latter is comparable with what was reported for the basolateral amygdala (BLA, right). The proportion of cells with poor firing frequency accommodation was much higher after treatment of slices with a high dose of corticosterone. In agreement, more spikes were observed during a depolarizing pulse  $>1$  h after corticosterone treatment than after vehicle treatment. Overall, these results show that glucocorticoids slowly reduce the likelihood that excitatory information is transferred through most of the hippocampal CA1 area, but increases excitability in the ventral-most hippocampal area as well as the BLA. [Modified from Joëls M and de Kloet ER (1990) Mineralocorticoid receptor-mediated changes in membrane properties of rat CA1 pyramidal neurons in vitro. *Proc Natl Acad Sci USA* **87**:4495–4498. Copyright © 1990 National Academy of Sciences, U.S.A.; Maggio N and Segal M (2009) Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. *J Neurosci* **29**:2857–2866. Copyright © 2009 Society for Neuroscience; Maggio N and Segal M (2009) Differential modulation of long-term depression by acute stress in the rat dorsal and ventral hippocampus. *J Neurosci* **29**:8633–8638. Copyright © 2009 Society for Neuroscience; and Duvarci S and Paré D (2007) Glucocorticoids enhance the excitability of principal basolateral amygdala neurons. *J Neurosci* **27**:4482–4491. Copyright © 2007 Society for Neuroscience. All used with permission.]

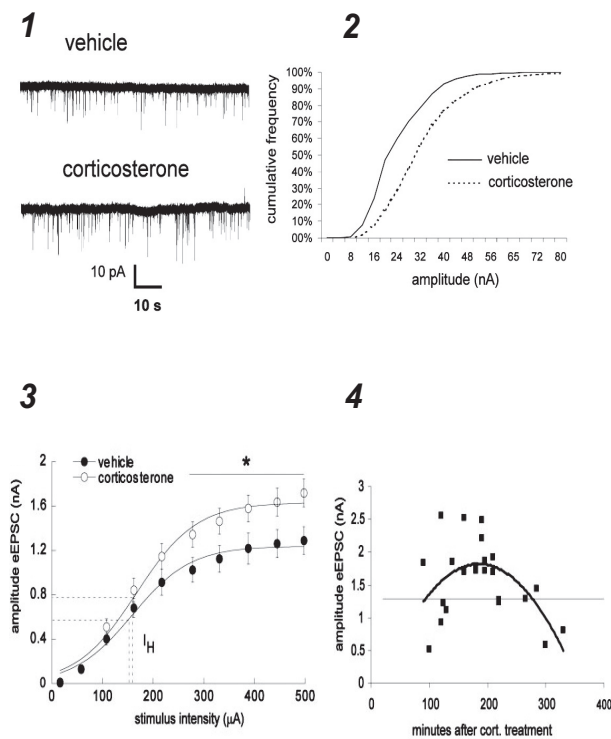


ing frequency accommodation and AHP) will not affect the likelihood of evoking a single spike upon depolarization but reduce the transfer of multiple spikes. High levels of corticosterone or glucocorticoids were found to enhance the amplitude of the  $I_{SAHP}$  and AHP in CA1 pyramidal neurons, resulting in fewer spikes upon depolarization (Joëls and de Kloet, 1989; Kerr et al., 1989; Liebmann et al., 2008) (Fig. 8); this differs from the situation of predominant MR activation (such as occurs under rest), which is characterized by more spikes during a depolarizing pulse than in the absence of steroids (Joëls and de Kloet, 1990), reflecting the same U-shaped dose dependence as observed with respect to calcium current amplitude. Similar effects were also seen in the CA3 area (Kole et al., 2001). The onset of the corticosterone-dependent modulation in firing frequency is slow and requires protein synthesis (Karst and Joëls, 1991). The ventral-most part of the hippocampus reacts differ-

ently to a high dose of corticosterone than the dorsal part, showing reduced firing frequency accommodation and more spikes upon depolarization (Maggio and Segal, 2009a) (Fig. 8).

At the level of single synapses, corticosteroids change glutamatergic transmission in a manner sharing characteristics of long-term potentiation. In CA1 and cultured hippocampal neurons, a pulse of corticosteroids enhanced the amplitude but not frequency of mEPSCs recorded several hours after corticosteroid exposure, via GRs (Karst and Joëls, 2005; Martin et al., 2009) (Fig. 9). This concurs with a slow GR-dependent increase in surface expression of GluA2 subunits, a process requiring protein synthesis and occluding chemically induced LTP (Groc et al., 2008; Martin et al., 2009). The effects on mEPSC amplitude peaked between 150 and 200 min and were not seen earlier than 1 h after starting with corticosterone delivery (Karst and Joëls, 2005; Groc et

## A Hippocampus (CA1)



## B Prefrontal cortex

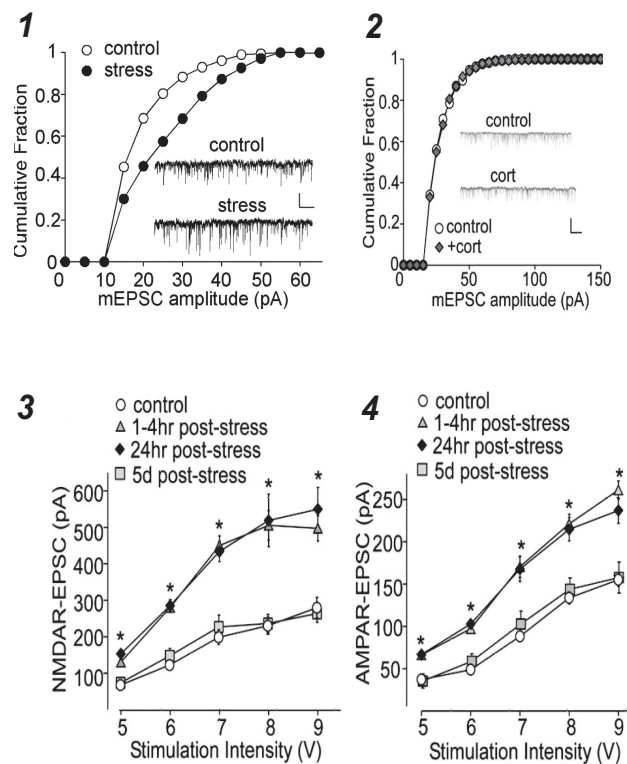


FIG. 9. Slow gene-mediated glucocorticoid effects on glutamatergic transmission in male rodents. A, several (1–4) hours after exposure of hippocampal slices to a brief pulse of corticosterone, the amplitude of mEPSCs is enhanced (1). This is also reflected in the cumulative frequency distribution of mEPSC amplitudes (2). Synaptically evoked EPSCs were also enhanced in amplitude (3), but only in a restricted time window after corticosterone exposure (4), approximately 3 to 4 h after treatment. [Modified from Karst H and Joëls M (2005) Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. *J Neurophysiol* **94**:3479–3486. Copyright © 2005 The American Physiological Society. Used with permission.] B, a similar enhancement in mEPSC amplitude has been reported for prefrontal neurons in the prefrontal cortex after stress exposure, as illustrated by the cumulative distribution of mEPSC amplitudes (1). The enhancement in mEPSC amplitude after stress was not observed when the function of serum and glucocorticoid kinase 1 was genetically reduced (2). Both the evoked NMDA (3) and AMPA (4) receptor-mediated synaptic responses were found to be enhanced in a period of 1 to 4 h after stress, as well as 24 h later, but not 5 days after stress. [Modified from Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, and Yan Z (2009) Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc Natl Acad Sci USA* **106**:14075–14079. Copyright © 2009 National Academy of Sciences, U.S.A. Used with permission; and Yuen EY, Liu W, Karatsoreos IN, Ren Y, Feng J, McEwen BS, and Yan Z (2011) Mechanisms for acute stress-induced enhancement of glutamatergic transmission and working memory. *Mol Psychiatry* **16**:156–170. Copyright © 2011 Nature Publishing Group. Both used with permission.]

al., 2008; Martin et al., 2009). It is noteworthy that inhibitory signals (i.e., sIPSC amplitude) are also enhanced in the dorsal hippocampus via GRs (Maggio and Segal, 2009a); in the ventral hippocampus, an MR-dependent reduction in sIPSC frequency was reported. The effects on sIPSCs started 25 min after onset of corticosterone administration, peaking at 55 min. This is in a much more rapid time domain than the effects on excitatory transmission.

Synaptically evoked responses recorded extracellularly in the various hippocampal areas were usually not affected by corticosterone or stress (Pavlidis et al., 1996; Bramham et al., 1998; Zhou et al., 2000; Yamada et al., 2003; Chen et al., 2010), although enhancements (Avital et al., 2006; Kavushansky et al., 2006) or reduced activity (Hirata et al., 2008) were reported in a few studies. Corticosteroid actions on excitatory or inhibitory transmission are restricted to a limited number of synapses and thus not discernible at a more general level, similar to what has been found after learning (Whitlock et al., 2006). It may also relate to the dose of corticosterone that was used or the intensity of the stressor. This is suggested by a study of Rey et al. (1987), showing that low doses of corticosterone enhance the amplitude of the population spike evoked by synaptic stimulation in the CA1 area, whereas high doses decreased the population spike.

**2. Basolateral Amygdala.** Slow corticosteroid actions on principal cells in the BLA resemble the responses in ventral rather than dorsal hippocampal CA1 neurons. Thus, a brief pulse of corticosterone resulted some hours later in an increased input resistance and more depolarized membrane potential (Duvarci and Paré, 2007). This was seen only in a subpopulation of neurons with very high input resistance, not in cells with a lower resistance (Duvarci and Paré, 2007; Liebmann et al., 2008). In BLA neurons, firing frequency accommodation and AHP amplitude were reduced or unaffected by corticosterone, whereas dorsal CA1 neurons measured in the same study showed a clear enhancement (Duvarci and Paré, 2007; Liebmann et al., 2008) (Fig. 8). It was argued that low expression of  $\alpha 1.3$  calcium channel subunits in the BLA contributes to the lack of modulation in  $I_{sAHP}$  (Liebmann et al., 2008), despite a clear GR-dependent increase in sustained high voltage-activated calcium currents (Karst et al., 2002). Corticosterone furthermore shifted the reversal potential of GABA receptor-linked chloride channels to more depolarized potentials, causing a reduced inhibitory postsynaptic potential amplitude with synaptic stimulation. Overall, these changes are expected to cause a slow enhancement in excitability after a single pulse of corticosterone. This was indeed observed at the field potential level after elevated platform stress or corticosterone injection, both in vivo and in vitro (Kavushansky and Richter-Levin, 2006; Kavushansky et al., 2006), although not 24 h after restraint stress (Rodríguez Manzanera et al., 2005).

**3. Medial Prefrontal Cortex.** Glutamatergic transmission in layer V prelimbic neurons also seems to be slowly enhanced by corticosterone and stress, similar to what has been described in the CA1 area (Fig. 9). Thus, in cells recorded >2 h after exposure to stress, the amplitude of EPSCs via AMPA or NMDA receptors was increased (Yuen et al., 2009, 2011; Liu et al., 2010). In parallel, the mEPSC amplitude but not frequency was enhanced, as was the surface expression of AMPA and NMDA receptor subunits. The slow corticosteroid effects on glutamatergic transmission are mediated by GRs.

A high dose of corticosterone (presumably activating both MR and GR) reduced mIPSC frequency but not amplitude in layer V prelimbic neurons. In view of the enhanced paired pulse depression, this effect seems to be caused by a reduction in GABA release mediated by endocannabinoids (Hill et al., 2011).

**4. Ventral Tegmental Area.** Several studies show increased firing rates of dopaminergic neurons and LTP-like changes after corticosterone administration or stress exposure. Low levels of corticosterone were reported to enhance basal firing rate and glutamate-induced burst firing of presumed dopaminergic cells (Overton et al., 1996). Although this would argue for involvement of MRs, Cho and Little (1999) found effects on NMDA or AMPA induced cell firing that could be blocked with the GR-antagonist mifepristone. Restraint stress (Anstrom and Woodward, 2005; Anstrom et al., 2009) and foot shock (Brischoux et al., 2009) also increased burst firing, the latter only in the ventral tegmental area; inhibition after foot shock was observed in dorsal cells. It is noteworthy that the effect of restraint stress persisted for >24 h. This may explain why Saal et al. (2003) observed an enhanced AMPA/NMDA ratio 24 h after forced swim stress, an effect that was blocked by mifepristone and required GluA1 subunits to develop (Dong et al., 2004).

### B. Slow Modulation of Synaptic Plasticity

Numerous studies have shown that the induction of LTP in the CA1 hippocampal area is severely hampered several hours after administration of corticosterone in vitro or in vivo or after exposure to stress, especially stress of an uncontrollable nature (Foy et al., 1987; Shors et al., 1989; Diamond et al., 1992; Shors and Thompson, 1992; Diamond and Rose, 1994; Kim et al., 1996, 2001; Zhou et al., 2000; Xiong et al., 2004; Kavushansky et al., 2006; Hirata et al., 2008, 2009; Li et al., 2008; Yang et al., 2008a; Czakoff and Howland, 2010; Ryan et al., 2010; Ooishi et al., 2012; for review, see Kim and Diamond, 2002) (Supplemental Table II). This is a GR-dependent phenomenon (Pavlidis et al., 1996); depends on NMDA-receptor mediated transmission (Kim et al., 1996); depends on phosphatidylinositol 3-kinase (Yang et al., 2008b); requires the basolateral amygdala, particularly ERK1/2 phosphorylation (Kim et al., 2001; Yang et al., 2008a); and can be rescued by estradiol

administration *in vitro* (Ooishi et al., 2012). Enhanced LTP was reported for selective MR activation (Pavlidis et al., 1996), particularly in the ventral-most part of the CA1 hippocampal area (Maggio and Segal, 2007, 2009b). GR activation not only impairs LTP induction but also slowly promotes LTD (Xiong et al., 2004; Yang et al., 2004, 2006; Kim et al., 2006; Wong et al., 2007; Gao et al., 2008; Niehusmann et al., 2010). Spillover of glutamate as a result of inadequate reuptake, thereby activating extrasynaptic GluN2B subunits, seems crucial (Yang et al., 2005; Wong et al., 2007). Stress also enhances a metabotropic glutamate receptor-dependent type of LTD (Chaouloff et al., 2007).

Reduced LTP after stress via GRs was also observed for the mossy fiber projection to the hippocampal CA3 region, requiring the conversion of cAMP into adenosine (Chen et al., 2010). Likewise, stress was found to impair LTP in the projection from the ventral subiculum or basolateral amygdala to the prelimbic area, again involving GRs (Maroun and Richter-Levin, 2003; Rocher et al., 2004; Mailliet et al., 2008; Qi et al., 2009; Richter-Levin and Maroun, 2010). The latter was not seen when the BLA had already been stimulated earlier or when animals had recently experienced stress (Richter-Levin and Maroun, 2010), another example of metaplasticity. In contrast to these findings, most studies agree that stress facilitates LTP in projections to the (baso)lateral amygdala, originating in the entorhinal cortex, external capsule or prelimbic cortex (Vouimba et al., 2004; Rodríguez Manzanares et al., 2005; Kavushansky et al., 2006; Maroun, 2006; but see Kavushansky and Richter-Levin, 2006).

Results in the dentate gyrus have been somewhat ambiguous. There is evidence that LTP is enhanced via MR activation and reduced or even turned into LTD after GR activation (Pavlidis et al., 1993, 1994, 1995; Smriga et al., 1996; Yamada et al., 2003; Avital et al., 2006; Kavushansky et al., 2006; Vouimba et al., 2007; Yarom et al., 2008), similar to what has been described for the CA1 area. Abrari et al. (2009) reported facilitated induction of LTP in association with improved memory when rats were treated with a moderately high dose of corticosterone directly after training in a fear conditioning paradigm. However, others found no change after inescapable or cold stress (Shors and Dryver, 1994; Vouimba et al., 2004) or could not link stress-induced changes in LTP/LTD to known corticosteroid receptor types (Spyrka et al., 2011). Stress exposure after LTP induction has also been studied in the dentate gyrus. Low-stress conditions such as handling of the animal were found to impair weak LTP, whereas exposure to a high-stress condition (forced swim) prolonged the late phase of LTP via an MR-dependent process (Korz and Frey, 2003). The latter required an intact BLA (Korz and Frey, 2005). The relevance of the BLA for LTP in the dentate was also evident from work by Akirav and Richter-Levin (1999, 2002). They showed that stimulation of

the BLA in the short term facilitates LTP in the perforant path-dentate projection but in the long-term impairs LTP. The latter was mimicked by stress exposure, and stress interfered with BLA-induced facilitation of LTP in the dentate gyrus. The modulatory effects of BLA stimulation on LTP in the dentate gyrus depends on noradrenergic and corticosteroid actions in the BLA.

### *C. Underlying Mechanisms and Functional Consequences*

One striking observation is that corticosterone via GRs slowly promotes glutamatergic transmission (at least in part of the synapses), involving phosphorylation of specific AMPA-receptor subunits (Caudal et al., 2010). As a consequence, mEPSC amplitude is enhanced in both the hippocampus and mPFC (Karst and Joëls, 2005; Yuen et al., 2009), and surface expression of GluA2 subunits increased (Groc et al., 2008; Martin et al., 2009; see Krugers et al., 2010); stimulation of glutamate release via a presynaptic SNARE-dependent mechanism (Musazzi et al., 2010; for review, see Popoli et al., 2012) may also contribute to the overall higher glutamatergic tone, but whether these effects are due to a genomic action has not been proven yet. The gradually developing enhanced glutamatergic transmission after stress shares properties with those seen after LTP (Ho et al., 2011). This would be in line with the view that stress induces LTP-like phenomena (Shors and Dryver, 1994; Saal et al., 2003; Diamond et al., 2004; Huang et al., 2005; Karst and Joëls, 2005; Groc et al., 2008), partly impinging on the same signaling pathways, thus leading to occlusion (Groc et al., 2008). Prior activation of these pathways would raise the threshold for subsequent LTP induction and facilitate induction of LTD, which was indeed consistently observed in nearly all brain regions after stress; notable exceptions are the ventral-most part of the hippocampus and the BLA. This follows the principles of metaplasticity as it was proposed for LTP (Bear and Abraham, 1996). Metaplasticity in relation to stress was indeed mentioned over a decade ago (Kim and Yoon, 1998), and experimental evidence for metaplasticity is accumulating, both in the rapid time domain (Karst et al., 2010) and in the genomic window (Richter-Levin and Maroun, 2010).

Exactly how these slow GR-dependent effects on glutamatergic transmission develop is not fully understood. In the mPFC, evidence was supplied for a role of the serum and glucocorticoid-inducible kinase SGK, which subsequently regulates the activity of Rab4, a small GTPase, controlling recycling of, for example, GluA2 subunits between the endosome and plasma membrane (Liu et al., 2010; Yuen et al., 2011). An interesting analogy can be found in the formation of fear memory. A recent article described that a single fear stimulus promotes GluA2-containing AMPA receptors in mouse cerebellar stellate cells via noradrenaline (Liu et al., 2010). The subsequent rise in intracellular calcium and hence

activation of the calcium-sensitive ERK/mitogen-activated protein kinase signaling pathway triggered new GluA2 gene transcription over the course of hours and thus a more permanent shift toward GluA2-containing receptors in the membrane. Although the specific properties of this process clearly differ from what is seen with stress (i.e., different area, no obvious transcriptional regulation of GluA2 by stress in the hippocampus), it nevertheless shows that early events may trigger a cascade developing into more lasting changes. Along these lines, rapid effects of corticosterone could lead to more glutamate release and associated postsynaptic changes, which subsequently through a slower GR-dependent mechanism promote synaptic localization of GluA2 subunits. In this model, those synapses activated during the stressful event and exposed to elevated levels of stress hormones will be strengthened for a considerable time, raising the threshold for subsequent synaptic strengthening. This could protect strengthened synapses from retrograde interference and promote higher cognitive processes in the PFC and dorsal hippocampus such as consolidation of relevant contextual information. There is indeed abundant evidence that stress/glucocorticoids either directly (Oitzl and de Kloet, 1992; Oitzl et al., 2001) or conditionally (Roozendaal et al., 2004) promote consolidation of spatial information, as well as exert beneficial effects on working memory (Yuen et al., 2009), via a GR-dependent mechanism (Fig. 10).

The strengthening of certain synapses does not imply that all excitatory information reaching hippocampal or mPFC cells some hours after stress is facilitated; the contrary is true. For instance, a larger spike frequency accommodation and AHP amplitude (Joëls and de Kloet, 1989; Kerr et al., 1989; Kole et al., 2001) could serve as a brake to steady excitatory inputs, particularly when unrelated to the stressful event. The increased AHP amplitude probably develops secondary to enhanced calcium influx. The latter pathway is one of the best resolved examples how GR activation can change neuronal function: GR-homodimers bind to DNA of responsive genes (Karst et al., 2000) and transcriptionally up-regulate many genes (Morsink et al., 2006b), including the  $\beta 4$  calcium channel subunit (Chameau et al., 2007; van Gemert et al., 2009), resulting in higher  $\beta 4$  protein levels (van Gemert et al., 2009) and a higher availability of L-type calcium channels in the membrane (Chameau et al., 2007).

The dorsal CA1 and CA3 hippocampal regions as well as the prelimbic PFC seem to respond in a very comparable manner to stress or corticosterone acting via GRs. This clearly differs from the ventral-most CA1 region, BLA, and, to a lesser degree, the dentate gyrus. In the BLA, GR-dependent pathways maintain the rapid increase in mEPSC frequency induced by corticosterone; in the ventral hippocampus, sIPSC frequency is reduced. In both regions, LTP is enhanced by stress or corticosterone, and mechanisms to restrain responses to excit-

atory transmission, such as firing frequency accommodation, are not in place. This suggests that behavioral (e.g., emotional) aspects involving activation of these regions have a prolonged window in time for encoding. This could contribute to the fact that cortisol generally promotes the memory of emotional rather than neutral aspects of information (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006; van Stegeren et al., 2010; but see Abercrombie et al., 2003 and Rimmele et al., 2003, who report effects on neutral information).

Delayed effects of stress or corticosterone administration are generally mediated by GRs. Notable exceptions are the excitatory effects observed in the ventral-most part of the CA1 hippocampal area (Maggio and Segal, 2007, 2009a,b), and facilitating effects on LTP (be it induction or maintenance of late-phase LTP) in the dentate gyrus (Pavlidis et al., 1993, 1994; Korz and Frey, 2003, 2005; Avital et al., 2006). Other than that, the importance of intracellular MR occupation is only revealed against an ADX background. Under these conditions, actions via intracellular MRs are important for maintenance of excitability and confining calcium influx (Karst and Joëls, 2001), most likely contributing to a viable state of the cells. Most MR-mediated actions are opposite those exerted via GRs, with regard not only to the slow gene-mediated processes but also to rapid nongenomic actions (Karst et al., 2010).

#### IV. Chronic Corticosteroid Exposure

Although brief exposure to stress—as discussed in sections II and III—usually serves an adaptive role, chronic exposure to stress or high levels of corticosterone is considered to be less beneficial. In humans, prolonged episodes of stress—particularly when experienced as uncontrollable and unpredictable—have been reported to increase the vulnerability to all kind of diseases in the genetically predisposed, including psychiatric and neurological illnesses (see section VI.D).

Many animal models have been developed to examine the effects of chronic stress in more detail under very controlled experimental conditions. In these models, animals are usually exposed to 3 weeks of restraining once per day or a mixture of mild unpredictable physical or psychological stressors (Supplemental Table III). A model that is almost exclusively based on psychological stressors involves exposure of animals to repetitive social defeat, sometimes in combination with isolated housing. Some studies have made use of repeated corticosterone injections, to probe the contribution of corticosteroids in comparison to other stress mediators. Because these models differ from each other in many respects, including the neuroendocrine properties, such as HPA-axis reactivity, we have categorized the available literature in Supplemental Table III primarily on the basis of the paradigm that was used.

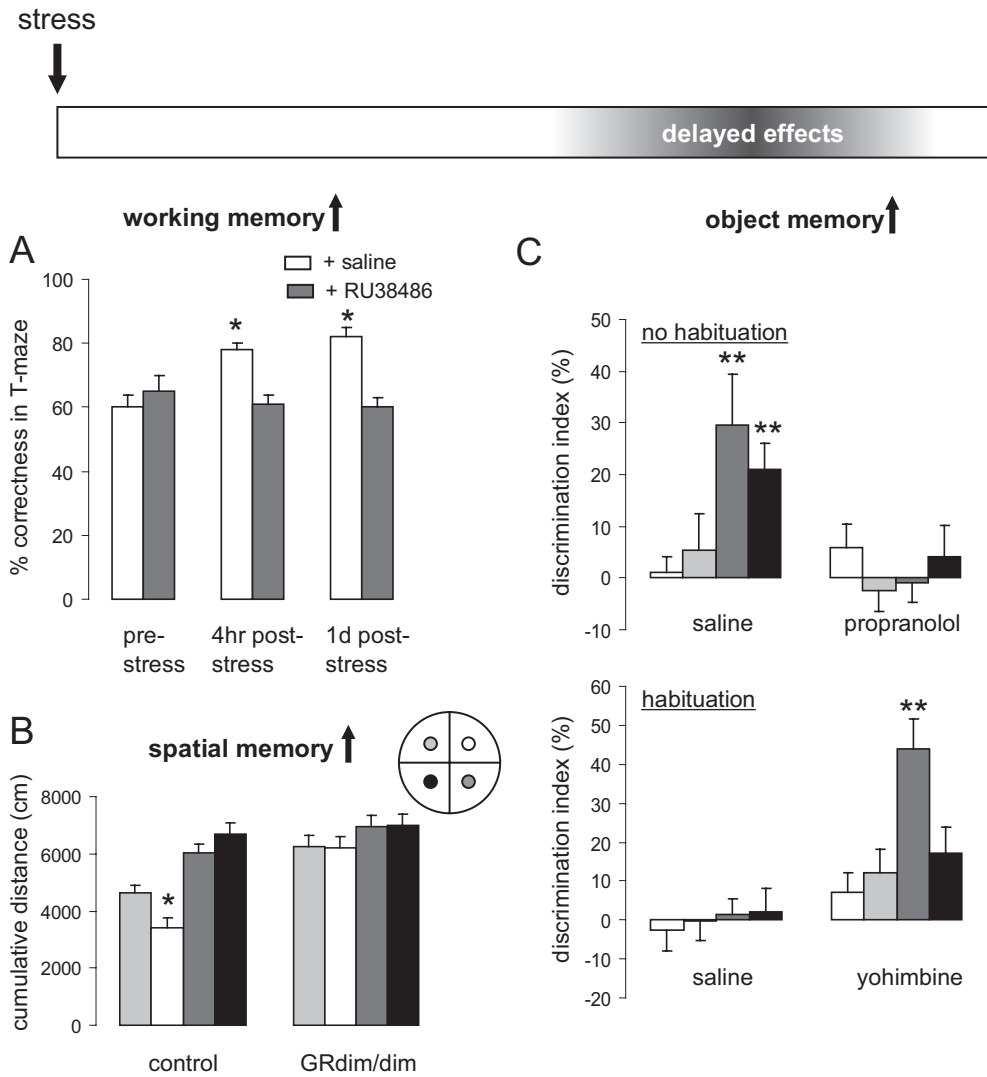


FIG. 10. Slow gene-mediated effects of corticosteroid hormones on cognitive processing. A, young male rats were forced to swim for 20 min. Working memory performance (T-maze delayed alternation task) was tested before a stressor or 4 h or 1 day after stress exposure. Working memory performance was improved after stress. This was blocked by the glucocorticoid receptor antagonist RU38486 (10 mg/kg injected 30 min before stress exposure), indicating that the poststress improvement in working memory performance is carried by glucocorticoid receptors. [Modified from Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, and Yan Z (2009) Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc Natl Acad Sci USA* **106**:14075–14079. Copyright © 2009 National Academy of Sciences, U.S.A. Used with permission.] B, in control male mice, the cumulative distance (in cm) during a free swim trial was shortest for the earlier trained platform, whereas no distinction between the earlier trained location and other quadrants was observed in mice carrying a point mutation in the DNA-binding domain of the glucocorticoid receptor (GRdim/dim), precluding DNA-binding of the receptor homodimers. This supports an important role of gene-mediated glucocorticoid actions on spatial memory. [Modified from Oitzl MS, Reichardt HM, Joëls M, and de Kloet ER (2001) Point mutation in the mouse glucocorticoid receptor preventing DNA binding impairs spatial memory. *Proc Natl Acad Sci USA* **98**:12790–12795. Copyright © 2001 National Academy of Sciences, U.S.A. Permission for re-use not required.] C, in nonhabituated male rats (top), the discrimination between an earlier seen object and a new object was dose dependently increased by corticosterone subcutaneously administered (0, 0.3, 1.0, or 3.0 mg/kg, from left to right) directly after training. This was not seen when the  $\beta$ -adrenoceptor antagonist propranolol was coadministered (3 mg/kg), suggesting that corticosteroid actions are conditional on  $\beta$ -adrenoceptor activation. This was confirmed in habituated animals (bottom), where noradrenaline levels are presumably less elevated during the test. In these animals, corticosterone was ineffective but did improve memory when coadministered with the  $\alpha$ 2-adrenoceptor antagonist yohimbine. [Modified from Roozendaal B, Okuda S, Van der Zee EA, and McGaugh JL (2006) Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc Natl Acad Sci USA* **103**:6741–6746. Copyright © 2006 National Academy of Sciences, U.S.A. Used with permission.]

Many studies demonstrated changes in dendritic complexity after exposure to chronic stress and/or overexposure to corticosteroid hormones, regardless of the paradigm that was used (for reviews, see McEwen and Magarinos, 1997; Fuchs and Bode, 2006; Holmes and Wellman, 2009; Roozendaal et al., 2009; Shansky and Morrison, 2009). In most areas (e.g., CA3 or infralimbic cortical pyramidal neurons), dendritic complexity was found to

be reduced. However, increased dendritic complexity has also been reported in principal cells of the BLA and the orbitofrontal cortex (for review, see Roozendaal et al., 2009). Moreover, there is evidence that chronic exposure to high levels of stress hormones affects spine density. In general, spine density is increased by chronic stress in those areas where dendritic complexity is also increased (e.g., in the basolateral amygdala; Mitra et al.,

2005) and decreased if dendritic complexity is decreased (e.g., in neurons of the PFC) (Li et al., 2011). Besides affecting dendritic complexity, chronic stress has been reported to suppress proliferation, differentiation and survival of progenitor cells in the dentate gyrus (for reviews, see Joëls et al., 2007; Leuner and Gould, 2010; Lucassen et al., 2010), which may or may not be linked to dendritic remodeling in the dentate gyrus (Bessa et al., 2009). Moreover, the expression levels of many molecules involved in neurotransmission—including subunits for glutamate or GABA receptors—are modulated by chronic stress (for review, see McEwen et al., 2007).

All of these changes are expected to affect neural activity. Overall, this led to a theory proposing that chronic stress imposes a condition of increased excitability, at least in the CA3 hippocampal area, which, through excitotoxicity, may lead to dendritic atrophy (McEwen, 1999). The latter could then be interpreted as a “protective” mechanism by which cells, through reduction in the number of their synaptic contacts, would restrain the enhanced excitatory input. In support of this theory, treatment of animals with, for example, NMDA receptor blockers was found to prevent dendritic remodeling in the CA3 area and mPFC (McEwen and Magarinos, 1997; Christian et al., 2011; Li et al., 2011).

According to this theory, enhanced excitatory transmission would precede dendritic retraction rather than occur simultaneously or as a consequence. However, neither experimental nor mathematical evidence seems to support this. In a biologically realistic computational model, Narayanan and Chattarji (2010) demonstrated that dendritic retraction increases input resistance, which is directly translated into higher spiking frequencies in response to both somatic current injections and synaptic inputs. It is noteworthy that studies examining basal neuronal properties or synaptic responses after chronic stress very often find enhanced activity (Supplemental Table III). Thus, in the hippocampus, chronic stress was found to enhance NMDA receptor-mediated EPSCs in CA3 neurons (whereas intrinsic properties were largely unchanged) (Kole et al., 2002, 2004a,b), to reduce the threshold for induction of fEPSPs in the CA1 area (Kerr et al., 1991), and to increase the amplitude of AMPA receptor-mediated synaptic currents in DG granule cells, the latter in combination with only acute exposure to corticosterone (Karst and Joëls, 2003) (Fig. 11). In the dorsomedial PFC, cell-firing activity is enhanced starting 4 days after stress onset, although a reduction is seen in the ventromedial PFC some time later (Lee et al., 2011); in agreement with the latter, 5 to 7 days of restraint or unpredictable stress in young (4 week-old) rats was reported to cause reduction of both AMPA- and NMDA-receptor mediated synaptic responses in pyramidal PFC cells, in association with ubiquitin/proteasome-mediated degradation of GluR1 and NR1 subunits (Yuen et al., 2012). In the nucleus accumbens, brief swim stress enhanced AMPA receptor-mediated mEPSC am-

plitude (Campioni et al., 2009), whereas social defeat caused increased mEPSC frequency in medium spiny neurons (Christoffel et al., 2011). Increased basal firing and reduced afterhyperpolarization was observed in the locus ceruleus after cold stress (Mana and Grace, 1997; Jedema and Grace, 2003). Several studies reported altered GABAergic activity after chronic stress, indirectly causing enhanced excitability in the dentate gyrus (Holm et al., 2011), anterior cingulate cortex (Ito et al., 2010), nucleus accumbens (Wang et al., 2010), and PVN (Verkuyl et al., 2004; Wamsteeker et al., 2010). Nevertheless, some studies reported reduced basal or synaptic activity after chronic stress (Hu et al., 2010; Li et al., 2011; Quan et al., 2011a,b; Zhang et al., 2011). Most studies using field potential recordings found no change in basal synaptic responses (Bodnoff et al., 1995; Gerges et al., 2001; Pavlides et al., 2002; Alfarez et al., 2003; Aleisa et al., 2006a,b,c; Kessal et al., 2006; Krugers et al., 2006; Holderbach et al., 2007; Goldwater et al., 2009; Srivareerat et al., 2009; but Dumas et al., 2010; Tran et al., 2011), possibly because the effects are too subtle to be noticed extracellularly or depend on GABAergic transmission (which is also not well captured with field potential recordings). Overall, nearly all studies demonstrate that several weeks of stress either enhance intrinsic/synaptically evoked cell activity or are ineffective in this respect, regardless of the area under investigation.

This contrasts with the effects of chronic stress on synaptic plasticity. Irrespective of the models that have been used, chronic overexposure to stress hormones has generally been found to reduce the ability to induce or maintain LTP and to enhance the likelihood to induce LTD, even when circulating corticosteroid levels at the time of recording were very low. This was observed for projections to the (dorsal) hippocampal CA1 area (Bodnoff et al., 1995; Gerges et al., 2001; Von Frijtag et al., 2001; Alfarez et al., 2003; Zheng et al., 2004; Aleisa et al., 2006a,b,c; Artola et al., 2006; Krugers et al., 2006; Holderbach et al., 2007; Ma et al., 2007; Srivareerat et al., 2009; Kamal et al., 2010; Sterlemann et al., 2010; Tran et al., 2011), the CA3 area (Kole et al., 2002, 2004; Pavlides et al., 2002; Maggio and Segal, 2011), the PFC (Cerqueira et al., 2007; Goldwater et al., 2009; Lee and Goto, 2011; Lee et al., 2011b; Quan et al., 2011a,b; Zhang et al., 2011), and the bed nucleus stria terminalis (Conrad et al., 2011). The reverse, however, was seen in the ventral-most part of the hippocampus (Maggio and Segal, 2011). The effects in the DG were variable (Gerges et al., 2001; Pavlides et al., 2002; Alfarez et al., 2003; Aleisa et al., 2006a,b,c; Dumas et al., 2010; Spyrka and Hess, 2010), and reduced LTD was observed in the bed nucleus stria terminalis (McElliott et al., 2010) and nucleus accumbens (Wang et al., 2010).

How these chronic stress-induced changes in basal transmission and synaptic plasticity develop is still far from being resolved, in part because it is very difficult to monitor cellular changes over the course of weeks. Some

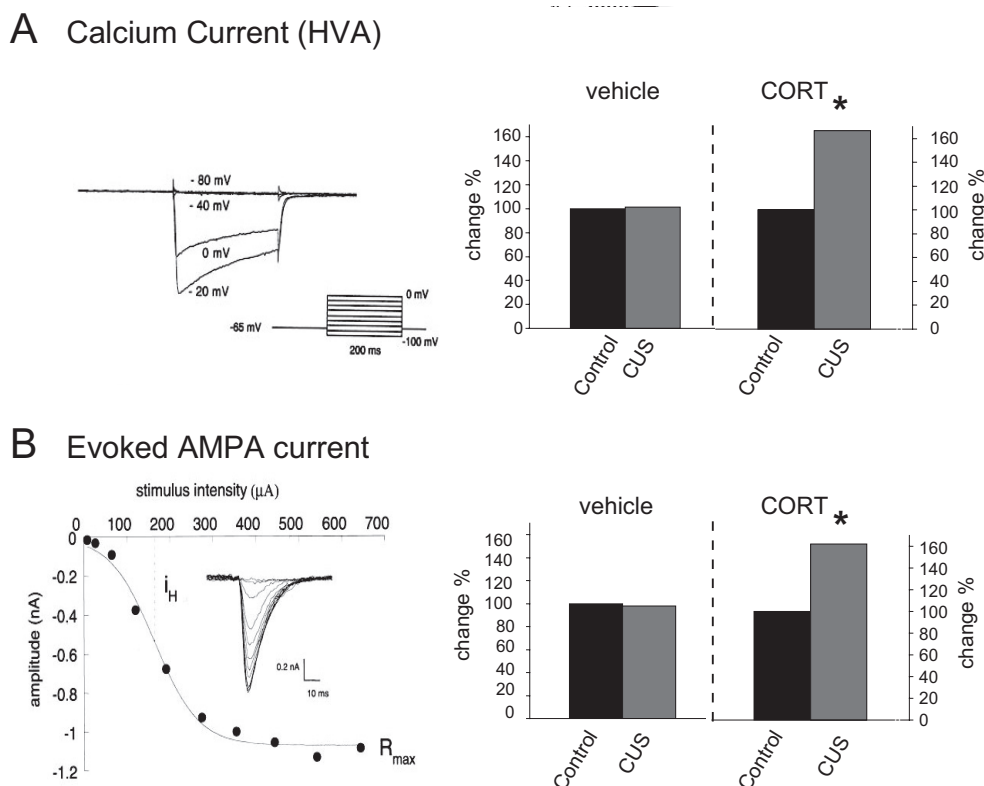


FIG. 11. Effects of chronic stress in the rat dentate gyrus. A, depolarizing voltage steps activate sustained high-voltage activated (HVA) calcium currents in dentate granule cells. Typical traces are depicted on the left, using the protocol as shown in the inset. When the circulating levels of corticosterone (CORT) are low, calcium current amplitude of granule cells is comparable for animals with or without a history of chronic stress (right). However, the influence of chronic stress becomes apparent when tissue is acutely exposed to high levels of corticosterone. Thus, a combination of chronic stress and acute corticosterone exposure (recordings made  $>1$  h after corticosterone administration) results in a significantly enhanced amplitude of the calcium current compared with vehicle-treated slices. Calcium current amplitude of the naive rats was normalized to 100%, in both the vehicle and the corticosterone-treated cells. CUS, chronic unpredictable stress. [Modified from van Gemert NG and Joëls M (2006) Effect of chronic stress and mifepristone treatment on voltage-dependent  $\text{Ca}^{2+}$  currents in rat hippocampal dentate gyrus. *J Neuroendocrinol* 18:732–741. Copyright © 2006 British Society for Neuroendocrinology. Used with permission.] B, a highly similar pattern was observed in granule cells of chronically stressed rats with respect to the synaptically evoked AMPA receptor-mediated responses (left, typical traces shown as inset). Here too, the combination of a history of chronic stress and exposure to corticosterone in vitro resulted in large current amplitudes compared with treatment with only chronic stress or only acute corticosterone. All data were obtained in male rats. [Modified from Karst H and Joëls M (2003) Effect of chronic stress on synaptic currents in rat hippocampal dentate gyrus neurons. *J Neurophysiol* 89:625–633. Copyright © 2003 The American Physiological Society. Used with permission.]

of the above-mentioned studies demonstrated that particular molecules are critical for the electrophysiological changes to occur, such as calcineurin and  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (Aleisa et al., 2006a,b,c), NR2B subunits, inhibitor of nuclear factor- $\kappa\text{B}$  (Christoffel et al., 2011), and brain-derived neurotrophic factor (Zhou et al., 2000; Radecki et al., 2005; Aleisa et al., 2006c). Compounds that prevented or normalized the development of changes in neural activity include nicotine (Aleisa et al., 2006a,b,c), antidepressants (Von Frijtag et al., 2001; Kole et al., 2002, 2004; Kessal et al., 2006; Holderbach et al., 2007; Wang et al., 2010; Holm et al., 2011), ketamine (Li et al., 2011), memantine (Quan et al., 2011), antiglycocorticoids (Krugers et al., 2006; Karst and Joëls, 2007; Spyrka and Hess, 2010), and phenytoin (Zheng et al., 2004), whereas  $\beta$ -amyloid exacerbated the effects of chronic stress (Srivareerat et al., 2009; Tran et al., 2011). However, it is unclear whether these compounds 1) directly interfere with chronic-stress-dependent signaling pathways, 2) tap indirectly into the same pathways, or 3) compensate for/

counteract the effects of chronic stress through independent mechanisms.

Clearly, investigation of the development of electrical activity over time is called for, but this has rarely been done (e.g., Lee et al., 2011). A nice exception is a study by Spyrka and Hess (2010), who examined LTP in the dentate gyrus at 1, 3, 7, 14, and 21 days of restraint (neck) stress. They observed that the induction of LTP was reduced after 3 and 7 days of restraint, but enhanced after 14 or 21 days, through a GR- and MR-dependent mechanism, respectively. Although this time course may be specific for the dentate gyrus, the study illustrates that much information may be lost when investigating animals only at the end of a period of 3 or more weeks. It is noteworthy that the effects of chronic stress on synaptic plasticity under basal—i.e., unstressed—conditions (e.g., in the hippocampal CA1 area) are quite similar to what is seen in naive animals shortly after an acute period of stress. The signaling pathways involved in the latter may give insight in how synaptic plasticity

may become dysregulated on a more permanent basis after chronic stress.

Another aspect that has rarely been addressed is the importance of the circulating corticosteroid levels just before and during recording. For instance, the amplitude of L-type calcium currents in CA1 pyramidal neurons is enhanced after chronic stress compared with control neurons when circulating corticosteroid levels during and several hours before the moment of investigation are low (Karst and Joëls, 2007). However, the current amplitude is low in the stressed compared with control group when measuring 1 to 4 h after a stress-like surge of corticosterone. In dentate granule cells, AMPA receptor-mediated synaptic responses and calcium-current amplitude were increased in chronically stressed animals only in combination with a brief exposure to high levels of corticosterone 1 to 4 h before recording (Karst and Joëls, 2003; van Gemert and Joëls, 2006) (Fig. 11). This indicates that the influence of chronic stress sometimes will become apparent only after the HPA axis has been acutely activated. The extent to which this applies to the articles summarized in Supplemental Table III is unclear, because the issue was usually not specifically addressed. Tissue may have been prepared from animals transported in an unfamiliar cage (causing stress due to novelty) or sacrificed at the peak of the circadian cycle, which is the case, for example, when the animals are maintained on a reversed day-night rhythm (Hu et al., 2010). Regardless, the data indicate that the responsiveness to corticosterone may change depending on the prior history of chronic stress, a phenomenon also observed when animals have been exposed to stress early in life (see section V).

What are the consequences of all these changes in electrical activity after chronic stress for brain function in general? It is a big step from electrophysiological phenomena (frequently examined *in vitro*) to the systems level *in vivo*. By concentrating on electrical activity only, the influence of many other important factors is disregarded. For instance, chronic stress will certainly affect the synthesis, release, and reuptake of essential transmitters such as glutamate and GABA (see, for instance, Grønli et al., 2007; Elizalde et al., 2010; Tordera et al., 2011). The bioavailability of these transmitters is as important for their overall effect as the processes downstream of receptor activation that eventually cause the changes in electrical activity measured with electrophysiological methods.

With respect to global consequences, chronic stress-induced changes in neural activity have in some instances been directly linked to the function of the HPA axis itself, supporting disinhibition or impaired negative feedback of the HPA axis after chronic stress (Verkuyl et al., 2004; Wamsteeker et al., 2010). Although the consequences of chronic stress for various behavioral tasks have been addressed in detail in numerous studies (for reviews, see Shors, 2006; Conrad, 2010; Marin et al., 2011), we here

highlight only those studies combining electrophysiological measurements with behavioral performance. These showed that chronic stress reduces hippocampal synaptic plasticity in parallel with impaired spatial memory, including the reversal learning aspect (Bodnoff et al., 1995; Zheng et al., 2004; Aleisa et al., 2006a; Ma et al., 2007; Quan et al., 2011a,b), even many months after stress exposure (Sterlemann et al., 2010). Chronic stress also exacerbates cognitive decline due to amyloid- $\beta$  treatment (Srivareerat et al., 2009; Tran et al., 2011). Furthermore, working memory (Cerqueira et al., 2007) and reward anticipatory behavior (Kamal et al., 2010) were found to be disturbed. However, this selection of articles gives only a glimpse of the complexity associated with cognitive outcome after chronic stress, which seems to be task-specific (Conrad, 2010). For instance, chronic stress impairs spatial learning on appetitively motivated tasks, such as the radial arm maze or holeboard, tasks that evoke relatively mild to low arousal components from fear; but under testing conditions that evoke moderate to strong arousal components from fear, such as during radial arm water-maze testing, chronic stress seems to have minimal impairing effects or may even facilitate spatial learning. Moreover, the effects in female animals may differ from those observed in male animals (Luine, 2002). These behaviorally relevant issues have not been addressed so far with electrophysiological approaches.

Overall, chronic stress has profound effects on electrical activity in the brain. In general, the ability to induce LTP is impaired and glutamatergic activity is increased, although the latter is less consistent than the former. Evidently, these changes will have consequences for behavioral functions that critically depend on synaptic transmission and synaptic strengthening. In accordance, chronically stressed animals do perform differently in many behavioral tasks. However, the step from altered electrical activity to disturbed behavior after chronic stress is still heavily understudied.

## V. Perinatal Stress

Stress during the perinatal period can have powerful and long-lasting consequences for brain function (Pryce et al., 2005; Fenoglio et al., 2006; Sullivan et al., 2006; Maccari and Morley-Fletcher, 2007; Schmidt, 2010; Zhang and Meaney, 2010). Corticosteroids may exert their influence by changing connections in the brain at a time that these are being established and pruned (e.g., Sullivan et al., 2006), thus affecting brain organization in a similar way, as has been recognized for decades already in the case of gonadal hormones. A special case of such developmental influences pertains to the circuit involved in the stress response itself. By targeting this circuit, those exposed to perinatal stress might respond differently to stress later in life than naive control subjects. The lasting changes in stress responsiveness refer not only to, for example, activation of the HPA-axis itself



but also to other pathways downstream of brain corticosteroid receptors, which in part depend on (intra)cellular proteins.

An extensive number of studies reported that perinatal stress changes synaptic properties in adulthood, both under “basal” conditions (i.e., when animals are not stressed) and when brain tissue of adult animals is exposed to a surge of corticosteroid hormones (for review, see also Ali et al., 2011) (Supplemental Table IV). How perinatal stress can induce such lasting effects on excitability has not yet been addressed. From what is presently known about other brain properties, though, it seems likely that epigenetic programming plays an important role (Meaney and Szyf, 2005; Franklin and Mansuy, 2010). Potential molecules mediating changes in brain function include the NMDA receptor (Kamphuis et al., 2003; Son et al., 2006; Yaka et al., 2007; Ryan et al., 2009; Judo et al., 2010; but see Lee et al., 2011a), AMPA receptors (Yaka et al., 2007; Ryan et al., 2009), cell adhesion molecules (Aisa et al., 2009), and brain-derived neurotrophic factor (van Hasselt et al., 2012a; Yeh et al., 2012). We will here discuss only some of the major variables and the principles that emerge from the currently available data set on electrophysiological effects after early-life stress (summarized in Supplemental Table IV).

The first principle is that rather mild disturbances early in life (such as 3-min novelty exposure for the first 3 postnatal weeks or pups being separated from the mother up to 1 h per day) generally seem to enhance excitability, for instance by facilitating LTP in the CA1 area or enhancing spontaneous firing in the PFC (Kehoe and Bronzino, 1999; Zou et al., 2001; Tang and Zou, 2002; Akers et al., 2006; Stevenson et al., 2008); there are, however, some indications for reduced activity as well (Hsu et al., 2003; Blaise et al., 2008). More severe conditions, though, are consistently linked with reduced synaptic plasticity. This is true for prenatal stress (Kamphuis et al., 2003; Son et al., 2006; Yang et al., 2006, 2007; Lee et al., 2011a; Yeh et al., 2012; but see Noorlander et al., 2008), low and/or fragmented maternal care including situations associated with impoverished environmental conditions (Bredy et al., 2003; Brunson et al., 2005; Cui et al., 2006; Champagne et al., 2008; Bagot et al., 2009, 2012; Ivy et al., 2010), prolonged maternal separation (Gruss et al., 2008; Stevenson et al., 2008; Oomen et al., 2010), or traumatic events (Akers et al., 2006; Judo et al., 2010). When investigated, basal synaptic properties or paired pulse responsiveness were not much altered (Domenici et al., 1996; Kamphuis et al., 2003; Yaka et al., 2007; Lee et al., 2011). This pattern seems more pronounced in male than in female offspring (Kehoe and Bronzino, 1999; Oomen et al., 2009, 2010; van Hasselt et al., 2012a,b).

A critical factor in the changes in neuronal function is the quality and amount of maternal care. For instance, in the dentate gyrus (but less so in the CA1 area) the amount of licking and grooming received from the

mother during the first postnatal week strongly predicts the ability to induce LTP during young adulthood (van Hasselt et al., 2012a,b; see Fig. 12). Another critical factor is the early overexposure to glucocorticoids, because postnatal glucocorticoid treatment either of the lactating dam or the pups results in a very similar phenotype, reducing LTP (Domenici et al., 1996; Lin et al., 2006) while enhancing LTD (Lin et al., 2006). However, other stress-mediators such as CRH are certainly also involved (Ivy et al., 2010; Wang et al., 2011). Because maternal care indirectly affects the circulating levels of stress hormones (Zhang and Meaney, 2010), these two factors are most likely interconnected.

The second principle that has emerged more recently is that the effect of perinatal stress apparent under nonstressful conditions later in life is not necessarily the same as when the (young) adult organism is tested in conditions under which corticosteroid levels are high. For instance, the effect of prenatal stress on LTP and LTD induction was particularly apparent when combined with an acute stress exposure in adulthood (Yang et al., 2007). It is noteworthy that several studies have supplied evidence that exposure to high corticosteroid levels or stress in adulthood against a background of early-life adversity may in fact result in an opposite pattern (i.e., facilitated LTP) (Stewart et al., 2004; Champagne et al., 2008; Bagot et al., 2009; Oomen et al., 2010; Fig. 12), from what is seen under basal conditions. This was also reflected at the behavioral level. Thus, early-life adversity impaired memory performance in relatively nonstressful tasks, but improved memory in stressful learning tasks (Champagne et al., 2008; Bagot et al., 2009; Oomen et al., 2010). This has led to the hypothesis that early-life adversity may adjust the development of the brain such that it is geared to optimally perform under comparable high-stress conditions later in life rather than under less stressful situations; the reverse seems to be the case in animals that grow up under quite favorable conditions. In other words, optimal performance in (young) adulthood is seen when the environment early and later in life match (Champagne et al., 2009; Oitzl et al., 2010; Nederhof and Schmidt, 2012). There are several examples regarding the link between electrical activity and behavioral performance to support the relevance of a matching beneficial environment or a mismatch in the case of early-life adversity (Kamphuis et al., 2003; Akers et al., 2006; Lin et al., 2006; Son et al., 2006; Yang et al., 2006, 2007; Judo et al., 2010; Lee et al., 2011a; but see Domenici et al., 1996; Noorlander et al., 2008), but very few studies so far have supplied evidence for the importance of a mismatch in animals without early-life stress or a match in animals with a “bad start in life” (Stewart et al., 2004; Champagne et al., 2008; Bagot et al., 2009; Oomen et al., 2010).

The data set on early-life stress is quite complex because of nonuniformity in many variables. One such

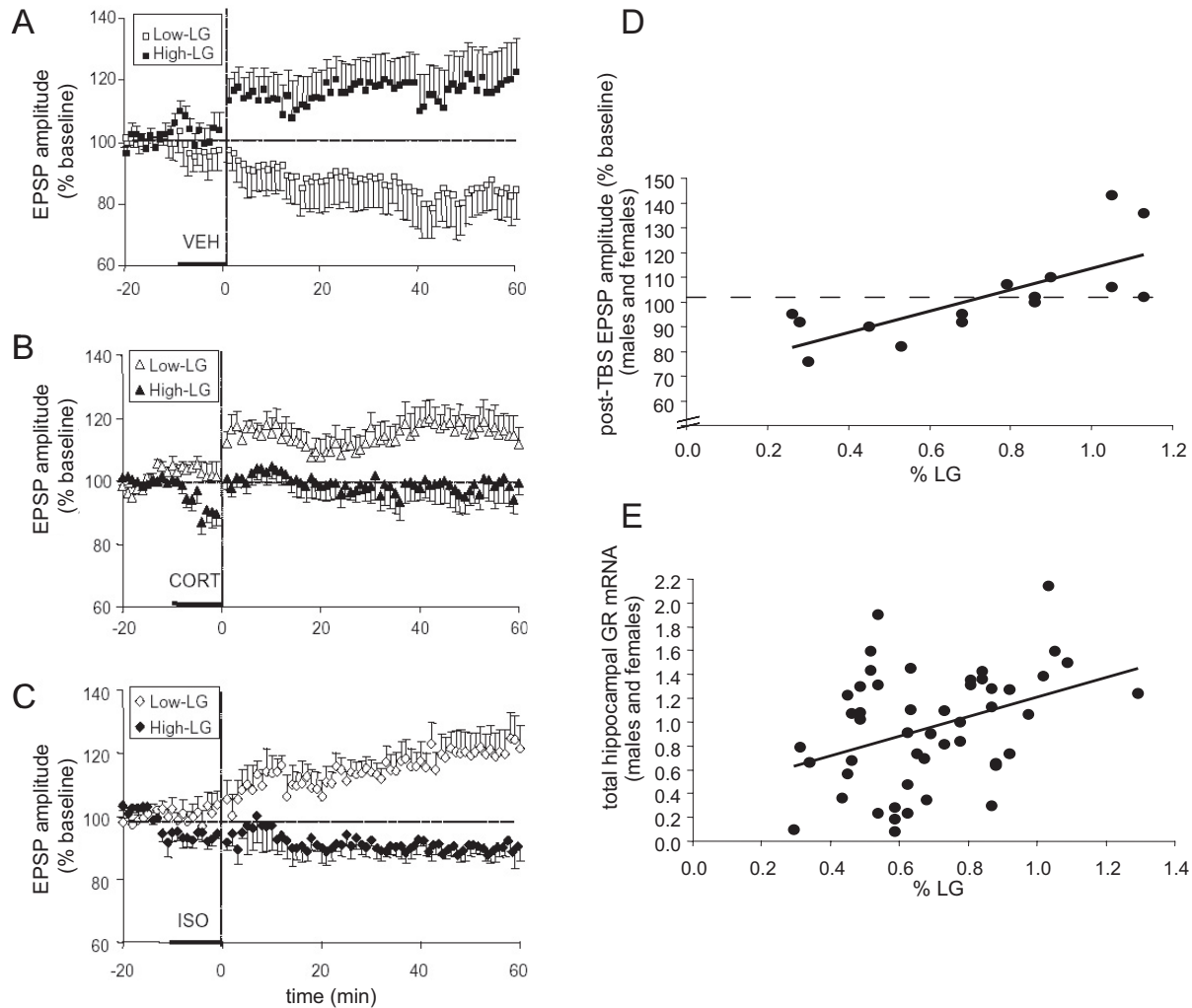


FIG. 12. Induction of long-term potentiation in the adult dentate gyrus depends on early-life environment. A, adult male offspring from mothers spending very high amounts of care on their litter (High-LG) compared with offspring from low licking/grooming (Low-LG) mothers display more effective LTP in the dentate gyrus in vitro. B, if slices were treated with 100 nM corticosterone for 10 min just before and during high-frequency stimulation, LTP was reduced in tissue from High-LG offspring but enhanced in that from Low-LG rats. C, a similar flip in physiological “phenotype” was observed when slices were treated with the  $\beta$ -adrenergic agonist isoproterenol. D, a positive correlation was observed between the degree to which LTP is induced in the dentate gyrus from adult rats and the amount of licking/grooming they received during the first postnatal week. Licking/grooming scores in this experiment were determined at the level of individual male and female pups (as opposed to entire litters, as in A–C). E, transcript levels for the glucocorticoid receptor also positively correlated with the amount of licking/grooming received during the first postnatal week. [Modified from Bagot RC, van Hasselt FN, Champagne DL, Meaney MJ, Krugers HJ, and Joëls M (2009) Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. *Neurobiol Learn Mem* **92**:292–300. Copyright © 2009 Elsevier B.V.; and van Hasselt FN, Boudewijns ZS, van der Knaap NJ, Krugers HJ, and Joëls M (2012) Maternal care received by individual pups correlates with adult CA1 dendritic morphology and synaptic plasticity in a sex-dependent manner. *J Neuroendocrinol* **24**:331–340. Copyright © 2012 British Society for Neuroendocrinology. Both used with permission.]

variable is the moment in life at which the stressor is applied. In some studies, the stressor (or glucocorticoid treatment) was applied to the pregnant female animal, thus prenatally and indirectly affecting the pups, indirectly because corticosteroids circulating in the mother may reach the pups via the placenta (Seckl and Holmes, 2007) and because the behavior of the mother to the pups may be altered once they are born. More often, though, stress was applied directly to the pups, during the first 1 to 2 postnatal weeks. A second variable concerns the type and severity of the stressor that was applied. In the case of the mother being stressed, some studies used restraint stress for several days, others

used variable stress or treatment with glucocorticoids. Postnatal stress administered to the pups ranged from exposure to a traumatic event (anoxia on PND 1 or foot shocks during PNDs 15–17) and very brief (minutes) or prolonged (ranging from 3 to 24 h) separation of pups from the dam to administration of glucocorticoids. The studies furthermore differ with respect to the delay between stress and investigation of its consequences for electrical activity. Most electrophysiological studies established the effects of perinatal stress for brain function in young adulthood. To our knowledge, none followed up the consequences for electrical activity into aging or even senescence. The outcome may very well be

different for each of these stages in life, as was observed, for instance, with respect to the lasting consequences of 24-h maternal separation on PND 3 for spatial learning and memory performance throughout the lifespan (Oitzl et al., 2000). It is also important to emphasize that nearly all studies were carried out in male offspring. This is somewhat surprising, because the rationale in many cases was that early-life events are a major risk factor for psychopathology later in life, such as major depression, a condition that is much more prevalent in women than in men. And finally, although some genetic heterogeneity may occur in outbred rat or mouse strains, the relevance of gene-by-environment interactions, which is so evident from human studies, has scarcely been touched upon in rodent models (Ryan et al., 2009).

Despite these considerations, it is clear that stress experienced at an early stage of (brain) development has tremendous consequences on synaptic plasticity later in life: stress at this sensitive period may wire the brain such that it optimally functions under comparable circumstances later on. Nearly all of the currently available studies focused on consequences of perinatal stress for LTP or LTD in the Schaffer collateral projection to the hippocampal CA1 area. There is no reason to believe, however, that other projections in the brain are not equally sensitive to perinatal stress, as is in fact supported by the limited number of studies that did examine other areas. Likewise, it seems very likely that the changes are not restricted to synaptic plasticity but also apply to the underlying voltage- and ligand-gated currents (see for example Hsu et al., 2003; Lee et al., 2011a).

## VI. Concluding Remarks

After more than 2 decades of research, there is ample evidence that corticosteroid hormones profoundly change neural activity, not only via the classic gene-mediated signaling pathway but also more rapidly, via G-protein-coupled pathways or protein-protein interactions. The general ideas that emerged and challenges for the future are summarized below.

### A. Overarching Principles

Brain cells are continuously exposed to corticosteroid hormones, although the levels vary throughout the day (e.g., due to ultradian pulses, circadian rhythmicity, stressful experiences, but also factors determining corticosteroid transport over membranes and local enzymatic conversion). Although the hormones in principle reach every cell, they can only directly change the function of those cells expressing receptors. Nuclear MRs are nearly always substantially occupied because of their high affinity, and in those cells that express them—particularly neurons in the hippocampus and lateral septum—are thought to safeguard the viability and basal activity of the cells. More recently, it has become

evident that these receptors may also reside in the plasma membrane and then serve as quick sensors for shifts in corticosteroid level. Nuclear GRs become fully activated when corticosteroid levels are very high and are therefore optimally equipped to assist in the brain's reaction to stressful conditions.

Via rapid nongenomic pathways, MRs mostly enhance neural activity, whereas GRs suppress activity (see summarizing Fig. 13). In the PVN, rapid GR-dependent effects are thought to contribute to rapid negative feedback of HPA axis activity. The role of rapid effects in extrahypothalamic brain regions is still debated, but behavioral data support the idea that nongenomic MR actions are particularly important during acquisition of relevant information, aiding the organism to select an appropriate strategy that is the best option in the short term, albeit at the cost of losing flexibility, a strategy that may not be beneficial in the long run. These rapid effects can also alter the responsiveness to subsequent corticosteroid exposure (e.g., in the BLA), but this does not occur in all brain regions.

When a wave of corticosteroids hits the brain, this not only causes rapid effects but also starts signaling pathways that change neural activity much later, ranging from approximately 20 min after steroid arrival to many hours or even days. These effects are primarily carried by GRs. In most hippocampal CA1 and CA3 neurons as well as in mPFC cells, GR activation increases surface expression of AMPA receptors and strengthens glutamatergic signaling through pathways partly overlapping with LTP. This might raise the threshold for subsequent induction of LTP and promotes LTD. In conjunction with a propensity to dampen transfer of overall excitatory information as a result of enhanced function of calcium-dependent potassium currents, GRs thus help to strengthen some synapses—presumably those synapses activated at the time of stress exposure—but protect cells against excitatory inputs reaching the cells at a later point in time. This is thought to contribute to appropriate higher cognitive functions, such as the consolidation of stress-related contextual information and working memory performance >20 min after stress. The dampening of information transfer 20 min to several hours after stress is not seen in the ventral-most part of the CA1 hippocampal area and the basolateral amygdala, providing an extended window for encoding of aspects of information that are processed via these areas. This may contribute to the fact that emotional aspects of a stressful event are extremely well retained.

It is noteworthy that the idea of corticosteroids acting in several time domains is not new; it was brought up in the 1980s by the work of Gillman and Jones (e.g., Beckford et al., 1983), showing that corticosteroids can inhibit HPA axis activity both rapidly and in a more delayed manner compatible with the classic genomic signaling pathway. In that case, the net result of both actions is the same: normalization of HPA axis activity,

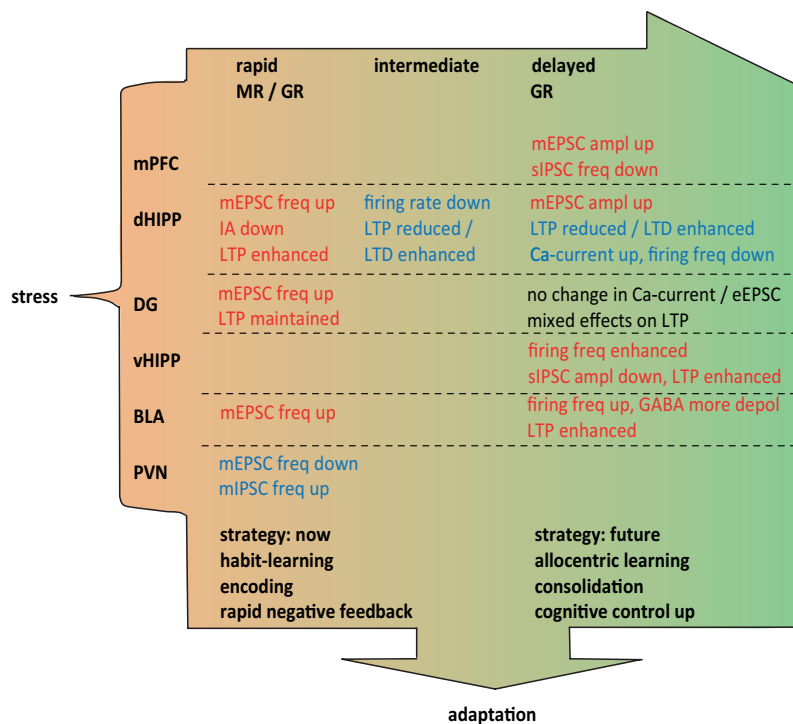


FIG. 13. Summary of main electrophysiological and cognitive effects after stress. Shortly after stress, corticosteroid levels in the brain rise and exert rapid nongenomic actions via MR and GR. In this phase, corticosteroid hormones increase neural activity in the dorsal hippocampus (dHIPP), DG, and BLA (e.g., by increasing the mEPSC frequency or reducing the K conductance  $I_A$ ). These effects of corticosterone—in concert with other stress mediators—may contribute to the behavioral effects reported for this rapid domain that help the organism to select an appropriate strategy to face the immediate challenge. For instance, corticosteroid hormones facilitate habit-type of learning, which is beneficial in the short term. Encoding of relevant information may start at this time and be promoted by corticosteroid hormones. In the rapid time domain, neurons in the PVN are inhibited by a reduction in mEPSC frequency and enhanced mIPSC frequency. This is involved in the rapid negative feedback of the HPA axis. After this immediate domain, neural activity in the dorsal hippocampus is reduced, although the amplitude of mEPSCs is enhanced, in an LTP-like fashion. This also occurs in the mPFC. Both effects are thought to promote consolidation of earlier encoded stress-related information for future use and to protect this information against input arriving 1 to 4 h after stress. In the ventral (v) hippocampus and BLA, activity remains at a high level, probably leading to preferential memory of emotional aspects related to the stressful event.

be it rapidly or slowly. What is new is that the two time domains in which corticosteroid hormones affect limbic cell function seem to serve two entirely different functions. The rapid mode helps the organism select the best strategy in the short term, to withstand an imminently dangerous situation, whereas the slow mode is more in line with the role of neuroendocrine negative feedback: normalization of activity, restoration of cognitive control, and preparation for the future.

When the organism is not exposed to a single stressor but to several weeks of stress, the ability to induce or maintain LTP is strongly reduced, and the likelihood to induce LTD enhanced, even under nonstress conditions. Exposing animals to stress/corticosteroids against a background of chronic stress does not cause additional suppression of LTP. Intrinsic or synaptically evoked cell activity can be either enhanced or unaffected by chronic stress. Stress experienced early in life also has strong and lasting effects on neural activity. Mild disturbances early in life generally enhance excitability, for instance by facilitating the induction of LTP. By contrast, more severe conditions were consistently linked with a reduced ability to evoke synaptic plasticity under basal HPA conditions. It is noteworthy that in these animals

renewed exposure to high corticosteroid levels in adulthood causes highly efficient induction of LTP. This flip in phenotype appears to have behavioral relevance, because animals with adverse early-life conditions perform relatively poorly in learning tasks that are not very stressful but show strong memory performance in stressful learning tasks. Apparently, early-life conditions can direct brain development such that the circuits are optimally geared to perform well under comparable conditions later in life.

### B. The Average Male White Rat Neuron

These overarching principles are derived from the currently available studies, which have certain limitations. Nearly all studies have been performed in young-adult rodents. Given the strong influence of early-life environment and the fact that these influences vary over the lifespan (for review, see Lupien et al., 2009), it would be very useful to also examine animals at a more advanced age. Landfield and Eldridge (1994) have argued that many of the effects observed with corticosterone resemble what is seen in the aged brain, also with regard to electrical activity. The aged brain may thus respond differently to corticosteroids. Unfortunately, patch-clamp experi-

ments are difficult in aged rodents and much easier to carry out in very young animals. This is probably the reason that some studies discussed in this review were even performed in prepubertal rodents. Cultured cells are also derived from very young animals and usually have not matured beyond 21 days of age. There is no guarantee that corticosteroid effects at that age are the same as later in life.

A second limitation is that nearly all experiments were performed in male rats, not in female rats. Although this is understandable, given the complicating factor of the estrous cycle in female rats, it seriously hampers the extrapolation of findings in rodent models to the human brain, where stress-related psychopathology in fact is often more prevalent in women than in men. There are numerous examples in rodent models that the effects of stress are different in male and female rodents (for reviews, see Luine, 2002; Luine et al., 2007; Ter Horst et al., 2009; Weinstock, 2011) including for electrical activity (e.g., van Hasselt et al., 2012a).

Species and strain differences have also hardly been addressed with regard to corticosteroid effects on neural activity. Although the effects were comparable for mice and rats whenever tested (e.g., compare Karst et al., 1994 and Karst et al., 2000), this does not exclude the possibility that differences may exist. Stress responsivity differs largely among strains of rats or mice (for reviews, see Henn and Vollmayr, 2005; Millstein and Holmes, 2007), and this is certainly expected to result in adaptive changes in corticosteroid receptor properties and hence their role in altering neural activity.

A pharmacologically relevant issue is the fact that corticosteroid actions have very often been examined with very high concentrations, well beyond the  $K_d$  of the receptor. Subtle differences in local expression of receptor variants or post-translational modifications of receptors, resulting in altered binding affinity or receptor capacity, will remain unnoticed with these saturating levels of the hormone. Nevertheless, in "real life," these regional differences or changes during the life span are very meaningful and deserve more attention.

Regarding the issue of hormone concentrations, it is also relevant to consider the role of glial cells. As part of the tripartite glutamate synapse, glial cells play an important role in regulating the level of glutamate in the extracellular space (for review, see Popoli et al., 2012). In short, glial cells prevent glutamate spillover and consequent overactivation of extracellular glutamate receptors. This occurs mainly by active clearance and metabolism of glutamate into glutamine via high-affinity excitatory amino acid transporters in the plasma membrane of glial cells. This is widely accepted as the primary mechanism via which glutamatergic action in the extracellular space is terminated (Tzingounis and Wadiche, 2007). Acute stress, chronic stress, and/or glucocorticoid administration do affect glial cell glutamate uptake (Popoli et al., 2012). In general, although acute

stress and corticosteroid exposure seem to induce adaptive changes in glutamate clearance, chronic stress increases extrasynaptic glutamate levels by reducing the clearance rate via excitatory amino acid transporters in hippocampal and PFC cells. Although the underlying mechanism, and especially the role of MR and GR, is still unclear, the reduced clearance rate could certainly contribute to the commonly observed disruption in neurophysiology after chronic stress.

Finally, there are technical limitations linked to measuring electrical activity. Information on currents, particularly in subcortical areas, can be obtained only in vitro, in preparations lacking most afferent connections and maintained under artificial conditions. This presently precludes detailed investigation of rapid corticosteroid effects on electrical activity in association with their behavioral consequences, which would need to be carried out in vivo. Slow gene-mediated actions are easier to examine, because these seem to persist in slices prepared from animals earlier exposed to a stressor. For instance, increases in calcium current amplitude were observed several hours after stress exposure and were highly comparable with effects seen in corticosterone-treated slices prepared from naive animals (Joëls et al., 2003; van Gemert et al., 2009). A second drawback inherent to patch-clamp recording is the inevitable perfusion of the intracellular compartment. If any of the intracellular proteins is essential for the corticosteroid effects taking place but not included in the pipette solution, the hormonal effect may be lost if the cell is held in the whole-cell recording mode during the putative development of corticosteroid actions (see, for example, Teschemacher et al., 1996). In most studies, this was not a problem, though, because these compared groups of cells recorded before steroid exposure/after vehicle exposure with groups of cells that had been treated with steroids before establishing the whole-cell recording mode.

Although a direct link between corticosteroid actions on behavior and on intrinsic/synaptic currents is not (yet) possible, a tighter connection between behavior and neural firing frequency is feasible, using multielectrode recording in vivo. These advanced methods have rarely been applied so far (Kim et al., 2007; Passecker et al., 2011) but are essential to get better insight in the behavioral relevance of corticosteroid actions on neural activity.

### C. In Search of Multiple Dimensions

Most studies have concentrated on one aspect only of stress effects in the brain: one area at a time; rapid or slow effects, not both or the transition from the one to the other; only one of the stress hormones (e.g., corticosterone), not the (inter)actions with other stress mediators; and one manipulation to change corticosteroid levels. Such a reductionistic approach is very useful to establish the contribution of that particular aspect to the overall consequence of stress, but it is far removed from

real life events and makes it hard to piece the various bits of information together.

Although an overall pattern emerges from the current studies and shows that corticosterone affects neural activity of the BLA and ventral CA1 region (and possibly the dentate gyrus) in a different manner than the remainder of the hippocampus and mPFC, the response of multiple areas has seldom been examined in one study. Direct comparisons were made between the dorsal and ventral hippocampus (Maggio and Segal, 2007, 2009a,b), the dorsal CA1 versus dentate gyrus (Kavushansky et al., 2006; Vouimba et al., 2007; van Gemert et al., 2009), the BLA and CA1 area (Karst et al., 2010), and the BLA and DG (Vouimba et al., 2004). Most probably, corticosterone will affect connections between many areas at a time, changing the responsiveness of entire circuits. Recording the connections between all of these areas is difficult with electrophysiological methods. Such insights could be obtained by applying neuroimaging methods, using (resting state) functional magnetic resonance imaging or diffusion tensor imaging (see, for example, Ferris and Stolberg, 2010).

A dimension that has received little attention until recently is the time frame in which corticosteroids are active. The slow gene-mediated actions that develop after a delay of approximately 1 h and depend on transactivation via GRs were expected on the basis of what is known about the intracellular signaling pathways. The other end of the spectrum is formed by those effects that develop within a few minutes, involve G-protein signaling, and occur in the absence of protein synthesis. However, there also seems to be a category of events taking place in the intermediate time domain. These effects become apparent after approximately 20 min and peak at approximately 40 to 60 min after corticosteroid exposure (Pfaff et al., 1971; Vidal et al., 1986; Joëls and de Kloet, 1993; Maggio and Segal, 2009a; Tse et al., 2011). These effects are usually evoked with relatively high corticosterone concentrations and may involve rapid nongenomic protein-protein interactions between GR and phospho-ERK1/2 (Yang et al., 2004, 2008b; Gutiérrez-Mecinas et al., 2011) or phospho-cAMP response element-binding protein (Ahmed et al., 2006; Roozendaal et al., 2010), subsequently activating enzymes such as MSK (Gutiérrez-Mecinas et al., 2011) or SGK (Liu et al., 2010). Apparently, once corticosteroids hit the brain, they can change neural activity from minutes to hours.

But when exactly do corticosteroids reach the brain after stress? Although not much is known about this issue, there is evidence for a delay of up to 20 min (Droste et al., 2008). This clearly needs further study. It drives home the point, though, that other stress-released hormones and transmitters may reach relevant brain areas well before corticosteroids and that the latter do not work in isolation. In this review, we highlighted effects of corticosteroid hormones on intrinsic cell properties and the main excitatory and inhibitory

inputs. Evidently, neurons also receive inputs mediated by other transmitters/modulators, many of which are enhanced in concentration after stress, such as noradrenaline, dopamine, serotonin or CRH. There is extensive evidence that stress and corticosterone are able to change not only the biosynthesis, release, and reuptake of these transmitters/modulators (Chaouloff et al., 1999; Czyrak et al., 2003; Kvetnansky et al., 2009; Bonfiglio et al., 2011), but also their influence on cellular excitability. This has been shown in detail with regard to serotonin (see, for example, Joëls et al., 1991; Laaris et al., 1999; Fairchild et al., 2003; for reviews, see Joëls et al., 2007; Haj-Dahmane and Shen, 2011), noradrenaline, and, to a lesser extent, CRH (Gallagher et al., 2008). For instance, noradrenaline (acting via  $\beta$ -receptors) targets the AHP (Madison and Nicoll, 1982; Faber and Sah, 2005; Oh et al., 2009), GluA2 subunit trafficking (Liu et al., 2010), and (maintenance of) LTP (Thomas et al., 1996; Straube and Frey, 2003; Gelinias and Nguyen, 2005), thereby mimicking effects described for corticosteroids. These common endpoints form potential platforms for interaction between various stress mediators (Joëls et al., 2011). There are indeed several examples of noradrenaline and corticosterone acting in concert to promote optimal neural function (Akirav and Richter-Levin, 2002; Korz and Frey, 2005; Zhou et al., 2011), which is also reflected at the behavioral level (Roozendaal et al., 2004). Yet when corticosterone is given >1 h in advance of noradrenaline or isoproterenol, the hormone suppresses noradrenergic function (Joëls and de Kloet, 1989; Pu et al., 2007, 2009; Liebmann et al., 2009). This is possibly caused by occlusion because the two compounds converge on the same functional endpoints, which would be another example of metaplastic changes induced by corticosteroids; right now this is pure speculation. This sequence of hormone exposure, of course, is pharmacological in nature, because in reality, noradrenaline will reach brain cells before and not after corticosterone. The complex interplay between all neurotransmitters, modulators and hormones released after stress and reaching specific neuronal compartments at various timepoints after stress needs further investigation to fully comprehend how the input-output relationship of neurons is altered by stress (Joëls and Baram, 2009).

Finally, an issue that has been neglected so far is the fact that fluctuations in corticosteroid level can be caused by different processes: stress, but also circadian or ultradian variations. These are not independent factors; for instance, stress exposure during the rising limb of an ultradian pulse affects transcriptional activity in the brain differently than during the falling limb (Sarabdjitsingh et al., 2010a). As illustrated by the metaplastic changes in the BLA, this interdependency may also occur in the brain: a stressor experienced at an ultradian or circadian peak may change BLA activity in another way than when this occurs at the trough. Along the same line, a number of stressors in succession could drive neural activity in the BLA in a different manner than

activity in the dorsal CA1 region. These aspects need dedicated experiments to be fully understood.

#### D. Disease and Targets for Treatment

The functional relevance of corticosteroid effects on neural activity in rodents has been discussed in sections II and III in terms of their contribution to behavioral adaptation, helping to survive challenging situations and to apply the gathered information when experiencing comparable situations in the future. Although these actions are beneficial under “normal” conditions, they can impose a serious risk for developing pathologic conditions when the stressful conditions are 1) very severe, 2) coinciding with additional challenges to the brain, 3) uncontrollable and persistent, or 4) occurring at a highly vulnerable moment in life (e.g., during early development or in senescence) (de Kloet et al., 2005). For example, an extended window for encoding emotional aspects of a stressful situation is beneficial when it helps to remember relevant aspects of a daily life situation more vividly than less relevant information, but in humans this can turn into psychopathology when people are haunted by these details day and night, as is the case with a post-traumatic stress disorder. Another example refers to the increased calcium influx seen after stress. Normally this may help to drive calcium-dependent potassium currents, serving as a brake on excitatory input several hours after stress. However, a calcium overload—due not only to enhanced influx but also to reduced efflux (Bhargava et al., 2000, 2002)—may exacerbate the consequences of conditions associated with strong depolarization or additional calcium exposure, such as epileptic seizures. In accordance, corticosterone administration during kindling accelerated the behavioral signs of epilepsy and was associated with large calcium currents in fully kindled rats (Karst et al., 1999).

The potential risk of chronic stress for human disease is well documented in the case of major depression (for review, see Holsboer and Ising, 2010). Dysregulation of the HPA axis, showing higher trough levels of cortisol (Herbert, 2012) and an exaggerated response to a dexamethasone-CRH challenge, occurs in a substantial proportion of people with major depression, even before the manifestation of any clinical symptoms in high-risk proband with a positive family history of affective disorders (Ising et al., 2005). Normalization of HPA axis activity turned out to be a valuable predictor of relapse probability (Künzel et al., 2003; Appelhof et al., 2006; Aubry et al., 2007). Considering the added risk of periods of stress and/or dysregulation of the HPA axis, and more particularly the role of GRs in the functional consequences, the prediction would be that restricting GR effects (e.g., by antiglucocorticoid treatment or the use of steroid synthesis inhibitors) would be beneficial for the outcome.

This possibility has been specifically addressed in an animal model for chronic unpredictable stress. The reduction in LTP observed after 21 days of stress turned out to be fully reversed by treatment with mifepristone during days 18 to 21 (Krugers et al., 2006). This was also true for the chronic stress-induced increase in calcium current amplitude (Karst and Joëls, 2007). Small currents were also observed in dentate granule cells from mifepristone-treated, chronically stressed animals receiving corticosterone in vitro (van Gemert and Joëls, 2006). Similar normalizing effects of mifepristone treatment were observed with regard to neurogenesis in the dentate gyrus (Oomen et al., 2007). These cellular actions of the antiglucocorticoid possibly contribute to its beneficial effect in severe cases of psychotic depression, provided sufficiently high concentrations in plasma are achieved (DeBattista et al., 2006; Gallagher et al., 2008; Blasey et al., 2011). Whether mifepristone exerts its effects only via blockade of GRs is hard to judge, given the many adaptive actions that may occur, both peripherally and in the brain (Kling et al., 2009).

Apart from drugs directly interfering with glucocorticoid action in the brain, the functionality of corticosteroid hormones and receptors, as well as the HPA axis in general, can also serve a more prognostic goal in health care, predicting the likelihood that individual patients will respond to pharmacotherapy. Genetic variants are increasingly seen as tools to achieve such personalized medical care (Holsboer, 2008). For instance, polymorphisms of FKBP5, a chaperone molecule of the GR, were found to predict recurrence of depressive episodes and response to antidepressant treatment (Binder et al., 2004; Kirchheiner et al., 2008; Lekman et al., 2008), although this finding could not always be replicated (Tsai et al., 2007; Sarginson et al., 2010). It remains a challenge for the future to study the consequences of these genetic variants for corticosteroid actions on neural activity (e.g., when expressed in induced pluripotent stem cells). Such clinically relevant test models can provide a quick and efficient means to examine the efficacy of already existing agents to normalize aberrant function.

#### Acknowledgments

This work was supported by Nederlandse Organisatie voor Wetenschappelijk Onderzoek—Aard-en Levenswetenschappen (NWO-ALW) [Grant 821.02.007] (to M.J.) and [Grant 817.02.017] (to H.K.).

#### Authorship Contributions

Wrote or contributed to the writing of the manuscript: Joëls, Sarabdjitsingh, and Karst.

#### References

- Abercrombie HC, Kalin NH, Thurow ME, Rosenkranz MA, and Davidson RJ (2003) Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behav Neurosci* **117**:505–516.
- Abrari K, Rashidy-Pour A, Semnani S, Fathollahi Y, and Jadid M (2009) Post-training administration of corticosterone enhances consolidation of contextual fear memory and hippocampal long-term potentiation in rats. *Neurobiol Learn Mem* **91**:260–265.
- Acconcia F, Ascenzi P, Bocedi A, Spisni E, Tomasi V, Trentalancia A, Visca P, and Marino M (2005) Palmitoylation-dependent estrogen receptor alpha membrane localization: regulation by 17beta-estradiol. *Mol Biol Cell* **16**:231–237.

- Ahmed T, Frey JU, and Korz V (2006) Long-term effects of brief acute stress on cellular signaling and hippocampal LTP. *J Neurosci* **26**:3951–3958.
- Aisa B, Elizalde N, Tordera R, Lasheras B, Del Río J, and Ramírez MJ (2009) Effects of neonatal stress on markers of synaptic plasticity in the hippocampus: implications for spatial memory. *Hippocampus* **19**:1222–1231.
- Akers KG, Nakazawa M, Romeo RD, Connor JA, McEwen BS, and Tang AC (2006) Early life modulators and predictors of adult synaptic plasticity. *Eur J Neurosci* **24**:547–554.
- Akirav I and Richter-Levin G (1999) Biphasic modulation of hippocampal plasticity by behavioral stress and basolateral amygdala stimulation in the rat. *J Neurosci* **19**:10530–10535.
- Akirav I and Richter-Levin G (2002) Mechanisms of amygdala modulation of hippocampal plasticity. *J Neurosci* **22**:9912–9921.
- Aleisa AM, Alzoubi KH, and Alkadhi KA (2006a) Nicotine prevents stress-induced enhancement of long-term depression in hippocampal area CA1: electrophysiological and molecular studies. *J Neurosci Res* **83**:309–317.
- Aleisa AM, Alzoubi KH, Gerges NZ, and Alkadhi KA (2006b) Chronic psychosocial stress-induced impairment of hippocampal LTP: possible role of BDNF. *Neurobiol Dis* **22**:453–462.
- Aleisa AM, Alzoubi KH, Gerges NZ, and Alkadhi KA (2006c) Nicotine blocks stress-induced impairment of spatial memory and long-term potentiation of the hippocampal CA1 region. *Int J Neuropsychopharmacol* **9**:417–426.
- Alfarez DN, Joëls M, and Krugers HJ (2003) Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. *Eur J Neurosci* **17**:1928–1934.
- Ali I, Salzberg MR, French C, and Jones NC (2011) Electrophysiological insights into the enduring effects of early life stress on the brain. *Psychopharmacology (Berl)* **214**:155–173.
- Amato G, Mazziotti G, Di Somma C, Lalli E, De Felice G, Conte M, Rotondi M, Pietrosante M, Lombardi G, Bellastella A, et al. (2000) Recombinant growth hormone (GH) therapy in GH-deficient adults: a long-term controlled study on daily versus thrice weekly injections. *J Clin Endocrinol Metab* **85**:3720–3725.
- Anstrom KK, Miczek KA, and Budygin EA (2009) Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. *Neuroscience* **161**:3–12.
- Anstrom KK and Woodward DJ (2005) Restraint increases dopaminergic burst firing in awake rats. *Neuropsychopharmacology* **30**:1832–1840.
- Appelhof BC, Huyser J, Verweij M, Brouwer JP, van Dyck R, Fliers E, Hoogendijk WJ, Tijssen JG, Wiersinga WM, and Schene AH (2006) Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). *Biol Psychiatry* **59**:696–701.
- Arriza JL, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, and Evans RM (1987) Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science* **237**:268–275.
- Artola A, von Frijtag JC, Fermont PC, Gispen WH, Schrama LH, Kamal A, and Spruijt BM (2006) Long-lasting modulation of the induction of LTD and LTP in rat hippocampal CA1 by behavioural stress and environmental enrichment. *Eur J Neurosci* **23**:261–272.
- Aubry JM, Gervasoni N, Osiek C, Perret G, Rossier MF, Bertschy G, and Bondolfi G (2007) The DEX/CRH neuroendocrine test and the prediction of depressive relapse in remitted depressed outpatients. *J Psychiatr Res* **41**:290–294.
- Avital A, Segal M, and Richter-Levin G (2006) Contrasting roles of corticosteroid receptors in hippocampal plasticity. *J Neurosci* **26**:9130–9134.
- Bagot RC, Tse YC, Nguyen HB, Wong AS, Meaney MJ and Wong TP (2012) Maternal care influences hippocampal N-methyl-D-aspartate receptor function and dynamic regulation by corticosterone in adulthood. *Biol Psych* <http://dx.doi.org/10.1016/j.biopsych.2012.03.016>.
- Bagot RC, van Hasselt FN, Champagne DL, Meaney MJ, Krugers HJ, and Joëls M (2009) Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. *Neurobiol Learn Mem* **92**:292–300.
- Basavarajappa BS, Ninan I, and Arancio O (2008) Acute ethanol suppresses glutamatergic neurotransmission through endocannabinoids in hippocampal neurons. *J Neurochem* **107**:1001–1013.
- Bear MF and Abraham WC (1996) Long-term depression in hippocampus. *Annu Rev Neurosci* **19**:437–462.
- Beck SG, Choi KC, List TJ, Okuhara DY, and Birnstein S (1996) Corticosterone alters 5-HT<sub>1A</sub> receptor-mediated hyperpolarization in area CA1 hippocampal pyramidal neurons. *Neuropsychopharmacology* **14**:27–33.
- Beckford U, Holmes MC, Gillham B, and Jones MT (1983) Biphasic inhibition of bioactive hypothalamic corticotrophin releasing factor secretion in vitro by corticosterone and prevention of the second phase by various steroids. *J Endocrinol* **97**:339–346.
- Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, Almeida OF, and Sousa N (2009) The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Mol Psychiatry* **14**:764–773, 739.
- Bhargava A, Mathias RS, McCormick JA, Dallman MF, and Pearce D (2002) Glucocorticoids prolong Ca<sup>2+</sup> transients in hippocampal-derived H19-7 neurons by repressing the plasma membrane Ca<sup>2+</sup>-ATPase-1. *Mol Endocrinol* **16**:1629–1637.
- Bhargava A, Meijer OC, Dallman MF, and Pearce D (2000) Plasma membrane calcium pump isoform 1 gene expression is repressed by corticosterone and stress in rat hippocampus. *J Neurosci* **20**:3129–3138.
- Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Pütz B, Papiol S, Seaman S, Lucae S, Kohli MA, et al. (2004) Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet* **36**:1319–1325.
- Blaise JH, Koranda JL, Chow U, Haines KE, and Dorward EC (2008) Neonatal isolation stress alters bidirectional long-term synaptic plasticity in amygdalo-hippocampal synapses in freely behaving adult rats. *Brain Res* **1193**:25–33.
- Blank T, Nijholt I, Eckart K, and Spiess J (2002) Priming of long-term potentiation in mouse hippocampus by corticotropin-releasing factor and acute stress: implications for hippocampus-dependent learning. *J Neurosci* **22**:3788–3794.
- Blasey CM, Block TS, Belanoff JK, and Roe RL (2011) Efficacy and safety of mifepristone for the treatment of psychotic depression. *J Clin Psychopharmacol* **31**:436–440.
- Bodnoff SR, Humphreys AG, Lehman JC, Diamond DM, Rose GM, and Meaney MJ (1995) Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *J Neurosci* **15**:61–69.
- Bonfiglio JJ, Inda C, Refojo D, Holsboer F, Arzt E, and Silberstein S (2011) The corticotropin-releasing hormone network and the hypothalamic-pituitary-adrenal axis: molecular and cellular mechanisms involved. *Neuroendocrinology* **94**:12–20.
- Borski RJ (2000) Nongenomic membrane actions of glucocorticoids in vertebrates. *Trends Endocrinol Metab* **11**:427–436.
- Bradbury MW (1993) The blood-brain barrier. *Exp Physiol* **78**:453–472.
- Bramham CR, Southard T, Ahlers ST, and Sarvey JM (1998) Acute cold stress leading to elevated corticosterone neither enhances synaptic efficacy nor impairs LTP in the dentate gyrus of freely moving rats. *Brain Res* **789**:245–255.
- Bredy TW, Humpartzoomian RA, Cain DP, and Meaney MJ (2003) Partial reversal of the effect of maternal care on cognitive function through environmental enrichment. *Neuroscience* **118**:571–576.
- Breuner CW and Orchinik M (2002) Plasma binding proteins as mediators of corticosteroid action in vertebrates. *J Endocrinol* **175**:99–112.
- Brinks V, Berger S, Gass P, de Kloet ER, and Oitzl MS (2009) Mineralocorticoid receptors in control of emotional arousal and fear memory. *Horm Behav* **56**:232–238.
- Brischoux F, Chakraborty S, Brierley DI, and Ungless MA (2009) Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci USA* **106**:4894–4899.
- Brunson KL, Kramár E, Lin B, Chen Y, Colgin LL, Yanagihara TK, Lynch G, and Baram TZ (2005) Mechanisms of late-onset cognitive decline after early-life stress. *J Neurosci* **25**:9328–9338.
- Buchanan TW and Lovallo WR (2001) Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* **26**:307–317.
- Campioni MR, Xu M, and McGehee DS (2009) Stress-induced changes in nucleus accumbens glutamate synaptic plasticity. *J Neurophysiol* **101**:3192–3198.
- Caudal D, Godsil BP, Mailliet F, Bergerot D, and Jay TM (2010) Acute stress induces contrasting changes in AMPA receptor subunit phosphorylation within the prefrontal cortex, amygdala and hippocampus. *PLoS One* **5**:e15282.
- Cazakoff BN and Howland JG (2010) Acute stress disrupts paired pulse facilitation and long-term potentiation in rat dorsal hippocampus through activation of glucocorticoid receptors. *Hippocampus* **20**:1327–1331.
- Cerqueira JJ, Mailliet F, Almeida OF, Jay TM, and Sousa N (2007) The prefrontal cortex as a key target of the maladaptive response to stress. *J Neurosci* **27**:2781–2787.
- Chameau P, Qin Y, Spijker S, Smit AB, Smit G, and Joëls M (2007) Glucocorticoids specifically enhance L-type calcium current amplitude and affect calcium channel subunit expression in the mouse hippocampus. *J Neurophysiol* **97**:5–14.
- Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, Joëls M, and Krugers H (2008) Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *J Neurosci* **28**:6037–6045.
- Champagne DL, de Kloet ER, and Joëls M (2009) Fundamental aspects of the impact of glucocorticoids on the (immature) brain. *Semin Fetal Neonatal Med* **14**:136–142.
- Chaouloff F, Berton O, and Mormède P (1999) Serotonin and stress. *Neuropsychopharmacology* **21**:28S–32S.
- Chaouloff F, Hémar A, and Manzoni O (2007) Acute stress facilitates hippocampal CA1 metabotropic glutamate receptor-dependent long-term depression. *J Neurosci* **27**:7130–7135.
- Chen CC, Yang CH, Huang CC, and Hsu KS (2010) Acute stress impairs hippocampal mossy fiber-CA3 long-term potentiation by enhancing cAMP-specific phosphodiesterase 4 activity. *Neuropsychopharmacology* **35**:1605–1617.
- Chen YZ, Hua SY, Wang CA, Wu LG, Gu Q, and Xing BR (1991) An electrophysiological study on the membrane receptor-mediated action of glucocorticoids in mammalian neurons. *Neuroendocrinology* **53**:25–30.
- Cho K and Little HJ (1999) Effects of corticosterone on excitatory amino acid responses in dopamine-sensitive neurons in the ventral tegmental area. *Neuroscience* **88**:837–845.
- Christian KM, Miracle AD, Wellman CL, and Nakazawa K (2011) Chronic stress-induced hippocampal dendritic retraction requires CA3 NMDA receptors. *Neuroscience* **174**:26–36.
- Christoffel DJ, Golden SA, Dumitriu D, Robison AJ, Janssen WG, Ahn HF, Krishnan V, Reyes CM, Han MH, Ables JL, et al. (2011) IkappaB kinase regulates social defeat stress-induced synaptic and behavioral plasticity. *J Neurosci* **31**:314–321.
- Conrad CD (2010) A critical review of chronic stress effects on spatial learning and memory. *Prog Neuropsychopharmacol Biol Psychiatry* **34**:742–755.
- Conrad KL, Louderback KM, Gessner CP, and Winder DG (2011) Stress-induced alterations in anxiety-like behavior and adaptations in plasticity in the bed nucleus of the stria terminalis. *Physiol Behav* **104**:248–256.
- Conway-Campbell BL, McKenna MA, Wiles CC, Atkinson HC, de Kloet ER, and Lightman SL (2007) Proteasome-dependent down-regulation of activated nuclear hippocampal glucocorticoid receptors determines dynamic responses to corticosterone. *Endocrinology* **148**:5470–5477.
- Conway-Campbell BL, Pooley JR, Hager GL, and Lightman SL (2012) Molecular dynamics of ultradian glucocorticoid receptor action. *Mol Cell Endocrinol* **348**:383–393.



- Conway-Campbell BL, Sarabjitsingh RA, McKenna MA, Pooley JR, Kershaw YM, Meijer OC, De Kloet ER, and Lightman SL (2010) Glucocorticoid ultradian rhythmicity directs cyclical gene pulsing of the clock gene period 1 in rat hippocampus. *J Neuroendocrinol* **22**:1093–1100.
- Cook CJ (2001) Measuring of extracellular cortisol and corticotropin-releasing hormone in the amygdala using immunosensor coupled microdialysis. *J Neurosci Methods* **110**:95–101.
- Cui M, Yang Y, Yang J, Zhang J, Han H, Ma W, Li H, Mao R, Xu L, Hao W, et al. (2006) Enriched environment experience overcomes the memory deficits and depressive-like behavior induced by early life stress. *Neurosci Lett* **404**:208–212.
- Czyrak A, Mackowiak M, Chocyk A, Fijał K, and Wedzony K (2003) Role of glucocorticoids in the regulation of dopaminergic neurotransmission. *Pol J Pharmacol* **55**:667–674.
- Datson NA, Morsink MC, Meijer OC, and de Kloet ER (2008) Central corticosteroid actions: search for gene targets. *Eur J Pharmacol* **583**:272–289.
- Datson NA, Polman JA, de Jonge RT, van Boheemen PT, van Maanen EM, Welten J, McEwen BS, Meiland HC, and Meijer OC (2011) Specific regulatory motifs predict glucocorticoid responsiveness of hippocampal gene expression. *Endocrinology* **152**:3749–3757.
- Datson NA, van der Perk J, de Kloet ER, and Vreugdenhil E (2001) Identification of corticosteroid-responsive genes in rat hippocampus using serial analysis of gene expression. *Eur J Neurosci* **14**:675–689.
- de Kloet ER, Joëls M, and Holsboer F (2005) Stress and the brain: from adaptation to disease. *Nat Rev Neurosci* **6**:463–475.
- de Kloet ER, Oitzl MS, and Joëls M (1999) Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci* **22**:422–426.
- de Quervain DJ, Roozendaal B, and McGaugh JL (1998) Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature* **394**:787–790.
- DeBattista C, Belanoff J, Glass S, Khan A, Horne RL, Blasey C, Carpenter LL, and Alva G (2006) Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol Psychiatry* **60**:1343–1349.
- Derijk RH and de Kloet ER (2008) Corticosteroid receptor polymorphisms: determinants of vulnerability and resilience. *Eur J Pharmacol* **583**:303–311.
- Di S, Malcher-Lopes R, Halmos KC, and Tasker JG (2003) Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *J Neurosci* **23**:4850–4857.
- Di S, Malcher-Lopes R, Marcheselli VL, Bazan NG, and Tasker JG (2005) Rapid glucocorticoid-mediated endocannabinoid release and opposing regulation of glutamate and gamma-aminobutyric acid inputs to hypothalamic magnocellular neurons. *Endocrinology* **146**:4292–4301.
- Di S, Maxson MM, Franco A, and Tasker JG (2009) Glucocorticoids regulate glutamate and GABA synapse-specific retrograde transmission via divergent nongenomic signaling pathways. *J Neurosci* **29**:393–401.
- Diamond DM and Rose GM (1994) Stress impairs LTP and hippocampal-dependent memory. *Ann NY Acad Sci* **746**:411–414.
- Diamond DM, Bennett MC, Fleshner M, and Rose GM (1992) Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus* **2**:421–430.
- Diamond DM, Park CR, and Woodson JC (2004) Stress generates emotional memories and retrograde amnesia by inducing an endogenous form of hippocampal LTP. *Hippocampus* **14**:281–291.
- Domenici MR, Casolini P, Catalani A, Ruggieri V, Angelucci L, and Sagratella S (1996) Reduced hippocampal in vitro CA1 long-term potentiation in rat offspring with increased circulating corticosterone during neonatal life. *Neurosci Lett* **218**:72–74.
- Dominguez R and Micevych P (2010) Estradiol rapidly regulates membrane estrogen receptor alpha levels in hypothalamic neurons. *J Neurosci* **30**:12589–12596.
- Dong Y, Saal D, Thomas M, Faust R, Bonci A, Robinson T, and Malenka RC (2004) Cocaine-induced potentiation of synaptic strength in dopamine neurons: behavioral correlates in GluRA(-/-) mice. *Proc Natl Acad Sci USA* **101**:14282–14287.
- Droste SK, de Groot L, Atkinson HC, Lightman SL, Reul JM, and Linthorst AC (2008) Corticosterone levels in the brain show a distinct ultradian rhythm but a delayed response to forced swim stress. *Endocrinology* **149**:3244–3253.
- Dumas TC, Gillette T, Ferguson D, Hamilton K, and Sapolsky RM (2010) Anti-glucocorticoid gene therapy reverses the impairing effects of elevated corticosterone on spatial memory, hippocampal neuronal excitability, and synaptic plasticity. *J Neurosci* **30**:1712–1720.
- Duvarci S and Paré D (2007) Glucocorticoids enhance the excitability of principal basolateral amygdala neurons. *J Neurosci* **27**:4482–4491.
- Elizalde N, Pastor PM, Garcia-García AL, Serres F, Venzala E, Huarte J, Ramírez MJ, Del Rio J, Sharp T, and Tordera RM (2010) Regulation of markers of synaptic function in mouse models of depression: chronic mild stress and decreased expression of VGLUT1. *J Neurochem* **114**:1302–1314.
- Engeland WC and Arnhold MM (2005) Neural circuitry in the regulation of adrenal corticosterone rhythmicity. *Endocrine* **28**:325–332.
- Evanson NK, Herman JP, Sakai RR, and Krause EG (2010) Nongenomic actions of adrenal steroids in the central nervous system. *J Neuroendocrinol* **22**:846–861.
- Evuarherhe O, Leggett JD, Waite EJ, Kershaw YM, Atkinson HC, and Lightman SL (2009) Organizational role for pubertal androgens on adult hypothalamic-pituitary-adrenal sensitivity to testosterone in the male rat. *J Physiol* **587**:2977–2985.
- Faber ES and Sah P (2005) Independent roles of calcium and voltage-dependent potassium currents in controlling spike frequency adaptation in lateral amygdala pyramidal neurons. *Eur J Neurosci* **22**:1627–1635.
- Fairchild G, Leitch MM, and Ingram CD (2003) Acute and chronic effects of corticosterone on 5-HT<sub>1A</sub> receptor-mediated autoinhibition in the rat dorsal raphe nucleus. *Neuropharmacology* **45**:925–934.
- Fenoglio KA, Brunson KL, and Baram TZ (2006) Hippocampal neuroplasticity induced by early-life stress: functional and molecular aspects. *Front Neuroendocrinol* **27**:180–192.
- Ferris CF and Stolberg T (2010) Imaging the immediate non-genomic effects of stress hormone on brain activity. *Psychoneuroendocrinology* **35**:5–14.
- french-Mullen JM (1995) Cortisol inhibition of calcium currents in guinea pig hippocampal CA1 neurons via G-protein-coupled activation of protein kinase C. *J Neurosci* **15**:903–911.
- Filipini D, Gijbsers K, Birmingham MK, and Dubrovsky B (1991) Effects of adrenal steroids and their reduced metabolites on hippocampal long-term potentiation. *J Steroid Biochem Mol Biol* **40**:87–92.
- Foy MR, Stanton ME, Levine S, and Thompson RF (1987) Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behav Neural Biol* **48**:138–149.
- Franklin TB and Mansuy IM (2010) Epigenetic inheritance in mammals: evidence for the impact of adverse environmental effects. *Neurobiol Dis* **39**:61–65.
- Fuchs BC and Bode BP (2006) Stressing out over survival: glutamine as an apoptotic modulator. *J Surg Res* **131**:26–40.
- Gagliardi L, Ho JT, and Torpy DJ (2010) Corticosteroid-binding globulin: the clinical significance of altered levels and heritable mutations. *Mol Cell Endocrinol* **316**:24–34.
- Gallagher JP, Orozco-Cabal LF, Liu J, and Shinnick-Gallagher P (2008) Synaptic physiology of central CRH system. *Eur J Pharmacol* **583**:215–225.
- Gao Y, Han H, Xu R, Cao J, Luo J, and Xu L (2008) Effects of prolonged exposure to context following contextual fear conditioning on synaptic properties in rat hippocampal slices. *Neurosci Res* **61**:385–389.
- Gelinas JN and Nguyen PV (2005) Beta-adrenergic receptor activation facilitates induction of a protein synthesis-dependent late phase of long-term potentiation. *J Neurosci* **25**:3294–3303.
- Gerges NZ, Stringer JL, and Alkadhi KA (2001) Combination of hypothyroidism and stress abolishes early LTP in the CA1 but not dentate gyrus of hippocampus of adult rats. *Brain Res* **922**:250–260.
- Gillies GE, Linton EA, and Lowry PJ (1982) Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. *Nature* **299**:355–357.
- Goldwater DS, Pavlides C, Hunter RG, Bloss EB, Hof PR, McEwen BS, and Morrison JH (2009) Structural and functional alterations to rat medial prefrontal cortex following chronic restraint stress and recovery. *Neuroscience* **164**:798–808.
- Gomez-Sanchez EP (2010) The mammalian mineralocorticoid receptor: tying down a promiscuous receptor. *Exp Physiol* **95**:13–18.
- Groc L, Choquet D, and Chauloff F (2008) The stress hormone corticosterone conditions AMPAR surface trafficking and synaptic potentiation. *Nat Neurosci* **11**:868–870.
- Grønli J, Fiske E, Murison R, Bjorvatn B, Sørensen E, Ursin R, and Portas CM (2007) Extracellular levels of serotonin and GABA in the hippocampus after chronic mild stress in rats. A microdialysis study in an animal model of depression. *Behav Brain Res* **181**:42–51.
- Gruss M, Braun K, Frey JU, and Korz V (2008) Maternal separation during a specific postnatal time window prevents reinforcement of hippocampal long-term potentiation in adolescent rats. *Neuroscience* **152**:1–7.
- Gutiérrez-Mecinas M, Trollope AF, Collins A, Morfett H, Hesketh SA, Kersanté F, and Reul JM (2011) Long-lasting behavioral responses to stress involve a direct interaction of glucocorticoid receptors with ERK1/2-MSK1-erk-1 signaling. *Proc Natl Acad Sci USA* **108**:13806–13811.
- Haam J, Halmos KC, Muglia LJ and Tasker G (2010) Rapid synaptic modulation of hypothalamic neurons by glucocorticoids requires the glucocorticoid receptor. *Soc Neurosci Abstract* **36**:389.19.
- Haj-Dahmane S and Shen RY (2011) Modulation of the serotonin system by endocannabinoid signaling. *Neuropharmacology* **61**:414–420.
- Hammond GL (1990) Molecular properties of corticosteroid binding globulin and the sex-steroid binding proteins. *Endocr Rev* **11**:65–79.
- Henley DE, Leendertz JA, Russell GM, Wood SA, Taheri S, Woltersdorf WW, and Lightman SL (2009) Development of an automated blood sampling system for use in humans. *J Med Eng Technol* **33**:199–208.
- Henley DE and Lightman SL (2011) New insights into corticosteroid-binding globulin and glucocorticoid delivery. *Neuroscience* **180**:1–8.
- Henn FA and Vollmayr B (2005) Stress models of depression: forming genetically vulnerable strains. *Neurosci Biobehav Rev* **29**:799–804.
- Herbert J (2012) Cortisol and depression: three questions for psychiatry. *Psychol Med* <http://dx.doi.org/10.1017/S0033291712000955>.
- Hesen W, Karst H, Meijer O, Cole TJ, Schmid W, de Kloet ER, Schütz G, and Joëls M (1996) Hippocampal cell responses in mice with a targeted glucocorticoid receptor gene disruption. *J Neurosci* **16**:6766–6774.
- Hill MN, McLaughlin RJ, Pan B, Fitzgerald ML, Roberts CJ, Lee TT, Karatsoreos IN, Mackie K, Viau V, Pickel VM, et al. (2011) Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. *J Neurosci* **31**:10506–10515.
- Hirata R, Matsumoto M, Judo C, Yamaguchi T, Izumi T, Yoshioka M, and Togashi H (2009) Possible relationship between the stress-induced synaptic response and metaplasticity in the hippocampal CA1 field of freely moving rats. *Synapse* **63**:549–556.
- Hirata R, Togashi H, Matsumoto M, Yamaguchi T, Izumi T, and Yoshioka M (2008) Characterization of stress-induced suppression of long-term potentiation in the hippocampal CA1 field of freely moving rats. *Brain Res* **1226**:27–32.
- Ho VM, Lee JA, and Martin KC (2011) The cell biology of synaptic plasticity. *Science* **334**:623–628.
- Holderbach R, Clark K, Moreau JL, Bischofberger J, and Normann C (2007) Enhanced long-term synaptic depression in an animal model of depression. *Biol Psychiatry* **62**:92–100.
- Hollenberg SM, Weinberger C, Ong ES, Cerelli G, Oro A, Lebo R, Thompson EB, Rosenfeld MG, and Evans RM (1985) Primary structure and expression of a functional human glucocorticoid receptor cDNA. *Nature* **318**:635–641.
- Holm MM, Nieto-Gonzalez JL, Vardya I, Henningsen K, Jayatissa MN, Wiborg O, and Jensen K (2011) Hippocampal GABAergic dysfunction in a rat chronic mild stress model of depression. *Hippocampus* **21**:422–433.

- Holmes A and Wellman CL (2009) Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neurosci Biobehav Rev* **33**:773–783.
- Holsboer F (2008) How can we realize the promise of personalized antidepressant medicines? *Nat Rev Neurosci* **9**:638–646.
- Holsboer F and Ising M (2010) Stress hormone regulation: biological role and translation into therapy. *Annu Rev Psychol* **61**:81–109, C101–C111.
- Hsu FC, Zhang GJ, Raol YS, Valentino RJ, Coulter DA, and Brooks-Kayal AR (2003) Repeated neonatal handling with maternal separation permanently alters hippocampal GABA<sub>A</sub> receptors and behavioral stress responses. *Proc Natl Acad Sci USA* **100**:12213–12218.
- Hu W, Zhang M, Czéh B, Flügge G, and Zhang W (2010) Stress impairs GABAergic network function in the hippocampus by activating nongenomic glucocorticoid receptors and affecting the integrity of the parvalbumin-expressing neuronal network. *Neuropsychopharmacology* **35**:1693–1707.
- Huang CC, Yang CH, and Hsu KS (2005) Do stress and long-term potentiation share the same molecular mechanisms? *Mol Neurobiol* **32**:223–235.
- Hugues S, Kessal K, Hunt MJ, and Garcia R (2003) A conditioned stressful environment causes short-term metaplastic-like changes in the rat nucleus accumbens. *J Neurophysiol* **90**:3224–3231.
- Isaac JT, Hjelmstad GO, Nicoll RA, and Malenka RC (1996) Long-term potentiation at single fiber inputs to hippocampal CA1 pyramidal cells. *Proc Natl Acad Sci USA* **93**:8710–8715.
- Ising M, Künzel HE, Binder EB, Nickel T, Modell S, and Holsboer F (2005) The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog Neuropsychopharmacol Biol Psychiatry* **29**:1085–1093.
- Ito H, Nagano M, Suzuki H, and Murakoshi T (2010) Chronic stress enhances synaptic plasticity due to disinhibition in the anterior cingulate cortex and induces hyper-locomotion in mice. *Neuropharmacology* **58**:746–757.
- Ivy AS, Rex CS, Chen Y, Dubé C, Maras PM, Grigoriadis DE, Gall CM, Lynch G, and Baram TZ (2010) Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *J Neurosci* **30**:13005–13015.
- Jasper MS and England WC (1991) Synchronous ultradian rhythms in adrenocortical secretion detected by microdialysis in awake rats. *Am J Physiol* **261**:R1257–68.
- Jedema HP and Grace AA (2003) Chronic exposure to cold stress alters electrophysiological properties of locus coeruleus neurons recorded in vitro. *Neuropsychopharmacology* **28**:63–72.
- Joëls M (2006) Corticosteroid effects in the brain: U-shape it. *Trends Pharmacol Sci* **27**:244–250.
- Joëls M and Baram TZ (2009) The neuro-symphony of stress. *Nat Rev Neurosci* **10**:459–466.
- Joëls M and de Kloet ER (1989) Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus. *Science* **245**:1502–1505.
- Joëls M and de Kloet ER (1990) Mineralocorticoid receptor-mediated changes in membrane properties of rat CA1 pyramidal neurons in vitro. *Proc Natl Acad Sci USA* **87**:4495–4498.
- Joëls M and de Kloet ER (1993) Corticosteroid actions on amino acid-mediated transmission in rat CA1 hippocampal cells. *J Neurosci* **13**:4082–4090.
- Joëls M, Fernandez G, and Roozendaal B (2011) Stress and emotional memory: a matter of timing. *Trends Cogn Sci* **15**:280–288.
- Joëls M, Hesen W, and de Kloet ER (1991) Mineralocorticoid hormones suppress serotonin-induced hyperpolarization of rat hippocampal CA1 neurons. *J Neurosci* **11**:2288–2294.
- Joëls M, Karst H, Krugers HJ, and Lucassen PJ (2007) Chronic stress: implications for neuronal morphology, function and neurogenesis. *Front Neuroendocrinol* **28**:72–96.
- Joëls M, Velzing E, Nair S, Verkuyl JM, and Karst H (2003) Acute stress increases calcium current amplitude in rat hippocampus: temporal changes in physiology and gene expression. *Eur J Neurosci* **18**:1315–1324.
- John S, Johnson TA, Sung MH, Biddie SC, Trump S, Koch-Paiz CA, Davis SR, Walker R, Meltzer PS, and Hager GL (2009) Kinetic complexity of the global response to glucocorticoid receptor action. *Endocrinology* **150**:1766–1774.
- John S, Sabo PJ, Thurman RE, Sung MH, Biddie SC, Johnson TA, Hager GL, and Stamatoyannopoulos JA (2011) Chromatin accessibility pre-determines glucocorticoid receptor binding patterns. *Nat Genet* **43**:264–268.
- Johnson LR, Farb C, Morrison JH, McEwen BS, and LeDoux JE (2005) Localization of glucocorticoid receptors at postsynaptic membranes in the lateral amygdala. *Neuroscience* **136**:289–299.
- Judo C, Matsumoto M, Yamazaki D, Hiraide S, Yanagawa Y, Kimura S, Shimamura K, and Togashi H (2010) Early stress exposure impairs synaptic potentiation in the rat medial prefrontal cortex underlying contextual fear extinction. *Neuroscience* **169**:1705–1714.
- Kalsbeek A and Buijs RM (2002) Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting. *Cell Tissue Res* **309**:109–118.
- Kamal A, Van der Harst JE, Kapteijn CM, Baars AJ, Spruijt BM, and Ramakers GM (2010) Announced reward counteracts the effects of chronic social stress on anticipatory behavior and hippocampal synaptic plasticity in rats. *Exp Brain Res* **201**:641–651.
- Kamphuis PJ, Gardoni F, Kamal A, Croiset G, Bakker JM, Cattabeni F, Gispen WH, van Bel F, Di Luca M, and Wiegand VM (2003) Long-lasting effects of neonatal dexamethasone treatment on spatial learning and hippocampal synaptic plasticity: involvement of the NMDA receptor complex. *FASEB J* **17**:911–913.
- Karssen AM, Meijer OC, van der Sandt IC, Lucassen PJ, de Lange EC, de Boer AG, and de Kloet ER (2001) Multidrug resistance P-glycoprotein hampers the access of cortisol but not of corticosterone to mouse and human brain. *Endocrinology* **142**:2686–2694.
- Karst H, Berger S, Erdmann G, Schütz G, and Joëls M (2010) Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proc Natl Acad Sci USA* **107**:14449–14454.
- Karst H, Berger S, Turiault M, Tronche F, Schütz G, and Joëls M (2005) Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc Natl Acad Sci USA* **102**:19204–19207.
- Karst H, de Kloet ER, and Joëls M (1999) Episodic corticosterone treatment accelerates kindling epileptogenesis and triggers long-term changes in hippocampal CA1 cells, in the fully kindled state. *Eur J Neurosci* **11**:889–898.
- Karst H and Joëls M (1991) The induction of corticosteroid actions on membrane properties of hippocampal CA1 neurons requires protein synthesis. *Neurosci Lett* **130**:27–31.
- Karst H and Joëls M (2001) Calcium currents in rat dentate granule cells are altered after adrenalectomy. *Eur J Neurosci* **14**:503–512.
- Karst H and Joëls M (2003) Effect of chronic stress on synaptic currents in rat hippocampal dentate gyrus neurons. *J Neurophysiol* **89**:625–633.
- Karst H and Joëls M (2005) Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. *J Neurophysiol* **94**:3479–3486.
- Karst H and Joëls M (2007) Brief RU 38486 treatment normalizes the effects of chronic stress on calcium currents in rat hippocampal CA1 neurons. *Neuropsychopharmacology* **32**:1830–1839.
- Karst H, Karten YJ, Reichardt HM, de Kloet ER, Schütz G, and Joëls M (2000) Corticosteroid actions in hippocampus require DNA binding of glucocorticoid receptor homodimers. *Nat Neurosci* **3**:977–978.
- Karst H, Nair S, Velzing E, Rumpff-van Essen L, Slagter E, Shinnick-Gallagher P, and Joëls M (2002) Glucocorticoids alter calcium conductances and calcium channel subunit expression in basolateral amygdala neurons. *Eur J Neurosci* **16**:1083–1089.
- Karst H, Wadman WJ, and Joëls M (1993) Long-term control by corticosteroids of the inward rectifier in rat CA1 pyramidal neurons, in vitro. *Brain Res* **612**:172–179.
- Karst H, Wadman WJ, and Joëls M (1994) Corticosteroid receptor-dependent modulation of calcium currents in rat hippocampal CA1 neurons. *Brain Res* **649**:234–242.
- Kavushansky A and Richter-Levin G (2006) Effects of stress and corticosterone on activity and plasticity in the amygdala. *J Neurosci Res* **84**:1580–1587.
- Kavushansky A, Vouimba RM, Cohen H, and Richter-Levin G (2006) Activity and plasticity in the CA1, the dentate gyrus, and the amygdala following controllable vs. uncontrollable water stress. *Hippocampus* **16**:35–42.
- Kehoe P and Bronzino JD (1999) Neonatal stress alters LTP in freely moving male and female adult rats. *Hippocampus* **9**:651–658.
- Kerr DS, Campbell LW, Applegate MD, Brodish A, and Landfield PW (1991) Chronic stress-induced acceleration of electrophysiological and morphometric biomarkers of hippocampal aging. *J Neurosci* **11**:1316–1324.
- Kerr DS, Campbell LW, Hao SY, and Landfield PW (1989) Corticosteroid modulation of hippocampal potentials: increased effect with aging. *Science* **245**:1505–1509.
- Kerr DS, Campbell LW, Thibault O, and Landfield PW (1992) Hippocampal glucocorticoid receptor activation enhances voltage-dependent Ca<sup>2+</sup> conductances: relevance to brain aging. *Proc Natl Acad Sci USA* **89**:8527–8531.
- Kessal K, Deschaux O, Chessel A, Xu L, Moreau JL, and Garcia R (2006) Fluoxetine reverses stress-induced fimbria-prefrontal long-term potentiation facilitation. *Neuroreport* **17**:319–322.
- Khakhsari M, Rashidy-Pour A, and Vafaei AA (2007) Central mineralocorticoid receptors are indispensable for corticosterone-induced impairment of memory retrieval in rats. *Neuroscience* **149**:729–738.
- Kim JJ and Diamond DM (2002) The stressed hippocampus, synaptic plasticity and lost memories. *Nat Rev Neurosci* **3**:453–462.
- Kim JJ, Foy MR, and Thompson RF (1996) Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. *Proc Natl Acad Sci USA* **93**:4750–4753.
- Kim JJ and Yoon KS (1998) Stress: metaplastic effects in the hippocampus. *Trends Neurosci* **21**:505–509.
- Kim JJ, Lee HJ, Han JS, and Packard MG (2001) Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *J Neurosci* **21**:5222–5228.
- Kim JJ, Lee HJ, Welday AC, Song E, Cho J, Sharp PE, Jung MW, and Blair HT (2007) Stress-induced alterations in hippocampal plasticity, place cells, and spatial memory. *Proc Natl Acad Sci USA* **104**:18297–18302.
- Kim JJ, Song EY, and Kosten TA (2006) Stress effects in the hippocampus: synaptic plasticity and memory. *Stress* **9**:1–11.
- Kirchheiner J, Lorch R, Lebedeva E, Seeringer A, Roots I, Sasse J, and Brockmüller J (2008) Genetic variants in FKBP5 affecting response to antidepressant drug treatment. *Pharmacogenomics* **9**:841–846.
- Kitchener P, Di Blasi F, Borrelli E, and Piazza PV (2004) Differences between brain structures in nuclear translocation and DNA binding of the glucocorticoid receptor during stress and the circadian cycle. *Eur J Neurosci* **19**:1837–1846.
- Klieber MA, Underhill C, Hammond GL, and Muller YA (2007) Corticosteroid-binding globulin, a structural basis for steroid transport and proteinase-triggered release. *J Biol Chem* **282**:29594–29603.
- Kling MA, Coleman VH, and Schulkin J (2009) Glucocorticoid inhibition in the treatment of depression: can we think outside the endocrine hypothalamus? *Depress Anxiety* **26**:641–649.
- Kole MH, Costoli T, Koolhaas JM, and Fuchs E (2004a) Bidirectional shift in the cornu ammonis 3 pyramidal dendritic organization following brief stress. *Neuroscience* **125**:337–347.
- Kole MH, Czéh B, and Fuchs E (2004b) Homeostatic maintenance in excitability of tree shrew hippocampal CA3 pyramidal neurons after chronic stress. *Hippocampus* **14**:742–751.
- Kole MH, Koolhaas JM, Luiten PG, and Fuchs E (2001) High-voltage-activated Ca<sup>2+</sup> currents and the excitability of pyramidal neurons in the hippocampal CA3 subfield in rats depend on corticosterone and time of day. *Neurosci Lett* **307**:53–56.
- Kole MH, Swan L, and Fuchs E (2002) The antidepressant tianeptine persistently modulates glutamate receptor currents of the hippocampal CA3 commissural associational synapse in chronically stressed rats. *Eur J Neurosci* **16**:807–816.

- Korz V and Frey JU (2003) Stress-related modulation of hippocampal long-term potentiation in rats: involvement of adrenal steroid receptors. *J Neurosci* **23**:7281–7287.
- Korz V and Frey JU (2005) Bidirectional modulation of hippocampal long-term potentiation under stress and no-stress conditions in basolateral amygdala-lesioned and intact rats. *J Neurosci* **25**:7393–7400.
- Krugers HJ, Goltstein PM, van der Linden S, and Joëls M (2006) Blockade of glucocorticoid receptors rapidly restores hippocampal CA1 synaptic plasticity after exposure to chronic stress. *Eur J Neurosci* **23**:3051–3055.
- Krugers HJ, Hoogenraad CC, and Groc L (2010) Stress hormones and AMPA receptor trafficking in synaptic plasticity and memory. *Nat Rev Neurosci* **11**:675–681.
- Krugers HJ, Zhou M, Joëls M, and Kindt M (2011) Regulation of excitatory synapses and fearful memories by stress hormones. *Front Behav Neurosci* **5**:62.
- Kruk MR, Halász J, Meelis W, and Haller J (2004) Fast positive feedback between the adrenocortical stress response and a brain mechanism involved in aggressive behavior. *Behav Neurosci* **118**:1062–1070.
- Kuhlmann S and Wolf OT (2006) Arousal and cortisol interact in modulating memory consolidation in healthy young men. *Behav Neurosci* **120**:217–223.
- Künzel HE, Binder EB, Nickel T, Ising M, Fuchs B, Majer M, Pfennig A, Ernst G, Kern N, Schmid DA, et al. (2003) Pharmacological and nonpharmacological factors influencing hypothalamic-pituitary-adrenocortical axis reactivity in acutely depressed psychiatric in-patients, measured by the dex-CRH test. *Neuropsychopharmacology* **28**:2169–2178.
- Kvetnansky R, Sabban EL, and Palkovits M (2009) Catecholaminergic systems in stress: structural and molecular genetic approaches. *Physiol Rev* **89**:535–606.
- Laaris N, Le Poul E, Laporte AM, Hamon M, and Lanfume Y (1999) Differential effects of stress on presynaptic and postsynaptic 5-hydroxytryptamine-1A receptors in the rat brain: an in vitro electrophysiological study. *Neuroscience* **91**:947–958.
- Landfield PW and Eldridge JC (1994) The glucocorticoid hypothesis of age-related hippocampal neurodegeneration: role of dysregulated intraneuronal calcium. *Ann NY Acad Sci* **746**:308–321; discussion 321–326.
- Lee EJ, Son GH, Chung S, Lee S, Kim J, Choi S, and Kim K (2011a) Impairment of fear memory consolidation in maternally stressed male mouse offspring: evidence for nongenomic glucocorticoid action on the amygdala. *J Neurosci* **31**:7131–7140.
- Lee YA and Goto Y (2011) Chronic stress modulation of prefrontal cortical NMDA receptor expression disrupts limbic structure–prefrontal cortex interaction. *Eur J Neurosci* **34**:426–436.
- Lee YA, Poirier P, Otani S, and Goto Y (2011b) Dorsal-ventral distinction of chronic stress-induced electrophysiological alterations in the rat medial prefrontal cortex. *Neuroscience* **183**:108–120.
- Lekman M, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ, Lipsky R, Wisniewski SR, Manji H, McMahon FJ, et al. (2008) The FKBP5-gene in depression and treatment response—an association study in the sequenced treatment alternatives to relieve depression (STAR\*D) cohort. *Biol Psychiatry* **63**:1103–1110.
- Leuner B and Gould E (2010) Structural plasticity and hippocampal function. *Annu Rev Psychol* **61**:111–140, C1–C3.
- Li HB, Mao RR, Zhang JC, Yang Y, Cao J, and Xu L (2008) Antistress effect of TRPV1 channel on synaptic plasticity and spatial memory. *Biol Psychiatry* **64**:286–292.
- Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, and Duman RS (2011) Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry* **69**:754–761.
- Liebmann L, Karst H, and Joëls M (2009) Effects of corticosterone and the beta-agonist isoproterenol on glutamate receptor-mediated synaptic currents in the rat basolateral amygdala. *Eur J Neurosci* **30**:800–807.
- Liebmann L, Karst H, Sidropoulou K, van Gemert N, Meijer OC, Poirazi P, and Joëls M (2008) Differential effects of corticosterone on the slow afterhyperpolarization in the basolateral amygdala and CA1 region: possible role of calcium channel subunits. *J Neurophysiol* **99**:958–968.
- Lightman SL and Conway-Campbell BL (2010) The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration. *Nat Rev Neurosci* **11**:710–718.
- Lightman SL, Windle RJ, Julian MD, Harbuz MS, Shanks N, Wood SA, Kershaw YM, and Ingram CD (2000) Significance of pulsatility in the HPA axis. *Novartis Found Symp* **227**:244–257, discussion 257–260.
- Lin HJ, Huang CC, and Hsu KS (2006) Effects of neonatal dexamethasone treatment on hippocampal synaptic function. *Ann Neurol* **59**:939–951.
- Liu L, Wang C, Ni X, and Sun J (2007) A rapid inhibition of NMDA receptor current by corticosterone in cultured hippocampal neurons. *Neurosci Lett* **420**:245–250.
- Liu W, Yuen EY, and Yan Z (2010a) The stress hormone corticosterone increases synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors via serum- and glucocorticoid-inducible kinase (SGK) regulation of the GDI-Rab4 complex. *J Biol Chem* **285**:6101–6108.
- Liu Y, Formisano L, Savtchouk I, Takayasu Y, Szabó G, Zukin RS, and Liu SJ (2010b) A single fear-inducing stimulus induces a transcription-dependent switch in synaptic AMPAR phenotype. *Nat Neurosci* **13**:223–231.
- Lösel RM and Wehling M (2008) Classic versus non-classic receptors for nongenomic mineralocorticoid responses: emerging evidence. *Front Neuroendocrinol* **29**:258–267.
- Lucassen PJ, Meerlo P, Naylor AS, van Dam AM, Dayer AG, Fuchs E, Oomen CA, and Czéh B (2010) Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: implications for depression and antidepressant action. *Eur Neuropsychopharmacol* **20**:1–17.
- Luine V (2002) Sex differences in chronic stress effects on memory in rats. *Stress* **5**:205–216.
- Luine VN, Beck KD, Bowman RE, Frankfurt M, and Macluskus NJ (2007) Chronic stress and neural function: accounting for sex and age. *J Neuroendocrinol* **19**:743–751.
- Lupien SJ, McEwen BS, Gunnar MR, and Heim C (2009) Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* **10**:434–445.
- Ma WP, Cao J, Tian M, Cui MH, Han HL, Yang YX, and Xu L (2007) Exposure to chronic constant light impairs spatial memory and influences long-term depression in rats. *Neurosci Res* **59**:224–230.
- Maccari S and Morley-Fletcher S (2007) Effects of prenatal restraint stress on the hypothalamus-pituitary-adrenal axis and related behavioural and neurobiological alterations. *Psychoneuroendocrinology* **32** (Suppl 1):S10–S15.
- Madison DV and Nicoll RA (1982) Noradrenaline blocks accommodation of pyramidal cell discharge in the hippocampus. *Nature* **299**:636–638.
- Maggio N and Segal M (2007) Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. *J Neurosci* **27**:5757–5765.
- Maggio N and Segal M (2009a) Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. *J Neurosci* **29**:2857–2866.
- Maggio N and Segal M (2009b) Differential modulation of long-term depression by acute stress in the rat dorsal and ventral hippocampus. *J Neurosci* **29**:8633–8638.
- Maggio N and Segal M (2010) Corticosteroid regulation of synaptic plasticity in the hippocampus. *Scientific World Journal* **10**:462–469.
- Maggio N and Segal M (2011) Persistent changes in ability to express long-term potentiation/depression in the rat hippocampus after juvenile/adult stress. *Biol Psychiatry* **69**:748–753.
- Maillet F, Qi H, Rocher C, Spedding M, Svenningsson P, and Jay TM (2008) Protection of stress-induced impairment of hippocampal/prefrontal LTP through blockade of glucocorticoid receptors: implication of MEK signaling. *Exp Neurol* **211**:593–596.
- Mana MJ and Grace AA (1997) Chronic cold stress alters the basal and evoked electrophysiological activity of rat locus coeruleus neurons. *Neuroscience* **81**:1055–1064.
- Manahan-Vaughan D and Braunewell KH (1999) Novelty acquisition is associated with induction of hippocampal long-term depression. *Proc Natl Acad Sci USA* **96**:8739–8744.
- Marin MF, Lord C, Andrews J, Juster RP, Sindi S, Arseneault-Lapierre G, Fiocco AJ, and Lupien SJ (2011) Chronic stress, cognitive functioning and mental health. *Neurobiol Learn Mem* **96**:583–595.
- Maroun M (2006) Stress reverses plasticity in the pathway projecting from the ventromedial prefrontal cortex to the basolateral amygdala. *Eur J Neurosci* **24**:2917–2922.
- Maroun M and Richter-Levin G (2003) Exposure to acute stress blocks the induction of long-term potentiation of the amygdala-prefrontal cortex pathway in vivo. *J Neurosci* **23**:4406–4409.
- Martin S, Henley JM, Holman D, Zhou M, Wiegert O, van Spronsen M, Joëls M, Hoogenraad CC, and Krugers HJ (2009) Corticosterone alters AMPAR mobility and facilitates bidirectional synaptic plasticity. *PLoS One* **4**:e4714.
- Matthews L, Berry A, Ohanian V, Ohanian J, Garside H, and Ray D (2008) Caveolin mediates rapid glucocorticoid effects and couples glucocorticoid action to the antiproliferative program. *Mol Endocrinol* **22**:1320–1330.
- McElligott ZA, Klug JR, Nobis WP, Patel S, Grueter BA, Kash TL, and Winder DG (2010) Distinct forms of Gq-receptor-dependent plasticity of excitatory transmission in the BNST are differentially affected by stress. *Proc Natl Acad Sci USA* **107**:2271–2276.
- McEwen BS (1999) Stress and hippocampal plasticity. *Annu Rev Neurosci* **22**:105–122.
- McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev* **87**:873–904.
- McEwen BS and Magarinos AM (1997) Stress effects on morphology and function of the hippocampus. *Ann NY Acad Sci* **821**:271–284.
- Meaney MJ and Szyf M (2005) Maternal care as a model for experience-dependent chromatin plasticity? *Trends Neurosci* **28**:456–463.
- Meijer OC, de Lange EC, Breimer DD, de Boer AG, Workel JO, and de Kloet ER (1998) Penetration of dexamethasone into brain glucocorticoid targets is enhanced in mdr1a P-glycoprotein knockout mice. *Endocrinology* **139**:1789–1793.
- Millstein RA and Holmes A (2007) Effects of repeated maternal separation on anxiety- and depression-related phenotypes in different mouse strains. *Neurosci Biobehav Rev* **31**:3–17.
- Mitra R, Jadhav S, McEwen BS, Vyas A, and Chattarji S (2005) Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proc Natl Acad Sci USA* **102**:9371–9376.
- Morsink MC, Joëls M, Sarabdjitsingh RA, Meijer OC, De Kloet ER, and Datson NA (2006a) The dynamic pattern of glucocorticoid receptor-mediated transcriptional responses in neuronal PC12 cells. *J Neurochem* **99**:1282–1298.
- Morsink MC, Steenbergen PJ, Vos JB, Karst H, Joëls M, De Kloet ER, and Datson NA (2006b) Acute activation of hippocampal glucocorticoid receptors results in different waves of gene expression throughout time. *J Neuroendocrinol* **18**:239–252.
- Musazzi L, Milanese M, Farisello P, Zappettini S, Tardito D, Barbiero VS, Bonifacino T, Mallei A, Baldelli P, Racagni G, et al. (2010) Acute stress increases depolarization-evoked glutamate release in the rat prefrontal/frontal cortex: the dampening action of antidepressants. *PLoS One* **5**:e8566.
- Narayanan R and Chattarji S (2010) Computational analysis of the impact of chronic stress on intrinsic and synaptic excitability in the hippocampus. *J Neurophysiol* **103**:3070–3083.
- Nederhof E and Schmidt MV (2012) Mismatch or cumulative stress: toward an integrated hypothesis of programming effects. *Physiol Behav* **106**:691–700.
- Nicoll RA and Schmitz D (2005) Synaptic plasticity at hippocampal mossy fibre synapses. *Nat Rev Neurosci* **6**:863–876.
- Niehusmann P, Seifert G, Clark K, Atas HC, Herpfer I, Fiebich B, Bischofberger J, and Normann C (2010) Coincidence detection and stress modulation of spike time-dependent long-term depression in the hippocampus. *J Neurosci* **30**:6225–6235.

- Noorlander CW, Visser GH, Ramakers GM, Nikkels PG, and de Graan PN (2008) Prenatal corticosteroid exposure affects hippocampal plasticity and reduces lifespan. *Dev Neurobiol* **68**:237–246.
- Oh MM, McKay BM, Power JM, and Disterhoft JF (2009) Learning-related postburst afterhyperpolarization reduction in CA1 pyramidal neurons is mediated by protein kinase A. *Proc Natl Acad Sci USA* **106**:1620–1625.
- Oitzl MS, Champagne DL, van der Veen R, and de Kloet ER (2010) Brain development under stress: hypotheses of glucocorticoid actions revisited. *Neurosci Biobehav Rev* **34**:853–866.
- Oitzl MS and de Kloet ER (1992) Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. *Behav Neurosci* **106**:62–71.
- Oitzl MS, Reichardt HM, Joëls M, and de Kloet ER (2001) Point mutation in the mouse glucocorticoid receptor preventing DNA binding impairs spatial memory. *Proc Natl Acad Sci USA* **98**:12790–12795.
- Oitzl MS, Workel JO, Flutterm J, Frösch F, and De Kloet ER (2000) Maternal deprivation affects behaviour from youth to senescence: amplification of individual differences in spatial learning and memory in senescent Brown Norway rats. *Eur J Neurosci* **12**:3771–3780.
- Olijslagers JE, de Kloet ER, Elgersma Y, van Woerden GM, Joëls M, and Karst H (2008) Rapid changes in hippocampal CA1 pyramidal cell function via pre- as well as postsynaptic membrane mineralocorticoid receptors. *Eur J Neurosci* **27**:2542–2550.
- Ooishi Y, Mukai H, Hojo Y, Murakami G, Hasegawa Y, Shindo T, Morrison JH, Kimoto T, and Kawato S (2012) Estradiol rapidly rescues synaptic transmission from corticosterone-induced suppression via synaptic/extranuclear steroid receptors in the hippocampus. *Cereb Cortex* **22**:926–936.
- Oomen CA, Girardi CE, Cahyadi R, Verbeek EC, Krugers H, Joëls M, and Lucassen PJ (2009) Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS One* **4**:e3675.
- Oomen CA, Mayer JL, de Kloet ER, Joëls M, and Lucassen PJ (2007) Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. *Eur J Neurosci* **26**:3395–3401.
- Oomen CA, Soeters H, Audureau N, Vermunt L, van Hasselt FN, Manders EM, Joëls M, Lucassen PJ, and Krugers H (2010) Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *J Neurosci* **30**:6635–6645.
- Orchinik M, Murray TF, and Moore FL (1991) A corticosteroid receptor in neuronal membranes. *Science* **252**:1848–1851.
- Orchinik M, Murray TF, Franklin PH, and Moore FL (1992) Guanyl nucleotides modulate binding to steroid receptors in neuronal membranes. *Proc Natl Acad Sci USA* **89**:3830–3834.
- Overton PG, Tong ZY, Brain PF, and Clark D (1996) Preferential occupation of mineralocorticoid receptors by corticosterone enhances glutamate-induced burst firing in rat midbrain dopaminergic neurons. *Brain Res* **737**:146–154.
- Pariante CM (2008) The role of multi-drug resistance p-glycoprotein in glucocorticoid function: studies in animals and relevance in humans. *Eur J Pharmacol* **583**:263–271.
- Pascual-Le Tallec L and Lombès M (2005) The mineralocorticoid receptor: a journey exploring its diversity and specificity of action. *Mol Endocrinol* **19**:2211–2221.
- Pasricha N, Joëls M, and Karst H (2011) Rapid effects of corticosterone in the mouse dentate gyrus via a nongenomic pathway. *J Neuroendocrinol* **23**:143–147.
- Passecker J, Hok V, Della-Chiesa A, Chah E, and O'Mara SM (2011) Dissociation of dorsal hippocampal regional activation under the influence of stress in freely behaving rats. *Front Behav Neurosci* **5**:66.
- Pavlidis C, Kimura A, Magariños AM, and McEwen BS (1994) Type I adrenal steroid receptors prolong hippocampal long-term potentiation. *Neuroreport* **5**:2673–2677.
- Pavlidis C, Kimura A, Magariños AM, and McEwen BS (1995) Hippocampal homosynaptic long-term depression/depotentiation induced by adrenal steroids. *Neuroscience* **68**:379–385.
- Pavlidis C, Nivón LG, and McEwen BS (2002) Effects of chronic stress on hippocampal long-term potentiation. *Hippocampus* **12**:245–257.
- Pavlidis C, Ogawa S, Kimura A, and McEwen BS (1996) Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. *Brain Res* **738**:229–235.
- Pavlidis C, Watanabe Y, and McEwen BS (1993) Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus* **3**:183–192.
- Pedram A, Razandi M, Sainson RC, Kim JK, Hughes CC, and Levin ER (2007) A conserved mechanism for steroid receptor translocation to the plasma membrane. *J Biol Chem* **282**:22278–22288.
- Peoples RW, White G, Lovinger DM, and Weight FF (1997) Ethanol inhibition of N-methyl-D-aspartate-activated current in mouse hippocampal neurones: whole-cell patch-clamp analysis. *Br J Pharmacol* **122**:1035–1042.
- Pfaff DW, Silva MT, and Weiss JM (1971) Telemetered recording of hormone effects on hippocampal neurones. *Science* **172**:394–395.
- Pojoga LH, Romero JR, Yao TM, Loutraris P, Ricchiuti V, Coutinho P, Guo C, Lapointe N, Stone JR, Adler GK, et al. (2010) Caveolin-1 ablation reduces the adverse cardiovascular effects of N-omega-nitro-L-arginine methyl ester and angiotensin II. *Endocrinology* **151**:1236–1246.
- Popoli M, Yan Z, McEwen BS, and Sanacora G (2012) The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci* **13**:22–37.
- Prager EM, Brielmaier J, Bergstrom HC, McGuire J, and Johnson LR (2010) Localization of mineralocorticoid receptors at mammalian synapses. *PLoS One* **5**:e14344.
- Prossnitz ER, Arterburn JB, Smith HO, Oprea TI, Sklar LA, and Hathaway HJ (2008) Estrogen signaling through the transmembrane G protein-coupled receptor GPR30. *Annu Rev Physiol* **70**:165–190.
- Pryce CR, Rüedi-Bettschen D, Dettling AC, Weston A, Rüssig H, Ferger B, and Feldon J (2005) Long-term effects of early-life environmental manipulations in rodents and primates: potential animal models in depression research. *Neurosci Biobehav Rev* **29**:649–674.
- Pu Z, Krugers HJ, and Joëls M (2007) Corticosterone time-dependently modulates beta-adrenergic effects on long-term potentiation in the hippocampal dentate gyrus. *Learn Mem* **14**:359–367.
- Pu Z, Krugers HJ, and Joëls M (2009) Beta-adrenergic facilitation of synaptic plasticity in the rat basolateral amygdala in vitro is gradually reversed by corticosterone. *Learn Mem* **16**:155–160.
- Qi H, Mailliet F, Spedding M, Rocher C, Zhang X, Delagrangé P, McEwen B, Jay TM, and Svenningsson P (2009) Antidepressants reverse the attenuation of the neurotrophic MEK/MAPK cascade in frontal cortex by elevated platform stress; reversal of effects on LTP is associated with GluA1 phosphorylation. *Neuropharmacology* **56**:37–46.
- Qiu S, Champagne DL, Peters M, Catania EH, Weeber EJ, Levitt P, and Pimenta AF (2010) Loss of limbic system-associated membrane protein leads to reduced hippocampal mineralocorticoid receptor expression, impaired synaptic plasticity, and spatial memory deficit. *Biol Psychiatry* **68**:197–204.
- Quan M, Zheng C, Zhang N, Han D, Tian Y, Zhang T, and Yang Z (2011a) Impairments of behavior, information flow between thalamus and cortex, and prefrontal cortical synaptic plasticity in an animal model of depression. *Brain Res Bull* **85**:109–116.
- Quan MN, Zhang N, Wang YY, Zhang T, and Yang Z (2011b) Possible antidepressant effects and mechanisms of memantine in behaviors and synaptic plasticity of a depression rat model. *Neuroscience* **182**:88–97.
- Radecki DT, Brown LM, Martinez J, and Teyler TJ (2005) BDNF protects against stress-induced impairments in spatial learning and memory and LTP. *Hippocampus* **15**:246–253.
- Reiheld CT, Teyler TJ, and Vardaris RM (1984) Effects of corticosterone on the electrophysiology of hippocampal CA1 pyramidal cells in vitro. *Brain Res Bull* **12**:349–353.
- Reul JM and de Kloet ER (1985) Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology* **117**:2505–2511.
- Revollo JR and Cidlowski JA (2009) Mechanisms generating diversity in glucocorticoid receptor signaling. *Ann NY Acad Sci* **1179**:167–178.
- Rey M, Carlier E, and Soumireu-Mourat B (1987) Effects of corticosterone on hippocampal slice electrophysiology in normal and adrenalectomized BALB/c mice. *Neuroendocrinology* **46**:424–429.
- Richter-Levin G and Maroun M (2010) Stress and amygdala suppression of meta-plasticity in the medial prefrontal cortex. *Cereb Cortex* **20**:2433–2441.
- Rimmele U, Domes G, Mathiak K, and Hautzinger M (2003) Cortisol has different effects on human memory for emotional and neutral stimuli. *Neuroreport* **14**:2485–2488.
- Rocher C, Spedding M, Munoz C, and Jay TM (2004) Acute stress-induced changes in hippocampal/prefrontal circuits in rats: effects of antidepressants. *Cereb Cortex* **14**:224–229.
- Rodríguez Manzanares PA, Isoardi NA, Carrer HF, and Molina VA (2005) Previous stress facilitates fear memory, attenuates GABAergic inhibition, and increases synaptic plasticity in the rat basolateral amygdala. *J Neurosci* **25**:8725–8734.
- Rooszendaal B, de Quervain DJ, Schelling G, and McGaugh JL (2004) A systemically administered beta-adrenoceptor antagonist blocks corticosterone-induced impairment of contextual memory retrieval in rats. *Neurobiol Learn Mem* **81**:150–154.
- Rooszendaal B, Hernandez A, Cabrera SM, Hagewoud R, Malvaez M, Stefankov DP, Haettig J, and Wood MA (2010) Membrane-associated glucocorticoid activity is necessary for modulation of long-term memory via chromatin modification. *J Neurosci* **30**:5037–5046.
- Rooszendaal B, McEwen BS, and Chattarji S (2009) Stress, memory and the amygdala. *Nat Rev Neurosci* **10**:423–433.
- Rooszendaal B, Okuda S, Van der Zee EA, and McGaugh JL (2006) Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc Natl Acad Sci USA* **103**:6741–6746.
- Rose JD, Moore FL, and Orchinik M (1993) Rapid neurophysiological effects of corticosterone on medullary neurons: relationship to stress-induced suppression of courtship clasping in an amphibian. *Neuroendocrinology* **57**:815–824.
- Rosner W (1990) The functions of corticosteroid-binding globulin and sex hormone-binding globulin: recent advances. *Endocr Rev* **11**:80–91.
- Ryan B, Musazzi L, Mallei A, Tardito D, Gruber SH, El Khoury A, Anwyl R, Racagni G, Mathé AA, Rowan MJ, et al. (2009) Remodelling by early-life stress of NMDA receptor-dependent synaptic plasticity in a gene-environment rat model of depression. *Int J Neuropsychopharmacol* **12**:553–559.
- Ryan BK, Vollmayr B, Klyubin I, Gass P, and Rowan MJ (2010) Persistent inhibition of hippocampal long-term potentiation in vivo by learned helplessness stress. *Hippocampus* **20**:758–767.
- Saal D, Dong Y, Bonci A, and Malenka RC (2003) Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* **37**:577–582.
- Sajadi AA, Samaei SA, and Rashidy-Pour A (2006) Intra-hippocampal microinjections of anisomycin did not block glucocorticoid-induced impairment of memory retrieval in rats: an evidence for non-genomic effects of glucocorticoids. *Behav Brain Res* **173**:158–162.
- Saphier D and Feldman S (1988) Iontophoretic application of glucocorticoids inhibits identified neurones in the rat paraventricular nucleus. *Brain Res* **453**:183–190.
- Sarabdjitsingh RA, Conway-Campbell BL, Leggett JD, Waite EJ, Meijer OC, de Kloet ER, and Lightman SL (2010a) Stress responsiveness varies over the ultradian glucocorticoid cycle in a brain-region-specific manner. *Endocrinology* **151**:5369–5379.
- Sarabdjitsingh RA, Isenia S, Polman A, Mijalkovic J, Lachize S, Datson N, de Kloet ER, and Meijer OC (2010b) Disrupted corticosterone pulsatile patterns attenuate responsiveness to glucocorticoid signaling in rat brain. *Endocrinology* **151**:1177–1186.
- Sarabdjitsingh RA, Joëls M, and de Kloet ER (2012) Glucocorticoid pulsatility and rapid corticosteroid actions in the central stress response. *Physiol Behav* **106**:73–80.
- Sarabdjitsingh RA, Spiga F, Oitzl MS, Kershaw Y, Meijer OC, Lightman SL, and de

- Kloet ER (2010c) Recovery from disrupted ultradian glucocorticoid rhythmicity reveals a dissociation between hormonal and behavioural stress responsiveness. *J Neuroendocrinol* **22**:862–871.
- Sarginson JE, Lazzeroni LC, Ryan HS, Schatzberg AF, and Murphy GM Jr (2010) FKBP5 polymorphisms and antidepressant response in geriatric depression. *Am J Med Genet B Neuroepidemiol* **153B**:554–560.
- Sawchenko PE, Li HY, and Ericsson A (2000) Circuits and mechanisms governing hypothalamic responses to stress: a tale of two paradigms. *Prog Brain Res* **122**: 61–78.
- Schmidt MV (2010) Molecular mechanisms of early life stress—lessons from mouse models. *Neurosci Biobehav Rev* **34**:845–852.
- Schwabe L, Oitzl MS, Philippson C, Richter S, Bohringer A, Wippich W, and Schachinger H (2007) Stress modulates the use of spatial versus stimulus-response learning strategies in humans. *Learn Mem* **14**:109–116.
- Schwabe L, Schächinger H, de Kloet ER, and Oitzl MS (2010a) Corticosteroids operate as a switch between memory systems. *J Cogn Neurosci* **22**:1362–1372.
- Schwabe L, Tegenthoff M, Höfken O, and Wolf OT (2010b) Concurrent glucocorticoid and noradrenergic activity shifts instrumental behavior from goal-directed to habitual control. *J Neurosci* **30**:8190–8196.
- Seale JW, Wood SA, Atkinson HC, Lightman SL, and Harbuz MS (2005) Organizational role for testosterone and estrogen on adult hypothalamic-pituitary-adrenal axis activity in the male rat. *Endocrinology* **146**:1973–1982.
- Seckl JR and Holmes MC (2007) Mechanisms of disease: glucocorticoids, their placental metabolism and fetal ‘programming’ of adult pathophysiology. *Nat Clin Pract Endocrinol Metab* **3**:479–488.
- Seckl JR and Walker BR (2004) 11beta-hydroxysteroid dehydrogenase type 1 as a modulator of glucocorticoid action: from metabolism to memory. *Trends Endocrinol Metab* **15**:418–424.
- Shakesby AC, Anwyl R, and Rowan MJ (2002) Overcoming the effects of stress on synaptic plasticity in the intact hippocampus: rapid actions of serotonergic and antidepressant agents. *J Neurosci* **22**:3638–3644.
- Shanks N, Windle RJ, Perks PA, Harbuz MS, Jessop DS, Ingram CD, and Lightman SL (2000) Early-life exposure to endotoxin alters hypothalamic-pituitary-adrenal function and predisposition to inflammation. *Proc Natl Acad Sci USA* **97**:5645–5650.
- Shansky RM and Morrison JH (2009) Stress-induced dendritic remodeling in the medial prefrontal cortex: effects of circuit, hormones and rest. *Brain Res* **1293**: 108–113.
- Shors TJ (2006) Stressful experience and learning across the lifespan. *Annu Rev Psychol* **57**:55–85.
- Shors TJ and Dryver E (1994) Effect of stress and long-term potentiation (LTP) on subsequent LTP and the theta burst response in the dentate gyrus. *Brain Res* **666**:232–238.
- Shors TJ and Thompson RF (1992) Acute stress impairs (or induces) synaptic long-term potentiation (LTP) but does not affect paired-pulse facilitation in the stratum radiatum of rat hippocampus. *Synapse* **11**:262–265.
- Shors TJ, Seib TB, Levine S, and Thompson RF (1989) Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. *Science* **244**:224–226.
- Shoupe D (2001) HRT dosing regimens: continuous versus cyclic-pros and cons. *Int J Fertil Womens Med* **46**:7–15.
- Smriga M, Saito H, and Nishiyama N (1996) Hippocampal long- and short-term potentiation is modulated by adrenalectomy and corticosterone. *Neuroendocrinology* **64**:35–41.
- So AY, Chaivorapol C, Bolton EC, Li H, and Yamamoto KR (2007) Determinants of cell- and gene-specific transcriptional regulation by the glucocorticoid receptor. *PLoS Genet* **3**:e94.
- Son GH, Chung S, Choe HK, Kim HD, Baik SM, Lee H, Lee HW, Choi S, Sun W, Kim H, et al. (2008) Adrenal peripheral clock controls the autonomous circadian rhythm of glucocorticoid by causing rhythmic steroid production. *Proc Natl Acad Sci USA* **105**:20970–20975.
- Son GH, Geum D, Chung S, Kim EJ, Jo JH, Kim CM, Lee KH, Kim H, Choi S, Kim HT, et al. (2006) Maternal stress produces learning deficits associated with impairment of NMDA receptor-mediated synaptic plasticity. *J Neurosci* **26**:3309–3318.
- Spiga F, Waite EJ, Liu Y, Kershaw YM, Aguilera G, and Lightman SL (2011) ACTH-dependent ultradian rhythm of corticosterone secretion. *Endocrinology* **152**:1448–1457.
- Spyrka J, Danielewicz J, and Hess G (2011) Brief neck restraint stress enhances long-term potentiation and suppresses long-term depression in the dentate gyrus of the mouse. *Brain Res Bull* **85**:363–367.
- Spyrka J and Hess G (2010) Repeated restraint-induced modulation of long-term potentiation in the dentate gyrus of the mouse. *Brain Res* **1320**:28–33.
- Srivareerat M, Tran TT, Alzoubi KH, and Alkadhi KA (2009) Chronic psychosocial stress exacerbates impairment of cognition and long-term potentiation in beta-amyloid rat model of Alzheimer’s disease. *Biol Psychiatry* **65**:918–926.
- Stavreva DA, Wiench M, John S, Conway-Campbell BL, McKenna MA, Pooley JR, Johnson TA, Voss TC, Lightman SL, and Hager GL (2009) Ultradian hormone stimulation induces glucocorticoid receptor-mediated changes of gene transcription. *Nat Cell Biol* **11**:1093–1102.
- Sterlemann V, Rammes G, Wolf M, Liebl C, Ganea K, Müller MB, and Schmidt MV (2010) Chronic social stress during adolescence induces cognitive impairment in aged mice. *Hippocampus* **20**:540–549.
- Stevenson CW, Marsden CA, and Mason R (2008) Early life stress causes FG-7142-induced corticolimbic dysfunction in adulthood. *Brain Res* **1193**:43–50.
- Stewart CA, Petrie RX, Balfour DJ, Matthews K, and Reid IC (2004) Enhanced evoked responses after early adversity and repeated platform exposure: the neurobiology of vulnerability? *Biol Psychiatry* **55**:868–870.
- Straube T and Frey JU (2003) Involvement of beta-adrenergic receptors in protein synthesis-dependent late long-term potentiation (LTP) in the dentate gyrus of freely moving rats: the critical role of the LTP induction strength. *Neuroscience* **119**:473–479.
- Sullivan R, Wilson DA, Feldon J, Yee BK, Meyer U, Richter-Levin G, Avi A, Michael T, Gruss M, Bock J, et al. (2006) The International Society for Developmental Psychobiology Annual Meeting Symposium: impact of early life experiences on brain and behavioral development. *Dev Psychobiol* **48**:583–602.
- Tang AC and Zou B (2002) Neonatal exposure to novelty enhances long-term potentiation in CA1 of the rat hippocampus. *Hippocampus* **12**:398–404.
- Tapp WN, Holaday JW, and Natelson BH (1984) Ultradian glucocorticoid rhythms in monkeys and rats continue during stress. *Am J Physiol* **247**:R866–871.
- Tasker JG, Di S, and Malcher-Lopes R (2006) Minireview: rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology* **147**:5549–5556.
- Tasker JG and Herman JP (2011) Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic-pituitary-adrenal axis. *Stress* **14**:398–406.
- Ter Horst GJ, Wichmann R, Gerrits M, Westenbroek C, and Lin Y (2009) Sex differences in stress responses: focus on ovarian hormones. *Physiol Behav* **97**:239–249.
- Teschmacher A, Zeise ML, and Ziegglansberger W (1996) Corticosterone-induced decrease of inhibitory postsynaptic potentials in rat hippocampal pyramidal neurons in vitro depends on cytosolic factors. *Neurosci Lett* **215**:83–86.
- Thomas MJ, Moody TD, Makhinson M, and O’Dell TJ (1996) Activity-dependent beta-adrenergic modulation of low frequency stimulation induced LTP in the hippocampal CA1 region. *Neuron* **17**:475–482.
- Tordera RM, Garcia-García AL, Elizalde N, Segura V, Aso E, Venzala E, Ramírez MJ, and Del Río J (2011) Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. *Eur Neuropsychopharmacol* **21**:23–32.
- Tran TT, Srivareerat M, and Alkadhi KA (2011) Chronic psychosocial stress accelerates impairment of long-term memory and late-phase long-term potentiation in an at-risk model of Alzheimer’s disease. *Hippocampus* **21**:724–732.
- Tsai SJ, Hong CJ, Chen TJ, and Yu YW (2007) Lack of supporting evidence for a genetic association of the FKBP5 polymorphism and response to antidepressant treatment. *Am J Med Genet B Neuroepidemiol* **144B**:1097–1098.
- Tse YC, Bagot RC, Hutter JA, Wong AS, and Wong TP (2011) Modulation of synaptic plasticity by stress hormone associates with plastic alteration of synaptic NMDA receptor in the adult hippocampus. *PLoS One* **6**:e27215.
- Turner JD, Alt SR, Cao L, Vernocchi S, Trifonova S, Battello N, and Muller CP (2010) Transcriptional control of the glucocorticoid receptor: CpG islands, epigenetics and more. *Biochem Pharmacol* **80**:1860–1868.
- Tzingounis AV and Wadiche JI (2007) Glutamate transporters: confining runaway excitation by shaping synaptic transmission. *Nat Rev Neurosci* **8**:935–947.
- Ulrich-Lai YM and Herman JP (2009) Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* **10**:397–409.
- Ulrich-Lai YM, Arnold MM, and Engeland WC (2006) Adrenal splanchnic innervation contributes to the diurnal rhythm of plasma corticosterone in rats by modulating adrenal sensitivity to ACTH. *Am J Physiol Regul Integr Comp Physiol* **290**:R1128–1135.
- van Aken MO, Pereira AM, van Thiel SW, van den Berg G, Frölich M, Veldhuis JD, Romijn JA, and Roelfsema F (2005) Irregular and frequent cortisol secretory episodes with preserved diurnal rhythmicity in primary adrenal Cushing’s syndrome. *J Clin Endocrinol Metab* **90**:1570–1577.
- van der Laan S and Meijer OC (2008) Pharmacology of glucocorticoids: beyond receptors. *Eur J Pharmacol* **585**:483–491.
- van Gemert NG and Joëls M (2006) Effect of chronic stress and mifepristone treatment on voltage-dependent Ca<sup>2+</sup> currents in rat hippocampal dentate gyrus. *J Neuroendocrinol* **18**:732–741.
- van Gemert NG, Carvalho DM, Karst H, van der Laan S, Zhang M, Meijer OC, Hell JW, and Joëls M (2009) Dissociation between rat hippocampal CA1 and dentate gyrus cells in their response to corticosterone: effects on calcium channel protein and current. *Endocrinology* **150**:4615–4624.
- van Hasselt FN, Boudewijns ZS, van der Knaap NJ, Krugers HJ, and Joëls M (2012b) Maternal care received by individual pups correlates with adult CA1 dendritic morphology and synaptic plasticity in a sex-dependent manner. *J Neuroendocrinol* **24**:331–340.
- van Hasselt FN, Cornelisse S, Zhang TY, Meaney MJ, Velzing EH, Krugers HJ, and Joëls M (2012a) Adult hippocampal glucocorticoid receptor expression and dentate synaptic plasticity correlate with maternal care received by individuals early in life. *Hippocampus* **22**:255–266.
- van Stegeren AH, Roozendaal B, Kindt M, Wolf OT, and Joëls M (2010) Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. *Neurobiol Learn Mem* **93**:56–65.
- Verkuyil JM, Hemby SE, and Joëls M (2004) Chronic stress attenuates GABAergic inhibition and alters gene expression of parvocellular neurons in rat hypothalamus. *Eur J Neurosci* **20**:1665–1673.
- Verkuyil JM, Karst H, and Joëls M (2005) GABAergic transmission in the rat paraventricular nucleus of the hypothalamus is suppressed by corticosterone and stress. *Eur J Neurosci* **21**:113–121.
- Vidal C, Jordan W, and Ziegglansberger W (1986) Corticosterone reduces the excitability of hippocampal pyramidal cells in vitro. *Brain Res* **383**:54–59.
- Von Frijtag JC, Kamal A, Reijmers LG, Schrama LH, van den Bos R, and Spruijt BM (2001) Chronic imipramine treatment partially reverses the long-term changes of hippocampal synaptic plasticity in socially stressed rats. *Neurosci Lett* **309**:153–156.
- Vouimba RM, Yaniv D, and Richter-Levin G (2007) Glucocorticoid receptors and beta-adrenoreceptors in basolateral amygdala modulate synaptic plasticity in hippocampal dentate gyrus, but not in area CA1. *Neuropharmacology* **52**:244–252.
- Vouimba RM, Yaniv D, Diamond D, and Richter-Levin G (2004) Effects of inescapable stress on LTP in the amygdala versus the dentate gyrus of freely behaving rats. *Eur J Neurosci* **19**:1887–1894.
- Walker JJ, Terry JR, and Lightman SL (2010) Origin of ultradian pulsatility in the hypothalamic-pituitary-adrenal axis. *Proc Biol Sci* **277**:1627–1633.

- Wamsteeker JI, Kuzmiski JB, and Bains JS (2010) Repeated stress impairs endocannabinoid signaling in the paraventricular nucleus of the hypothalamus. *J Neurosci* **30**:11188–11196.
- Wang W, Sun D, Pan B, Roberts CJ, Sun X, Hillard CJ, and Liu QS (2010) Deficiency in endocannabinoid signaling in the nucleus accumbens induced by chronic unpredictable stress. *Neuropsychopharmacology* **35**:2249–2261.
- Wang XD, Rammes G, Kraev I, Wolf M, Liebl C, Scharf SH, Rice CJ, Wurst W, Holsboer F, Deussing JM, et al. (2011) Forebrain CRF<sub>1</sub> modulates early-life stress-programmed cognitive deficits. *J Neurosci* **31**:13625–13634.
- Weinstock M (2011) Sex-dependent changes induced by prenatal stress in cortical and hippocampal morphology and behaviour in rats: an update. *Stress* **14**:604–613.
- Weitzman ED, Fukushima D, Nogueira C, Roffwarg H, Gallagher TF, and Hellman L (1971) Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab* **33**:14–22.
- Werkman TR, Van der Linden S, and Joëls M (1997) Corticosteroid effects on sodium and calcium currents in acutely dissociated rat CA1 hippocampal neurons. *Neuroscience* **78**:663–672.
- Whitlock JR, Heynen AJ, Shuler MG, and Bear MF (2006) Learning induces long-term potentiation in the hippocampus. *Science* **313**:1093–1097.
- Wiegert JS, Hofmann F, Bading H, and Bengtson CP (2009) A transcription-dependent increase in miniature EPSC frequency accompanies late-phase plasticity in cultured hippocampal neurons. *BMC Neurosci* **10**:124.
- Wiegert O, Joëls M, and Krugers H (2006) Timing is essential for rapid effects of corticosterone on synaptic potentiation in the mouse hippocampus. *Learn Mem* **13**:110–113.
- Williams CL and McGaugh JL (1993) Reversible lesions of the nucleus of the solitary tract attenuate the memory-modulating effect of posttraining epinephrine. *Behav Neurosci* **107**:955–962.
- Windle RJ, Wood S, Shanks N, Perks P, Conde GL, da Costa AP, Ingram CD, and Lightman SL (1997) Endocrine and behavioural responses to noise stress: comparison of virgin and lactating female rats during non-disrupted maternal activity. *J Neuroendocrinol* **9**:407–414.
- Windle RJ, Wood SA, Kershaw YM, Lightman SL, Ingram CD, and Harbuz MS (2001) Increased corticosterone pulse frequency during adjuvant-induced arthritis and its relationship to alterations in stress responsiveness. *J Neuroendocrinol* **13**:905–911.
- Windle RJ, Wood SA, Lightman SL, and Ingram CD (1998a) The pulsatile characteristics of hypothalamo-pituitary-adrenal activity in female Lewis and Fischer 344 rats and its relationship to differential stress responses. *Endocrinology* **139**:4044–4052.
- Windle RJ, Wood SA, Shanks N, Lightman SL, and Ingram CD (1998b) Ultradian rhythm of basal corticosterone release in the female rat: dynamic interaction with the response to acute stress. *Endocrinology* **139**:443–450.
- Wong TP, Howland JG, Robillard JM, Ge Y, Yu W, Titterness AK, Brebner K, Liu L, Weinberg J, Christie BR, et al. (2007) Hippocampal long-term depression mediates acute stress-induced spatial memory retrieval impairment. *Proc Natl Acad Sci USA* **104**:11471–11476.
- Wyrwoll CS, Holmes MC, and Seckl JR (2011) 11 $\beta$ -Hydroxysteroid dehydrogenases and the brain: from zero to hero, a decade of progress. *Front Neuroendocrinol* **32**:265–286.
- Xiong W, Wei H, Xiang X, Cao J, Dong Z, Wang Y, Xu T, and Xu L (2004) The effect of acute stress on LTP and LTD induction in the hippocampal CA1 region of anesthetized rats at three different ages. *Brain Res* **1005**:187–192.
- Xu L, Anwyl R, and Rowan MJ (1997) Behavioural stress facilitates the induction of long-term depression in the hippocampus. *Nature* **387**:497–500.
- Xu L, Holscher C, Anwyl R, and Rowan MJ (1998) Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. *Proc Natl Acad Sci USA* **95**:3204–3208.
- Yaka R, Salomon S, Matzner H, and Weinstock M (2007) Effect of varied gestational stress on acquisition of spatial memory, hippocampal LTP and synaptic proteins in juvenile male rats. *Behav Brain Res* **179**:126–132.
- Yamada K, McEwen BS, and Pavlides C (2003) Site and time dependent effects of acute stress on hippocampal long-term potentiation in freely behaving rats. *Exp Brain Res* **152**:52–59.
- Yang CH, Huang CC, and Hsu KS (2004) Behavioral stress modifies hippocampal synaptic plasticity through corticosterone-induced sustained extracellular signal-regulated kinase/mitogen-activated protein kinase activation. *J Neurosci* **24**:11029–11034.
- Yang CH, Huang CC, and Hsu KS (2005) Behavioral stress enhances hippocampal CA1 long-term depression through the blockade of the glutamate uptake. *J Neurosci* **25**:4288–4293.
- Yang CH, Huang CC, and Hsu KS (2008a) Differential roles of basolateral and central amygdala on the effects of uncontrollable stress on hippocampal synaptic plasticity. *Hippocampus* **18**:548–563.
- Yang J, Han H, Cao J, Li L, and Xu L (2006) Prenatal stress modifies hippocampal synaptic plasticity and spatial learning in young rat offspring. *Hippocampus* **16**:431–436.
- Yang J, Hou C, Ma N, Liu J, Zhang Y, Zhou J, Xu L, and Li L (2007) Enriched environment treatment restores impaired hippocampal synaptic plasticity and cognitive deficits induced by prenatal chronic stress. *Neurobiol Learn Mem* **87**:257–263.
- Yang PC, Yang CH, Huang CC, and Hsu KS (2008b) Phosphatidylinositol 3-kinase activation is required for stress protocol-induced modification of hippocampal synaptic plasticity. *J Biol Chem* **283**:2631–2633.
- Yarom O, Maroun M, and Richter-Levin G (2008) Exposure to forced swim stress alters local circuit activity and plasticity in the dentate gyrus of the hippocampus. *Neural Plast* **2008**:194097.
- Yau JL, Noble J, Thomas S, Kerwin R, Morgan PE, Lightman S, Seckl JR, and Pariente CM (2007) The antidepressant desipramine requires the ABCB1 (Mdr1)-type p-glycoprotein to upregulate the glucocorticoid receptor in mice. *Neuropsychopharmacology* **32**:2520–2529.
- Yeh CM, Huang CC, and Hsu KS (2012) Prenatal stress alters hippocampal synaptic plasticity in young rat offspring through preventing the proteolytic conversion of pro-brain-derived neurotrophic factor (BDNF) to mature BDNF. *J Physiol* **590**:991–1010.
- Young EA, Abelson J, and Lightman SL (2004) Cortisol pulsatility and its role in stress regulation and health. *Front Neuroendocrinol* **25**:69–76.
- Young EA, Haskett RF, Grunhaus L, Pande A, Weinberg VM, Watson SJ, and Akil H (1994) Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. *Arch Gen Psychiatry* **51**:701–707.
- Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, and Yan Z (2009) Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc Natl Acad Sci USA* **106**:14075–14079.
- Yuen EY, Liu W, Karatsoreos IN, Ren Y, Feng J, McEwen BS, and Yan Z (2011) Mechanisms for acute stress-induced enhancement of glutamatergic transmission and working memory. *Mol Psychiatry* **16**:156–170.
- Yuen EY, Wei J, Liu W, Zhong P, Li X, and Yan Z (2012) Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex. *Neuron* **73**:962–977.
- Zeise ML, Teschemacher A, Arriagada J, and Ziegglänsberger W (1992) Corticosterone reduces synaptic inhibition in rat hippocampal and neocortical neurons in vitro. *J Neuroendocrinol* **4**:107–112.
- Zhang J, Yang Y, Li H, Cao J, and Xu L (2005) Amplitude/frequency of spontaneous mEPSC correlates to the degree of long-term depression in the CA1 region of the hippocampal slice. *Brain Res* **1050**:110–117.
- Zhang M, Zheng C, Quan M, An L, Yang Z, and Zhang T (2011) Directional indicator on neural oscillations as a measure of synaptic plasticity in chronic unpredictable stress rats. *Neurosignals* **19**:188–197.
- Zhang TY and Meaney MJ (2010) Epigenetics and the environmental regulation of the genome and its function. *Annu Rev Psychol* **61**:439–466, C1–C3.
- Zhang Y, Sheng H, Qi J, Ma B, Sun J, Li S, and Ni X (2012) Glucocorticoid acts on a putative G protein-coupled receptor to rapidly regulate the activity of NMDA receptors in hippocampal neurons. *Am J Physiol Endocrinol Metab* **302**:E747–E758.
- Zheng H, Yang Q, and Xu CT (2004) Effects of chronic stress and phenytoin on the long-term potentiation (LTP) in rat hippocampal CA1 region. *Acta Biochim Biophys Sin* **36**:375–378.
- Zhou J, Zhang F, and Zhang Y (2000) Corticosterone inhibits generation of long-term potentiation in rat hippocampal slice: involvement of brain-derived neurotrophic factor. *Brain Res* **885**:182–191.
- Zhou M, Bakker EH, Velzing EH, Berger S, Oitzl M, Joëls M, and Krugers HJ (2010) Both mineralocorticoid and glucocorticoid receptors regulate emotional memory in mice. *Neurobiol Learn Mem* **94**:530–537.
- Zhou M, Kindt M, Joëls M, and Krugers HJ (2011) Blocking mineralocorticoid receptors prior to retrieval reduces contextual fear memory in mice. *PLoS One* **6**:e26220.
- Zou B, Golarai G, Connor JA, and Tang AC (2001) Neonatal exposure to a novel environment enhances the effects of corticosterone on neuronal excitability and plasticity in adult hippocampus. *Brain Res Dev Brain Res* **130**:1–7.