

Review article

The emerging role of rapid corticosteroid actions on excitatory and inhibitory synaptic signaling in the brain

Marian Joëls^{a,b,1}, Henk Karst^{b,c,1}, Jeffrey G. Tasker^{d,1,*}

^a University Medical Center Groningen, University of Groningen, the Netherlands

^b University Medical Center Utrecht, Utrecht University, the Netherlands

^c SILS-CNS, University of Amsterdam, the Netherlands

^d Department of Cell and Molecular Biology and Tulane Brain Institute, Tulane University, and Southeast Louisiana Veterans Affairs Healthcare System, New Orleans, USA

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ABSTRACT

Over the past two decades, there has been increasing evidence for the importance of rapid-onset actions of corticosteroid hormones in the brain. Here, we highlight the distinct rapid corticosteroid actions that regulate excitatory and inhibitory synaptic transmission in the hypothalamus, the hippocampus, basolateral amygdala, and prefrontal cortex. The receptors that mediate rapid corticosteroid actions are located at or close to the plasma membrane, though many of the receptor characteristics remain unresolved. Rapid-onset corticosteroid effects play a role in fast neuroendocrine feedback as well as in higher brain functions, including increased aggression and anxiety, and impaired memory retrieval. The rapid non-genomic corticosteroid actions precede and complement slow-onset, long-lasting transcriptional actions of the steroids. Both rapid and slow corticosteroid actions appear to be indispensable to adapt to a continuously changing environment, and their imbalance can increase an individual's susceptibility to psychopathology.

1. Introduction

Adrenal corticosteroid hormones, like cortisol in humans and corticosterone in rodents, are secreted in ultradian pulses that produce an overarching circadian rhythm of circulating hormones (Upton et al., 2023). The circadian peak is reached just before waking, allowing corticosteroids to coordinate essential bodily processes in anticipation of the active period of the cycle. Cortisol and corticosterone are most well-known, however, for their role in the response to a stressor, i.e., any potential threat to homeostatic control, subjectively experienced as “stress”. Shortly after the onset of stress, corticotropin releasing hormone (CRH) is released from the hypothalamus into the pituitary portal blood, which causes the release of adrenocorticotropin releasing hormone (ACTH) from the pituitary gland, a process that can be amplified by vasopressin (Fink et al., 1991). This leads to the secretion of corticosteroid hormones from the adrenal cortex into the circulation, allowing the hormones to reach peripheral organs as well as the pituitary gland and the brain, a negative feedback loop by which the hypothalamic–pituitary–adrenal (HPA) neuroendocrine axis is

downregulated, so that approximately 2 h after stress onset, circulating levels are back to their baseline values. Stress-induced activation of the HPA-axis is coincident with, but proceeds more slowly than, activation of the sympathetic nervous system (Lamotte et al., 2021). Thus, post-stress, brain cells are exposed to partly overlapping waves of monoamines like (nor)epinephrine, neuropeptides such as CRH, and corticosteroid hormones (Fig. 1A).

In the circulation, corticosteroid hormones are bound to and transported by binding globulins that are, among other things, important in determining the delay between the secretion and the bioavailability of the corticosteroids in the brain (Reul et al., 2014). Microdialysis studies in rodents have shown that after the onset of severe (but not mild) stressors, corticosterone levels in the brain rise substantially with a delay of 20 min (Linthorst & Reul, 2008). Apart from *i*) the severity and nature of the stressor, *ii*) individual differences (e.g. age, sex, and the functionality of the HPA-axis), and *iii*) the presence of binding globulins, the amount of corticosteroids reaching brain cells is also determined by factors like *iv*) corticosteroid-converting enzymes such as 11-βHSD (Chapman et al., 2013; Holmes et al., 2003) and *v*) p-glycoproteins (Yau

* Corresponding author.

E-mail addresses: m.joels@umcg.nl (M. Joëls), h.karst1@gmail.com (H. Karst), tasker@tulane.edu (J.G. Tasker).

¹ All authors contributed equally.

et al., 2007), which, for example, favor the access to the human brain of corticosterone over cortisol (Karssen et al., 2001).

Corticosteroid hormones have a high affinity for the mineralocorticoid receptor (MR) and a lower affinity for the glucocorticoid receptor (GR) (Rosenfeld et al., 1990; Joëls & de Kloet, 2017) (see Fig. 1B). While the GR is ubiquitously expressed at relatively high levels in neurons and glial cells, high expression of MRs in the brain is restricted to neurons in some limbic areas, such as all hippocampal subregions (particularly area CA2), some cortical layers, a few nuclei in the brainstem, and several regions involved in salt appetite including the caudal part of the NTS, the subfornical and subcommissural organs, and the ventromedial nucleus of the hypothalamus (for review, see Joëls and de Kloet, 2017).

Both MR and GR belong to the superfamily of nuclear receptors and reside in the cytoplasm when unbound by corticosteroids. Upon binding of the steroid, chaperone proteins dissociate from the receptor and the hormone-receptor complex translocates to the nucleus, where it binds to a glucocorticoid response element in the DNA (Koning et al., 2019). In combination with cell-specific co-factors (Meijer, 2002), this leads to the transcriptional regulation of a subset of genes (Datson et al., 2008; Morsink et al., 2007; Meijer et al., 2023). Alternatively, corticosteroid receptors can also interfere with the activity of other transcriptional regulators such as NF- κ B (Ferreira et al., 2005; Bekkbat et al., 2017). As a result, the cellular content of a wide range of proteins, including those involved in neurotransmission, changes through transcriptional regulation, a process that usually requires at least an hour to become detectable (Meijer et al., 2023), although in some cases, like corticosteroid actions on glucose uptake, changes in expression have been observed within 15–20 min (Munck, 1968).

In addition to the rather slow genomic actions by corticosteroids, fast-onset corticosteroid actions that occur on a time scale of minutes, precluding transcriptional and translational mechanisms, have been reported for decades (Liu et al., 1995). These fast actions allow neurons in the brain to quickly follow and respond to changes in circulating corticosteroid levels. For many years, the signaling pathways underlying these rapid and presumably nongenomic actions in the brain were poorly understood, until in 2003, Tasker and colleagues (Di et al., 2003)

published the first paper addressing the mechanisms underlying rapid glucocorticoid actions in the paraventricular nucleus of the hypothalamus (PVN). Now, twenty years later, it is clear that rapid corticosteroid effects can be observed throughout the brain, as well as in other tissues such as the heart (Funder, 2010; Messaoudi et al., 2012) and the immune system (Buttgereit et al., 2006).

In addition to these fast-onset effects on the one hand and slow, genomic effects on the other, changes in neuronal excitability with intermediate kinetics have also been reported, which start between 10 and 30 min after corticosteroid administration and usually reverse within an hour (Funder, 2010; Joëls et al., 2012). Most of these effects were reported in the (dorsal) hippocampus and include increased GABAergic transmission (Teschemacher et al., 1996; Maggio & Segal, 2009) and reduced glutamatergic signaling or firing probability (Pfaff et al., 1971; Vidal et al., 1986; Zeise et al., 1992; Joëls & de Kloet, 1993; Takahashi et al., 2002), although the opposite has also been reported in the dorsal hippocampus (Zeise et al., 1992; Sato et al., 2004) and in the ventral hippocampus (Maggio & Segal, 2009). Here we will focus on corticosteroid actions that develop within minutes (with an upper limit of ~15 min), to the exclusion of the “intermediate” time-domain actions.

In Section 2, we first summarize the rapid effects of corticosteroid hormones on the main excitatory and inhibitory neurotransmitter systems in the brain, i.e., glutamatergic and GABAergic synapses, respectively, with an emphasis on the effects described over the past two decades. Next, in Section 3, we highlight the current view on the mechanistic underpinnings of rapid corticosteroid actions. Then, in Section 4, the functional relevance of rapid corticosteroid actions for the neuroendocrine and behavioral responses to stress is considered. Finally, in Section 5, we discuss the possible role of fast corticosteroid effects in healthy humans and how impairment might predispose individuals to a diseased state.

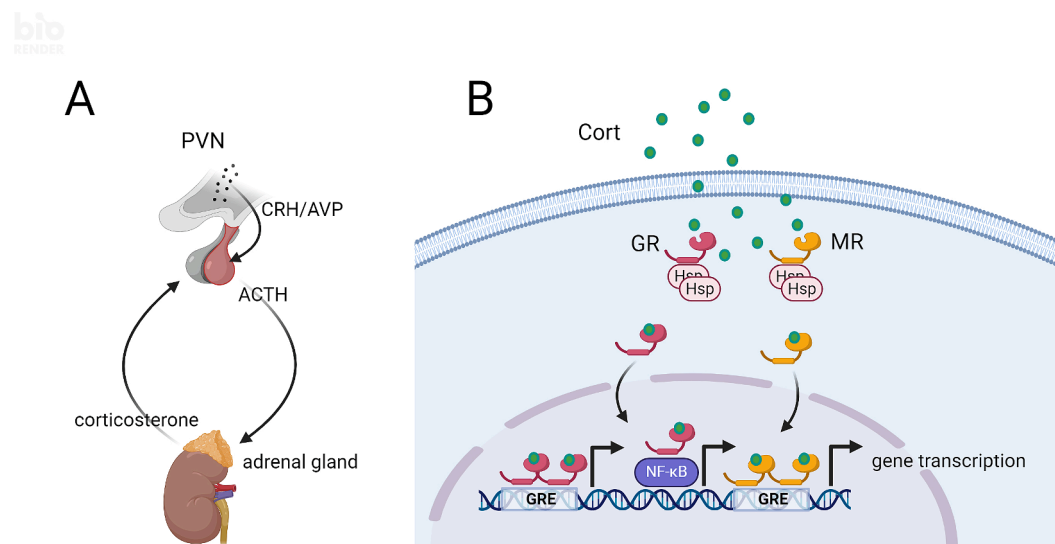


Fig. 1. Regulation of bodily and cellular processes by corticosteroids. **A.** The HPA axis. Stress causes the release of CRH and vasopressin (AVP) from the hypothalamic paraventricular nucleus (PVN) into the portal circulation of the pituitary gland. In the pituitary, CRH stimulates the release of adrenocorticotropic hormone (ACTH), which is amplified by AVP. ACTH reaches the adrenal glands via the general circulation, where it stimulates the synthesis and secretion of corticosteroids (cortisol in humans, corticosterone in rodents) from the adrenal cortex. Circulating corticosteroids feed back onto the brain, where they exert multiple effects at many different sites, including the suppression of CRH release in a negative feedback manner. **B.** Corticosteroid regulation of gene transcription. In the brain, corticosteroids (e.g., corticosterone, Cort) regulate gene transcription via activation of the nuclear mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). When corticosterone enters the cell, it binds to the MR and/or GR in the cytoplasm, causing them to dissociate from chaperone molecules (e.g., heat shock proteins, HSP). The steroid-bound receptors then translocate to the nucleus, where they bind as dimers to a glucocorticoid response element (GRE) on the DNA or interact with other transcription factors (e.g., NF- κ B) to enhance or suppress target gene transcription.

2. Rapid effects of corticosteroid hormones on neuronal excitability

2.1. Rapid CORT effects on excitatory and inhibitory synaptic transmission

Some of the earliest studies on the rapid effects of glucocorticoids in the brain came from the work of Mary Dallman and colleagues focusing on the rapid feedback inhibition of the HPA axis following acute stress exposure (for review, see [Dallman, 2005](#); [Keller-Wood & Dallman, 1984](#)). Glucocorticoids suppress HPA axis activation via rapid actions at multiple sites throughout the limbic forebrain, including the hypothalamus, hippocampus and prefrontal cortex, although the rapid actions in higher cortical and subcortical structures serve to exert cognitive and limbic control over HPA activation rather than simple feedback inhibitory regulation (see subsequent sections). The main rapid actions of glucocorticoids in the brain reported to date occur primarily at pre-synaptic and postsynaptic sites of excitatory and inhibitory synapses (for review, see [Harrison & Tasker, 2022](#); [Tasker & Herman, 2011](#); [Timmermans et al., 2013](#)), although rapid glucocorticoid effects on voltage-gated calcium channels ([French-Mullen, 1995](#)) and potassium channels ([Hynes & Harvey, 2019](#); [Wang et al., 2024](#); [Wu & Tasker, 2017](#)) have also been reported.

The corticosteroid actions discussed in this review are too fast to involve gene transcription and, when tested (see overview in Sup. Table S1), can be evoked by a bovine serum albumin (BSA) conjugate of corticosteroid, which cannot cross the membrane, suggesting the involvement of membrane-associated corticosteroid receptors (see section 3.1). The fast-onset corticosteroid actions generally do not change the passive membrane properties of target neurons, such as their resting

membrane potential or input resistance (although see [Kim et al., 2022](#)). The preparations and methods that have been used to study rapid corticosteroid actions vary greatly (see Fig. 2), ranging from synaptosomes, primary cell cultures, and brain slices to *in vivo* measurements (see Sup. Table S1).

2.1.1. Hypothalamus

Initial studies on hypothalamic neuroendocrine cells revealed a novel rapid action of glucocorticoids to stimulate the synthesis and dendritic release of non-canonical neurotransmitters that act as retrograde messengers at excitatory and inhibitory synapses (example in Fig. 3). Thus, corticosterone (CORT) and the synthetic glucocorticoid receptor agonist dexamethasone were found to suppress excitatory synaptic input to parvocellular neuroendocrine cells in the PVN, including CRH-producing neurons, and oxytocinergic and vasopressinergic magnocellular neuroendocrine cells in the PVN and supraoptic nucleus (SON) ([Di et al., 2003](#); [Di et al., 2005](#); [Groeneweg et al., 2011](#); [Nahar et al., 2016](#)) via the retrograde release of the endocannabinoid 2-arachidonoylglycerol (2-AG) at excitatory synapses ([Di et al., 2009](#)). The activation of presynaptic CB1 receptors inhibits glutamate release and suppresses synaptic excitation, which contributes to the rapid glucocorticoid feedback inhibition of both the hypothalamic-adenohypophyseal (i.e., the HPA axis, [Evanson et al., 2010](#)) and the hypothalamic-neurohypophyseal systems ([Ruginsk et al., 2012](#); [Vilela et al., 2013](#)). Under baseline conditions, this corticosteroid-induced stimulation of 2-AG release is specific to glutamate synapses on neuroendocrine cells, however, magnocellular neuroendocrine cells are also subject to a tonic endocannabinoid suppression of GABA release at inhibitory synapses ([Oliet et al., 2007](#)). This tonic endocannabinoid suppression of GABA release is mediated by the other main

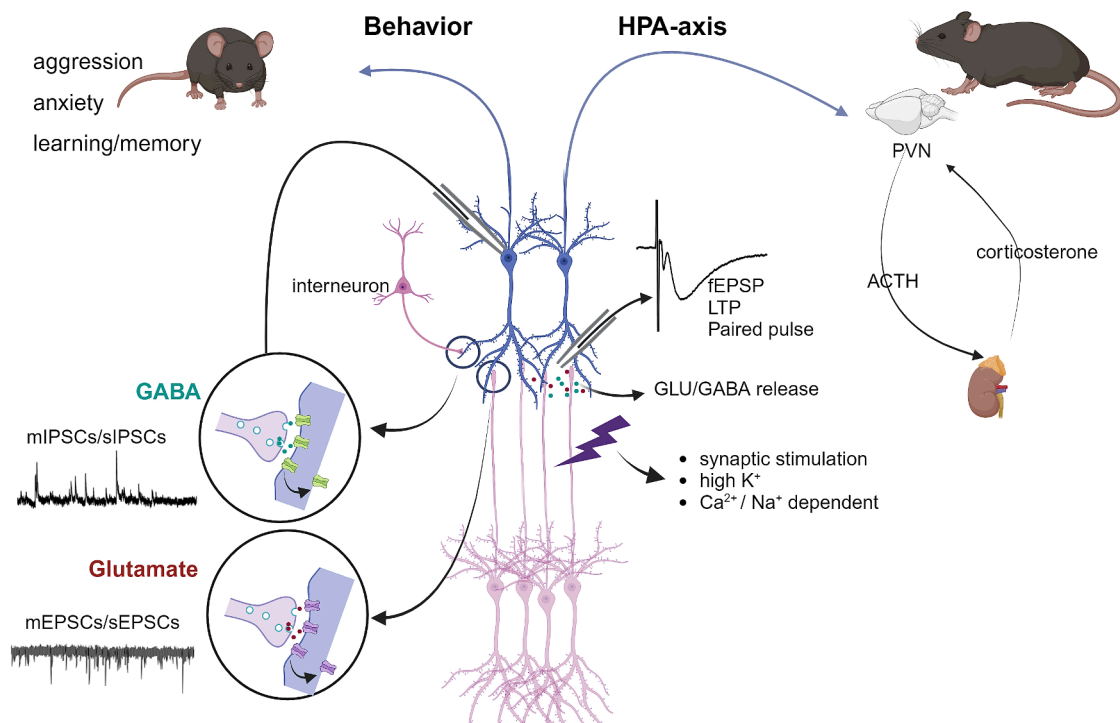


Fig. 2. Overview of the methods of analysis of rapid corticosteroid actions invoked in this review. Single-cell synaptic responses (lower left) to corticosteroids are measured with whole-cell electrophysiological techniques. Rapid corticosteroid effects on spontaneous (sEPSCs/sIPSCs), miniature (mEPSCs/mIPSCs), and stimulation-evoked EPSCs and IPSCs mediated by glutamate and GABA release at excitatory and inhibitory synapses, respectively, are recorded. At the network level (middle right), rapid corticosteroid effects on population synaptic activity are recorded as field potentials (fEPSP) with extracellular electrodes. Synaptic plasticity (e.g., long-term potentiation (LTP)) can be induced electrically by high-frequency stimulation of afferent axons or chemically by a combination of glycine and picrotoxin. Corticosteroid effects on glutamate and GABA release can be studied by raising the extracellular K⁺ concentration; and the calcium and sodium dependence of release by changing extracellular ion concentrations. The rapid effects of corticosteroids at the whole-animal level (top) are measured as changes in HPA activity or with different behavioral paradigms.

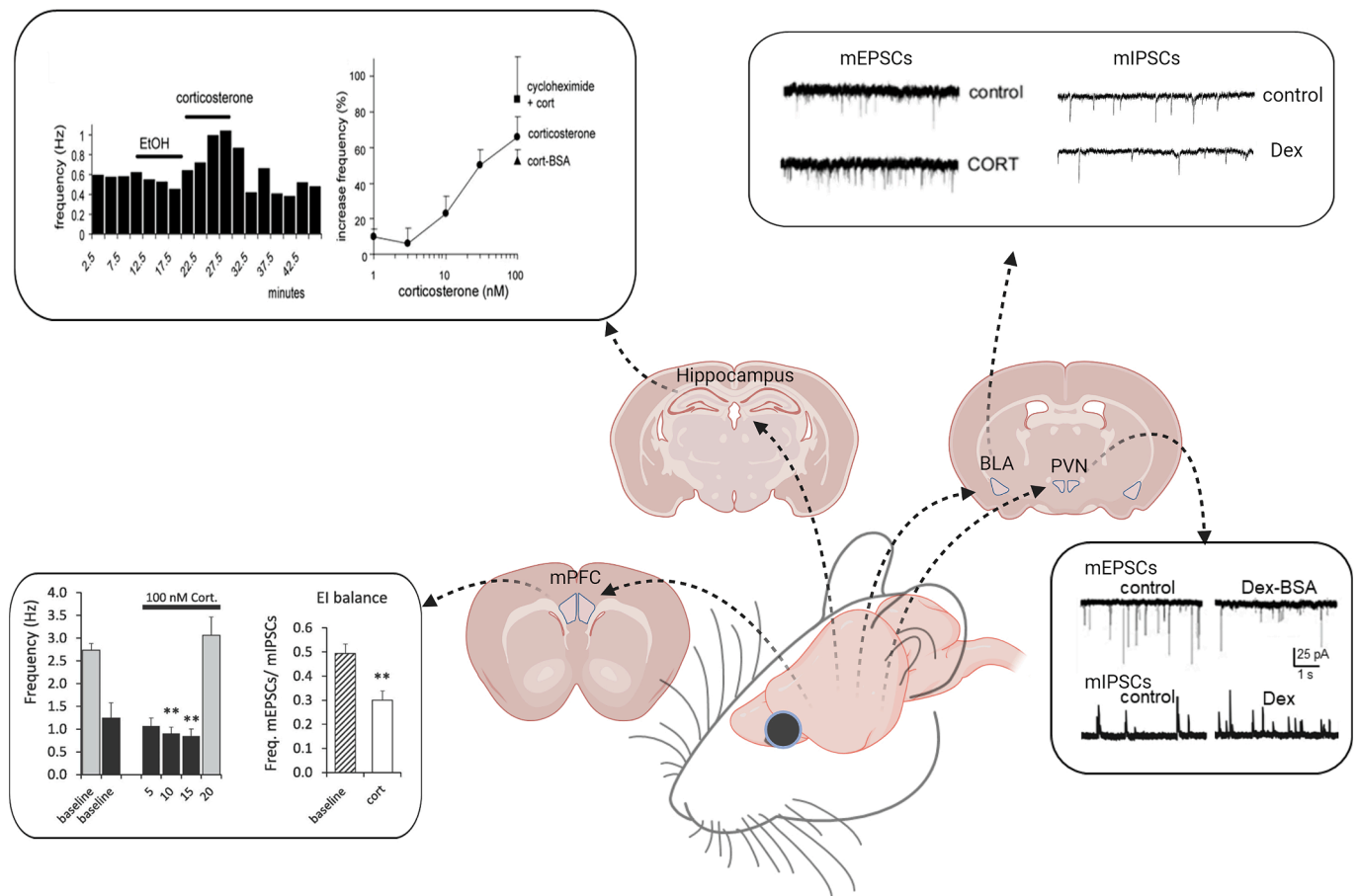


Fig. 3. Examples of rapid corticosteroid actions in the hypothalamus (PVN), hippocampus (CA1), amygdala (BLA) and medial prefrontal cortex (mPFC). In the dorsal hippocampus, corticosteroids produced a rapid increase in the frequency of miniature (i.e., spike-independent) EPSCs, which was caused by an increase in the vesicular release of glutamate. The rapid corticosteroid effect was non-genomic and mediated by membrane-associated receptors because membrane-impermeant CORT-BSA was able to reproduce the rapid effect and it was not blocked by the protein synthesis inhibitor cycloheximide (modified from (Karst et al., 2005)). In the amygdala, corticosterone (CORT) caused a rapid increase in mEPSC frequency via presynaptic MR-dependent suppression of glutamate release (modified from Karst et al., 2010), and the synthetic glucocorticoid dexamethasone (Dex) caused a rapid decrease in mIPSC frequency via postsynaptic receptor activation and retrograde eCB release (modified from (Di et al., 2016)). In the PVN, Dex and a membrane-impermeant Dex-BSA conjugate caused a decrease in mEPSC frequency (modified from Di et al., 2003). In the mPFC, Cort caused a rapid decrease in mEPSC frequency, but had little effect on mIPSCs, resulting in a decrease in the ratio of mEPSCs to mIPSCs (i.e., synaptic excitation-inhibition balance) (modified from Karst & Joëls, 2023).

endocannabinoid, anandamide. Interestingly, inhibitory synapses are also subject to phasic endocannabinoid regulation under conditions of reduced astrocyte activity. During chronic dehydration, for example, 2-AG released phasically at glutamate synapses escapes astrocytic control to spill over onto inhibitory synapses, where it activates presynaptic CB1 receptors to suppress GABA release (Di et al., 2013). The significance of the combined suppression of synaptic excitation and inhibition under conditions of astrocytic plasticity (e.g., during osmotic or reproductive stress) is currently not known, although it may serve to quiet the synaptic activity and increase the signal-to-noise ratio of the magnocellular neurons during high physiological demand. GABAergic synapses on magnocellular neurons are highly sensitive to changes in chloride buffering that can alter their signaling valence under different environmental conditions (Choe et al., 2015; Haam et al., 2012; Lee et al., 2015), which may contribute to baseline noise and interfere with the patterned activation of these cells required for phasic activity and pulsatile hormone release.

Parvocellular neuroendocrine cells in the PVN are not subject to rapid glucocorticoid regulation of synaptic GABA release at inhibitory synapses (Cusulin et al., 2013; Verkuyl et al., 2005), although CORT does induce an increase in their tonic GABA current via activation of extrasynaptic GABA_A receptors by ambient GABA (Colmers et al., 2018). Magnocellular neuroendocrine cells, on the other hand, in addition to

suppression of synaptic glutamate release, also respond to glucocorticoids with a rapid increase in synaptic GABA release at inhibitory synapses, which is mediated by the release of a distinct retrograde messenger, the gaseous transmitter nitric oxide (Di et al., 2009). The functional significance of this opposing glucocorticoid regulation of excitatory and inhibitory synapses is discussed further in Section 4.

A stress modality-specific rapid glucocorticoid negative feedback effect on HPA activation was recently reported. Rapid glucocorticoid desensitization of adrenoreceptor signaling was described in CRH neurons that suppresses noradrenergic activation of the HPA axis based on the recent stress history of the animal (Jiang et al., 2022). Since ascending noradrenergic afferent pathways to the PVN are a critical driver of activation of CRH neurons and the HPA axis by somatic stress (e.g., immune challenge) (Bienkowski & Rinaman, 2008), but not by psychological stress (Schiltz & Sawchenko, 2007), the rapid feedback desensitization of $\alpha 1$ adrenoreceptors by glucocorticoids selectively inhibits HPA activation by somatic stress exposure, leaving intact the HPA activation in response to psychological stress (Jiang et al., 2022). Since somatic stress exposure is often prolonged (e.g., immune challenge, hypoglycemia), this provides a means to prevent extended HPA activation and the protracted, potentially toxic effects of glucocorticoid exposure while maintaining the phasic HPA responsiveness necessary to attend to potentially life-threatening psychological stressors (e.g.,

predators).

Overall, fast feedback inhibition of the HPA axis can be traced, at least in large part, to rapid, direct glucocorticoid actions on the CRH neurons, which modulate the excitatory synaptic drive by suppressing glutamatergic synaptic inputs to the CRH neurons and by desensitizing the CRH neurons to excitatory noradrenergic inputs. Oxytocinergic and vasopressinergic magnocellular neuroendocrine cells are also subject to rapid glucocorticoid inhibition via modulation of their synaptic inputs, which regulates their homeostatic, social, and/or reproductive functions, but may also contribute to the feedback inhibition of the HPA response, inasmuch as vasopressin and oxytocin are also implicated in the stress activation of the HPA axis.

2.1.2. Hippocampus

CA1 pyramidal neurons in hippocampal slices from adult male mice respond rapidly to the application of CORT (100 nM) with a reversible increase in mEPSC frequency, but not mEPSC amplitude (example in Fig. 3) (Karst et al., 2005; Karst et al., 2010; Olijslagers et al., 2008). The CORT-induced increase in mEPSCs was mimicked by membrane-impermeant CORT-BSA, suggesting a membrane-delimited effect. The lowest effective dose was 10 nM CORT. MR-selective aldosterone (10 nM) was even more effective. An MR (but not GR) antagonist blocked the CORT actions. In agreement, CORT was ineffective in forebrain-selective MR (but not GR) knockout mice. Comparable effects were observed in granule cells of the dentate gyrus (Pasricha et al., 2011). The MR-dependent effects in CA1 neurons are presynaptic and depend on a presynaptic ERK1/2 signaling pathway, and are independent of retrograde endocannabinoid or NO release (Olijslagers et al., 2008).

Corticosteroids can also increase inhibitory synaptic inputs to dorsal hippocampal CA1 cells. Thus, the frequency and amplitude of sIPSCs, but not mIPSCs, in CA1 neurons recorded in rat brain slices were quickly increased by 25 nM DEX; these effects were blocked by inhibiting action potential generation, which indicated a presynaptic somato-dendritic site of steroid action in local inhibitory interneurons (Hu et al., 2010; Teng et al., 2013). In some cases, this effect waned during the DEX application, suggesting a desensitizing response to the steroid. In addition, clusters of high-frequency sIPSCs occurred intermittently during DEX administration, which may have been generated by bursting activity in the presynaptic neurons. The effect was mediated by a membrane receptor since it was mimicked by membrane-impermeant DEX-BSA. The increase in sIPSC frequency was not blocked by antagonists of the nuclear MR and GR and involved postsynaptic G-protein signaling as well as retrograde NO release. Neurons in slices prepared after acute stress (30 min restraint) exhibited increased basal sIPSC frequency and burst-like sIPSC activity, in the absence of exogenous DEX, compared to cells from controls (Hu et al., 2010). Of note, these studies on IPSCs differ from the earlier discussed studies on mEPSCs not only with respect to the species (rat versus mouse) but also the time of day (i.e., at the start of the active versus inactive period, respectively). The stage of the circadian cycle may be relevant for the direction of corticosteroid actions (see section 2.3).

Changes in mEPSC and mIPSC frequency are usually reflective of altered release of glutamate and GABA, respectively. Accordingly, high doses of the synthetic corticosteroids methylprednisolone and DEX were shown to rapidly increase basal and depolarization-induced glutamate but not GABA release in isolated synaptic terminals from rat hippocampus (Neiva et al., 2020). The enhanced glutamate release involved a calcium-independent / sodium-dependent pathway and was blocked by both MR- and GR-antagonists. Similar observations were made *in vivo* (Abraham et al., 1996; Venero & Borrell, 1999), since in freely moving rats, unilateral infusion of DEX into the dorsal hippocampus enhanced the glutamate concentration over the first 30 min, which then returned to baseline despite continued infusion of DEX (Abraham et al., 1996). Similarly, Venero & Borrell, 1999 reported that CORT administered i.p. to adrenalectomized rats increased extracellular glutamate but not GABA levels in the dorsal hippocampus within 15

min. Intrahippocampal perfusion of either CORT or DEX yielded similar fast-onset and reversible increases in glutamate levels. The effect of intrahippocampal CORT was not blocked by classical MR and GR antagonists and did not depend on protein synthesis. Of note, the microdialysis methodology used to sample neurotransmitters does not allow for fast sampling, so the precise time domain in which these changes took place is hard to establish. Future studies using recently developed silicon multifunctional biosensor probes, which can simultaneously record extracellular glutamate and GABA levels *in vivo* with sub-second time resolution (Billa et al., 2022), should provide higher spatial and temporal resolution of glucocorticoid-induced neurotransmitter release.

Several studies have focused on corticosteroids affecting post-synaptic glutamate receptor trafficking and effectiveness. Single quantum-dot imaging in primary rat hippocampal cultures demonstrated a fast-onset and dose-dependent increase in the trafficking and synaptic content of GluA2 AMPA receptor subunits by CORT (Groc et al., 2008). This was mimicked by membrane-impermeant CORT-BSA and the MR agonist aldosterone, and blocked by the MR-antagonist spironolactone.

In cultured neonatal hippocampal neurons, relatively high CORT concentrations (≥ 100 nM) rapidly and reversibly decreased an NMDA receptor-mediated inward current (Liu et al., 2007). This was mimicked by CORT-BSA and not blocked by the GR antagonist mifepristone. Interestingly, if protein kinase actions were non-selectively blocked by staurosporine, NMDA receptor-mediated currents were smaller to start with and were *enhanced* by CORT, indicating that the intracellular milieu, which is altered when recording in the whole-cell configuration, may be important for the valence of the CORT effects, reminiscent of earlier reports (Zeise et al., 1992; Teschemacher et al., 1996). Another report in primary hippocampal cell cultures (Mikasova et al., 2017) demonstrated that 100 nM CORT rapidly increases the surface dynamics and the GluN2B subunit content of synaptic NMDA receptors, causing a decreased synaptic GluN2A-to-GluN2B ratio. CORT-BSA and the MR agonist aldosterone mimicked this rapid effect, while a selective GR-agonist did not. Consistent with the increase in surface expression of GluN2B-containing NMDA receptors, CORT was also shown to increase NMDA receptor-mediated currents at spontaneously active glutamate synapses. The changes in NMDA receptor surface dynamics were necessary to observe CORT-induced potentiation of synaptic AMPA receptor content. The enhanced synaptic content may be explained by a fast CORT-stimulated G protein-signaling pathway activating PKC, Akt/PKB, and PKA, subsequently triggering the phosphorylation of the tyrosine kinases Pyk2, Src, and Abl (Yang et al., 2013). These changes led to rapid cytoskeletal rearrangements within the postsynaptic density, associated with increased surface expression of NMDA receptors. CORT-BSA was also effective, whereas a variety of classical MR and GR antagonists failed to block the rapid CORT effects.

If CORT (and stress) rapidly change glutamatergic and GABAergic signaling in the hippocampus, one would expect to also see fast-onset CORT effects on synaptically evoked hippocampal field potential responses and/or synaptic plasticity. Early studies confirmed this, showing dose-dependent CORT effects in the dorsal hippocampal CA1 area: relatively low CORT doses (i.e., < 100 nM) enhanced the population spike amplitude, presumably through MRs (Rey et al., 1991), although the kinetics differed between studies (Reiheld et al., 1984; Rey et al., 1987). Results with higher CORT concentrations (i.e., ≥ 100 nM) were less consistent (Reiheld et al., 1984; Rey et al., 1987; Treccani et al., 2014). Brief application of 100 nM CORT *in vitro* did not change the field response in the dentate gyrus (Pu et al., 2007).

CORT administered just before or concurrent with, but not after, high-frequency stimulation of afferent pathways was shown to enhance synaptic plasticity in the mouse dorsal hippocampal CA1 area (Wiegert et al., 2006). Classical MR and GR antagonists were ineffective in blocking this effect of CORT. In the rat dentate gyrus, CORT facilitated the early phase of synaptic potentiation induced in the presence of a GABA receptor blocker to relieve the strong inhibition seen *in vitro* (Pu

et al., 2007). These rapid facilitatory effects support observations in primary rat hippocampal cultures showing that CORT amplifies the increased surface GluA2-containing AMPA receptor density at glutamate synapses shortly after chemically inducing synaptic potentiation with glycine/picrotoxin application (Groc et al., 2008)).

In summary, as illustrated in Fig. 4, most studies conducted in the dorsal hippocampus to date indicate that CORT causes robust rapid facilitation of glutamatergic synaptic transmission, while the effects on GABAergic pathways are less consistent. How these rapid effects of CORT relate to the effects of stress on hippocampal transmission and synaptic plasticity *in vivo* (e.g. Shors et al., 1990; Abrahám et al., 1996; Yuen et al., 2011) is hard to say, as it is not entirely clear whether the *in vivo* effects of stress are truly caused by fast-onset CORT actions (see Section 4).

2.1.3. Basolateral amygdala

CORT rapidly modulates both excitatory and inhibitory synaptic transmission in principal neurons of the basolateral amygdala (BLA). [Karst et al., 2010](#) showed that CORT increases the frequency, but not amplitude, of mEPSCs at excitatory synapses of principal neurons in the BLA, but not central amygdala ([Fig. 3](#)), suggesting a rapid facilitation of glutamate release. Pharmacological experiments pointed to the involvement of MRs, and not GRs, in the development of these effects. The lowest effective dose of CORT to facilitate glutamate release in the BLA was 30 nM, with a delay of ~ 10 min ([Karst & Joëls, 2016](#)). Compared to the dorsal CA1 hippocampal area, in which the CORT actions occurred within 5 min and with a minimal effective dose of 10 nM, the effects of CORT in the BLA were somewhat slower in onset and higher threshold. There was also a difference in the reversibility of the effect between the two areas: whereas in the hippocampus CORT effects

are rapidly reversible upon washout of the drug, the CORT-induced increase in mEPSC frequency in the BLA is much more prolonged, lasting for the duration of recordings (i.e., over 85 min) (Karst et al., 2010; Karst & Joëls, 2016). These findings are similar to those reported at inhibitory synapses (see below) and suggest that CORT induces a long-lasting shift in the excitatory “state” of the BLA principal neurons. In support of such a notion, BLA neurons recorded *in vitro* in slices prepared from mice exposed (hours earlier) to acute stress *in vivo* (restraint stress) yielded a higher mEPSC frequency than cells in slices from naïve mice. Blocking translation with cycloheximide did not prevent the rapid MR-dependent increase in mEPSC frequency, but abrogated the long-lasting duration of the increase (see also section 2.3). Transient increases in mEPSC frequency were also observed when the MR agonist aldosterone was administered in combination with the selective GR blocker mifepristone, whereas the GR agonist dexamethasone caused a decrease in the mEPSC frequency (unpublished observation). These results reveal the MR as the receptor that mediates the rapid increase in mEPSC frequency in the BLA, whereas the GR may be responsible for the long-lasting nature of the increase. This was confirmed in forebrain-specific MR and GR knockout mice. Thus, in slices from the inducible GR knockout mouse, GR^{CaMKCreERT2}, CORT rapidly but transiently increased the mEPSC frequency of BLA principal cells, while it was ineffective in slices from MR KO mice, MR^{CaMKCreERT2}. In contrast to the hippocampus, synaptic plasticity at excitatory synapses on principal neurons in the BLA is suppressed by CORT administered concurrently with high-frequency stimulation of synaptic afferents (Sarabdjitsingh et al., 2014).

GABAergic signaling in the BLA is also regulated by CORT. Stress exposure and both DEX and CORT caused a long-lasting reduction in the frequency, but not amplitude, of mIPSCs in the BLA, suggesting a suppression of GABA release at inhibitory synapses (Di et al., 2016). The

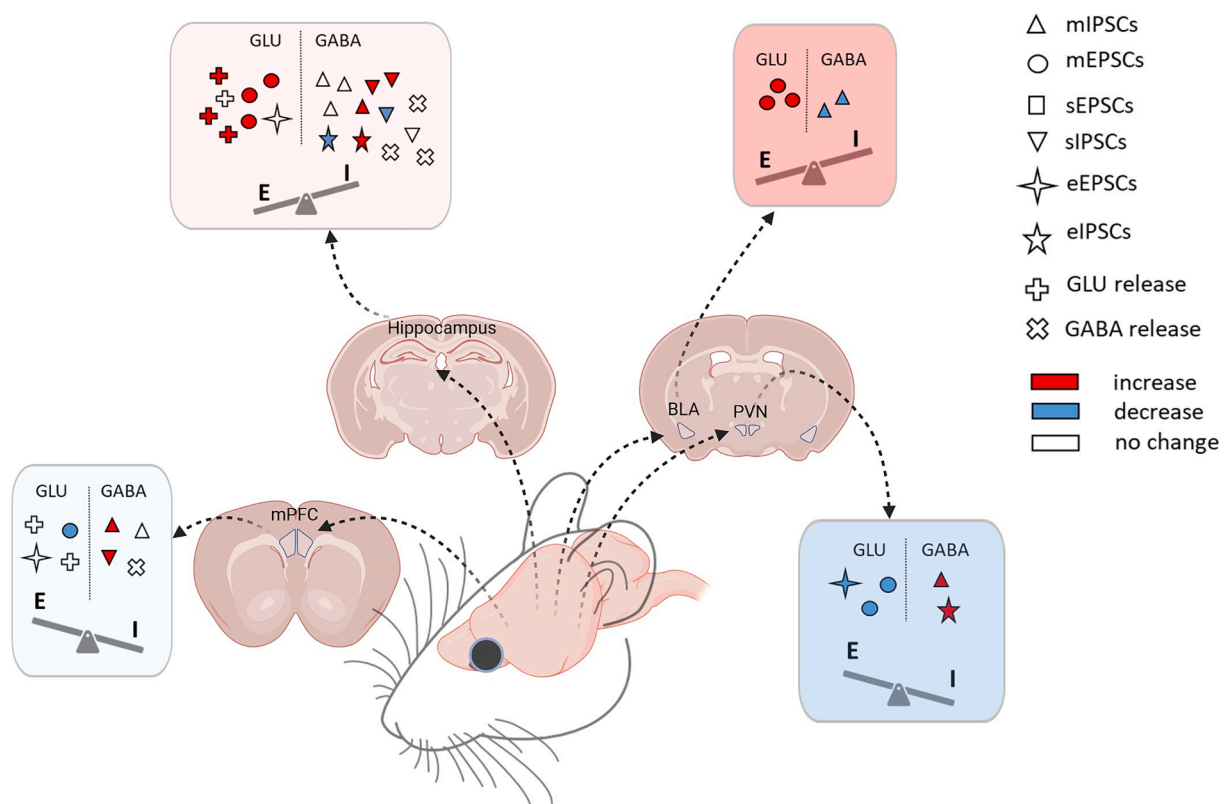


Fig. 4. Summary of rapid corticosteroid actions in glutamatergic and GABAergic circuits reported in four well-studied areas: the hypothalamic paraventricular nucleus (PVN), dorsal hippocampus, medial prefrontal cortex (mPFC), and basolateral amygdala (BLA). In the dorsal hippocampus and BLA, overall glutamatergic synaptic transmission is increased, while the excitation-inhibition balance is shifted towards excitation (red background). In the mPFC and PVN, a shift towards inhibition (blue background) emerges from the current evidence. Each symbol was generated from different studies (or separate experiments from the same study). The brightness of the background color indicates the agreement across the studies. For more detailed information, see Sup. Table S1.

reduction in GABA release was blocked by a CB1 receptor antagonist and a diacylglycerol lipase inhibitor, suggesting it is mediated by the retrograde actions of the endocannabinoid 2 arachidonoylglycerol (2-AG). Unlike the effect of CORT on excitatory synapses in the BLA, in which a presynaptic MR-dependent facilitation of glutamate release by a first exposure to CORT (or stress) is supplanted by a GR-dependent suppression of glutamate release upon re-exposure to CORT (Karst et al., 2010), a second exposure to CORT did not further change the mIPSC frequency (Di et al., 2016). The stress/CORT-induced, endocannabinoid-mediated suppression of synaptic inhibition was persistent, as it was non-reversible for the duration of recordings, and endured through brain slice preparation following *in vivo* acute stress presentation. A role of endocannabinoid signaling after acute stress in the regulation of excitatory synaptic transmission in the BLA has also been reported, but whether this is due to rapid CORT actions is not known. (Duan et al., 2017) reported relief of stress-induced anxiety by inhibiting fatty acid amide hydrolase (FAAH), which increased anandamide in BLA interstitial tissue, leading to the accumulation of interstitial glutamate, postsynaptic GluN2B receptor activation, AMPA receptor endocytosis, and long-term depression in the input from the prefrontal cortex. (Gray et al., 2015) found that CRH release in the BLA increases FAAH activity, which decreases tonic anandamide activation of CB1 receptors at excitatory synapses and causes an increase in glutamate release onto the principal cells and an increase in anxiety behavior. The discrepancy between the two findings may relate to timing, with the increase in FAAH activity mediated by CRH and the reduction in FAAH mediated potentially by CORT, although this is not yet known.

In summary, in the BLA, CORT rapidly *increases* glutamate release at excitatory synapses via non-genomic MR activation and *reduces* GABA release at inhibitory synapses via non-genomic GR activation in slices of non-stressed rodents. Different from the hippocampus, the fast-onset effects of CORT in the BLA appear to shift principal neurons into a persistently altered excitability state. The BLA also differs from the hippocampus in that excitatory synaptic plasticity induction in the presence of CORT impairs, rather than facilitates, long-term synaptic potentiation.

2.1.4. Prefrontal cortex

Fast corticosteroid actions in the prefrontal cortex (PFC) are more varied and complex than those observed in subcortical brain areas, which can be attributed at least in part to neocortical structural complexity, with its laminar organization and regional subspecialization, and to the concentration- and time-dependent actions of corticosteroid hormones. Recently, fast-onset actions of CORT observed in the PFC were found to reduce the frequency of mEPSCs, but not mIPSCs, in layer 2/3 pyramidal neurons of the mouse *infralimbic* PFC, which caused a rapid decrease in the excitation-inhibition balance (see Fig. 3) (Karst & Joëls, 2023); the mEPSC amplitude was unaffected, suggesting a presynaptic site of CORT action. The fast-onset reduction in synaptic excitation appeared to be MR-dependent because it was mimicked by the MR agonist aldosterone, but not the GR agonist RU28362, and blocked by the MR antagonist spironolactone. Surprisingly, the fast-onset effects of CORT on mEPSCs in PFC layer 2/3 pyramidal neurons were also prevented by a blocker of the G protein-coupled estrogen receptor, G-15 (see section 3.1).

Others have also described an enhancement of the frequency of both mIPSCs and sIPSCs (i.e., increase in GABA release) as well as intermittent bursting inhibitory synaptic activity in layer 2/3 neurons of the rat *prelimbic* PFC by a low concentration of DEX (25 nM) and by the membrane impermeant DEX-BSA (Teng et al., 2013). These membrane-limited steroid effects on inhibitory synaptic transmission had a slower onset (10–20 min) than those observed in the dorsal hippocampus (<5 min) by the same and other investigators, and they became more pronounced with time. MR antagonists did not block the facilitation of inhibitory synaptic signals, suggesting that the rapid, membrane receptor-mediated CORT effect in the prelimbic PFC differs from that

seen in the dorsal hippocampus. Like the rapid CORT effect in the hypothalamus, the CORT effect in the prelimbic PFC was seen to involve a PLC-DAG signaling pathway (Teng et al., 2013).

The extent to which these rapid corticosteroid actions in the PFC are linked with changes in glutamate and/or GABA release is unclear. Thus, acute stress quickly and strongly *increased* the readily releasable pool of vesicles and depolarization-evoked glutamate release via a non-genomic mechanism (Treccani et al., 2014). By contrast, *in vitro* administration of 100 nM CORT only transiently, and less robustly, increased the readily releasable pool of glutamate-containing vesicles. This effect was blocked by both MR and GR antagonists. It was concluded that CORT primes the terminals to rapidly increase the readily releasable pool size, but that CORT is not sufficient by itself to stimulate glutamate release. This largely agrees with another study in mouse and rat synaptosomes from the frontal lobes that reported no effect of DEX or CORT on the basal and depolarization-induced glutamate and GABA release, even at high steroid concentrations (Bitencourt et al., 2015).

Given the relatively faint fast-onset effects of CORT on glutamatergic and GABAergic transmission in different parts of the PFC, it is not surprising that evoked EPSPs were reported to be unaffected up to 20 min after CORT administration *in vitro* (Treccani et al., 2014) and that no fast-onset effects of CORT on NMDA receptor- and AMPA receptor-mediated EPSCs were detected (Yuen et al., 2011).

In summary (see Fig. 4), while stress rapidly increases glutamate transmission in the PFC, the role of CORT in these fast-onset effects appears to be limited. If anything, corticosteroids may increase the inhibitory tone in the PFC with a fast-to-moderately fast onset. Whether the effects of stress-induced CORT are non-genomic has yet to be studied in detail.

2.1.5. Other brain areas

Apart from the four brain areas discussed above, relatively few other areas have been examined for rapid corticosteroid actions. Hartner & Schrader (2018) reported that principal cells in layer II of the medial entorhinal cortex respond rapidly (within 10 min) to a high concentration of DEX or CORT (1 μ M) with a decrease in the sIPSC frequency, while sIPSC amplitude and mIPSC properties remained unchanged, suggesting a presynaptic somatic modulation. Interestingly, the percentage of entorhinal cortical neurons that responded to α 1-adrenoceptor activation increased from 75 % under normal conditions to 100 % following 15 min of exposure to DEX, which suggested a possible non-genomic corticosteroid priming effect on adrenoceptor signaling. As described above, glucocorticoids have also been shown to rapidly regulate α 1 adrenoceptor trafficking and sensitivity in hypothalamic CRH neurons (Jiang et al., 2022).

In the somatosensory cortex of mice, field potential recordings revealed a rapid CORT-induced suppression of local inhibitory networks (Wotton et al., 2018). The CORT effect was dependent on astrocyte activity and activation of purinergic signaling and involved a mechanism shared with serotonin. The data also point to a reduction in glutamate transmission compatible with a reduction in the readily releasable pool of glutamate-containing vesicles, an effect opposite to what was found in layer 2/3 PFC neurons (see Section 2.1.4 above).

Wang and colleagues (Wang et al., 2012) studied excitatory neurotransmission in serotonergic neurons in the dorsal raphe nucleus in brainstem slices from juvenile rats. They observed a fast-onset (<5 min) suppression of the evoked EPSC amplitude by both CORT and DEX, but not aldosterone, at high concentrations. The minimal effective concentration of DEX was 100 nM, with maximal effects seen at the supra-physiologically high concentration of 10 μ M. No effects were observed on the passive properties of the serotonergic neurons, such as holding current and membrane resistance. The results from paired-pulse and sEPSC analyses supported the conclusion that DEX reduces the probability of release of glutamate onto serotonergic neurons. They further demonstrated using the membrane-impermeant steroid DEX-BSA and intracellular infusion of CORT that the effects involve a membrane-

associated receptor that is different from the classical MR and GR and appears to be coupled to G-protein signaling.

Rapid CORT modulation of excitatory synapses in the nucleus of the solitary tract (NTS) has also been reported (Ragozzino et al., 2020). Corticosterone reduced the probability of glutamate release onto NTS neurons from vagal afferent axons via a rapid postsynaptic G protein-dependent signaling mechanism that induced the retrograde release of 2-AG and presynaptic CB1 receptor activation. This retrograde signaling at excitatory synapses is very similar to that seen in hypothalamic neuroendocrine cells (see Section 2.1.1).

2.2. Rapid morphological changes

It is conceivable that changes in glutamatergic and GABAergic transmission are a mere reflection of changes in dendritic morphology. This would pertain particularly to the postsynaptic effects (e.g. surface expression of AMPA and NMDA receptors) and less to presynaptic effects such as changes in release probability, although the presynaptic corticosteroid effects often develop secondary to postsynaptic actions (e.g. Di et al., 2003).

Nongenomic corticosteroid actions on spinogenesis have indeed been reported. Thus, activation of a presumed membrane-associated GR was found to specifically induce spinogenesis in hippocampal CA3 and CA1 neurons (Yoshiya et al., 2013; Murakami et al., 2018; Ikeda et al., 2015), see also Sup. Table S1). Rapid spinogenesis was prevented by the GR antagonist mifepristone but not by the MR antagonist spironolactone (Ikeda et al., 2015). Ikeda and colleagues (Ikeda et al., 2015) showed that inhibiting transcription with anisomycin D failed to block the CORT effects, but inhibiting protein translation with cycloheximide did prevent the CORT effects on spinogenesis, supporting a nongenomic signaling pathway that requires protein synthesis to produce new spines.

If functional changes develop secondary to morphological effects, one would expect the morphological changes to precede the changes in synaptic signaling. However, the time frame of the changes in spinogenesis is not easy to establish due to the relatively long interval between treatment and processing of the tissue. Whether or not such nongenomic morphological CORT actions play a role in the functional changes is therefore currently not yet known, but cannot be ruled out.

2.3. Regional differentiation

Fig. 4 provides a summary of the rapid corticosteroid actions reported to date in the main areas investigated. Although some findings are still not conclusive, by and large, rapid corticosteroid actions (i.e., with an onset of 5–10 min) suppress neuronal excitability in the PVN and enhance activity in the BLA and the hippocampus. The rapid-onset corticosteroid effects in the PFC appear to be mostly suppressive, though they may prime the readily releasable pool of glutamate vesicles for release. The findings from these main brain areas point, therefore, to a distinct regional differentiation of rapid CORT actions.

Regional differentiation was earlier also reported concerning the slow-onset, genomic effects of CORT via GRs (see e.g. Joëls et al., 2012). Thus, in the prelimbic PFC, CORT slowly enhances glutamatergic transmission (Yuen et al., 2009; Yuen et al., 2011) and suppresses GABAergic transmission (Hill et al., 2011). In the BLA, it generally causes a gradual suppression of excitability except under conditions of high hormone concentration, where it can increase principal neuron excitability (Di et al., 2016; Karst & Joëls, 2016). Findings in the dorsal hippocampus, on the other hand, are more ambiguous, with CORT generally producing slow trafficking of GluR2-AMPA receptors to the membrane and enhancement of mEPSC amplitude, thus mimicking synaptic potentiation. This may explain why high-frequency stimulation > 1 hr after CORT application (or after stress exposure) is unable to further enhance synaptic responses, suggesting an occlusion of the excitatory synaptic plasticity induction in hippocampal neurons (Pavlidis et al., 1993; Diamond et al., 1992; Joëls & Krugers, 2007).

Concurrently, other excitatory signals in the hippocampus are suppressed, and inhibitory signals, like those induced by serotonin, are enhanced. Overall, this may lead to a slow, GR-dependent improvement of the signal-to-noise ratio of hippocampal synaptic transmission. Of note, most studies on genomic CORT actions have been performed in the dorsal CA1 area. Granule neurons in the dentate gyrus, despite their high expression of MR and GR, respond less robustly to CORT (Karst & Joëls, 2003; van Gemert et al., 2009). CA1 neurons in the ventral hippocampus, in many respects, show effects opposite to those observed in the dorsal hippocampus (Maggio & Segal, 2009; Takata et al., 2015; Ritov et al., 2014), although most of these effects seem to develop in an intermediate time domain, too fast for gene-mediated actions and relatively slow in comparison to the non-genomic actions described above.

All in all, when considering the potential of CORT to alter excitatory and inhibitory synaptic transmission, differential effects are seen with regard to the region as well as the time domain. By and large, neuronal activity is quickly enhanced in the BLA and suppressed at a later stage, whereas the opposite is seen in the PFC. Results in the hippocampus mostly support enhanced excitability (although in a different manner) both in the fast and the delayed time domains. The functional consequences of these temporally distinct, brain region-specific actions of CORT are discussed in Section 4.

2.4. Factors modulating rapid actions

Most studies on rapid corticosteroid signaling to date have been conducted with *in vitro* administration of DEX or CORT, which has the advantage of achieving high temporal precision in identified (single) neurons. Unlike the delayed CORT actions, it remains to be seen if fast-onset and reversible CORT actions induced *in vivo* persist *in vitro* (e.g. after slice preparation) in all brain regions, as they do in the BLA.

The downside of *ex vivo* measurements is, of course, that the whole-organism context is lost and the contribution of natural metabolic changes (and the role, for example, of glial cells (Jaszczuk & Jaszczuk, 2021; Allaman et al., 2004) is less pronounced, given the controlled recording conditions. The extent to which these rapid effects actually occur *in vivo* is therefore not easy to establish. For instance, *in vivo*, fast-onset CORT actions could be masked by the effect of other stress hormones acting within the same time domain. Moreover, the kinetic properties of adrenal hormones reaching neurons are complex, such that intermediate-onset effects may confound the measurement of the fast-onset effects.

Recent studies have established that many other factors may also play a role in the response to CORT under physiological conditions, which are usually not taken into consideration in *ex vivo* studies (see Fig. 5). First, as described in section 1, following stress, neurons are not only exposed to CORT but also to myriad other stress hormones. In fact, monoamine and peptide neurotransmitters most likely reach neurons before CORT (Joëls & Baram, 2009), so that these neurons are already primed or in a different activity state by the time CORT reaches them than when they are exposed *in vitro* to CORT in isolation. This interaction between stress mediators has only begun to be tested for rapid CORT actions. For instance, potentiation of adrenergic effects, via $\alpha 1$ adrenoreceptors, was reported for a high concentration of DEX in the entorhinal cortex (Hartner & Schrader, 2018). Studies in the dentate gyrus (Pu et al., 2007) suggest that CORT rapidly increases the efficacy of the β -adrenergic agonist isoproterenol to induce synaptic plasticity in the perforant path afferents, which was not seen with respect to synaptic plasticity in the BLA (Pu et al., 2009) or in AMPA receptor-mediated single cell responses (Liebmann et al., 2009). However, CORT did amplify the effect of low concentrations of the β -adrenoreceptor agonist isoproterenol on mEPSC frequency in the BLA when the two drugs were applied concurrently (Karst & Joëls, 2016). Under physiological (moderate to severe) stress conditions, however, CORT is not expected to reach neurons concurrently with other stress mediators, but rather approximately 15–20 min later. This scenario was also tested in the same

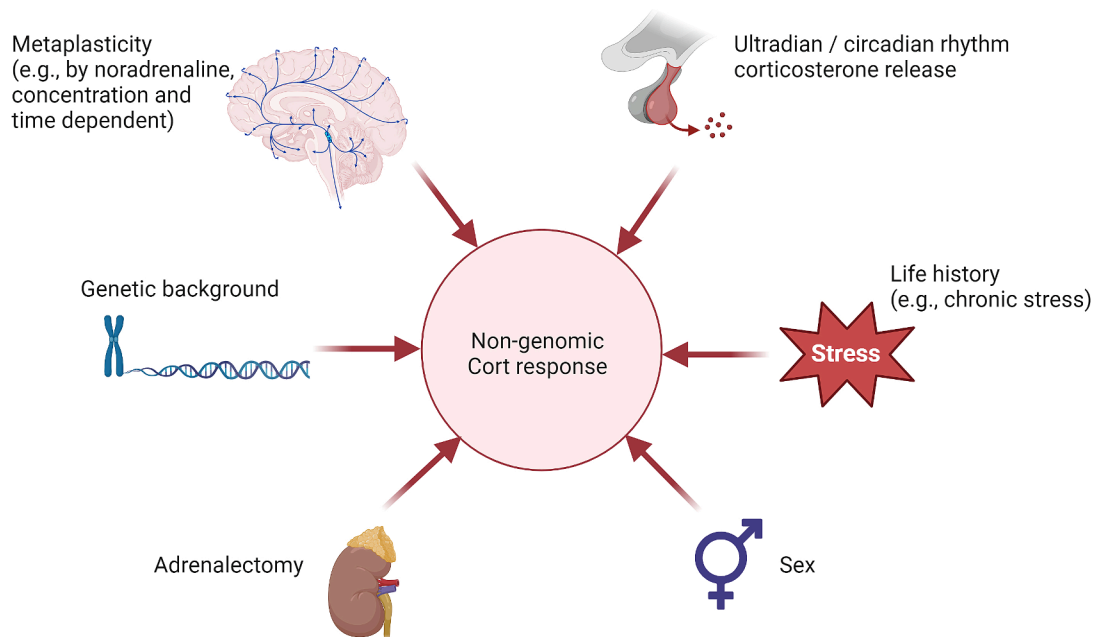


Fig. 5. Factors affecting non-genomic corticosteroid actions in the brain. Genetic background, sex, life history, prolonged disturbances in hormonal state (e.g., adrenalectomy), and ultradian or circadian release patterns determine the overall effectiveness of corticosteroids for rapidly changing glutamatergic or GABAergic synaptic signaling. In addition, the recent stress history of the organism leads to metaplastic responses in some areas studied, such as the BLA and PVN.

study (Fig. 5), in which it was observed that the effect of β -adrenoreceptor activation prevailed, first enhancing mEPSC frequency and then, after a delay of > 1 hr, suppressing it at moderately low concentrations of the two hormones. With high concentrations of the two hormones, the late suppression of mEPSCs was no longer observed, revealing instead a strong enhancement of mEPSC frequency by CORT. The timing of exposure to subsequent waves of stress mediators seems, therefore, to be very important, at least in the BLA. More specifically, with an interval of < 30 min between the peaks of isoproterenol and CORT, a high isoproterenol concentration may prime the subsequent CORT response, whereas with longer delays, it suppresses the CORT effect. The dynamic interactions between β adrenoreceptor and membrane corticosteroid receptor activation may be different with lower hormone concentrations.

The phenomenon of one stress mediator dynamically affecting the response to a subsequent CORT exposure, a form of “metaplasticity”, was also observed when BLA neurons were exposed to two or more pulses of CORT. Thus, when a principal neuron in the BLA was exposed to two pulses of CORT (100 nM) delivered within a 60-minute interval, both applications caused an increase in mEPSC frequency mediated by presynaptic MR activation. However, when the delay between the first and the second exposure to CORT was > 1 hr, the second pulse caused a rapid decrease in mEPSC frequency via GR activation (Karst et al., 2010; Karst & Joëls, 2016). Differential surface expression of MR and GR may underlie this form of metaplasticity (Karst et al., 2022). BLA neurons were found to be unresponsive to a third and fourth pulse of CORT (den Boon et al., 2019). The influence of the first CORT exposure on the response to the second exposure depends on a GR-dependent genomic mechanism (Karst et al., 2010). CA1 hippocampal neurons respond to two CORT pulses with similar increases in mEPSC frequency and GluA2 AMPA receptor trafficking, but here too metaplasticity can be seen in synaptic potentiation with subsequent pulses of CORT (Sarabdjitsingh et al., 2016).

On the one hand, metaplasticity of rapid CORT actions may be relevant when an organism is exposed to repeated stressors, a situation that is likely to happen in real life (Maras et al., 2014). For example, metaplastic changes in mEPSC frequency (Karst et al., 2010), mIPSC frequency (Di et al., 2016), and synaptic plasticity (Sarabdjitsingh &

Joëls, 2014) were observed when corticosteroid was applied *in vitro* after mice had been stressed *in vivo* before slice preparation. On the other hand, metaplasticity may also be relevant for neuronal activity in the face of ultradian (i.e., \sim hourly) pulsatility of CORT release. This was specifically tested by mimicking the rising and falling phases of the circadian cycle (den Boon et al., 2019). In slices prepared at the circadian nadir, BLA mEPSC frequency was not changed by pulses of ascending CORT concentrations (3/10/30/100 nM), but baseline mEPSC frequency gradually increased. In slices prepared at the circadian peak, the first pulse of CORT (100 nM) induced a small increase in mEPSC frequency. Subsequent pulses of descending concentrations (30/10/3 nM) were no longer able to induce an acute response, but the baseline mEPSC amplitude gradually decreased comparable to that seen in slices prepared at the nadir. It cannot be excluded that similar circadian variations in glutamatergic and GABAergic transmission, and rapid responses to CORT, may exist in other brain areas as a function of ultradian CORT pulsatility. If so, the strength and/or direction of the rapid CORT effects may vary depending on the point in time, relative to the circadian cycle, at which cells are tested.

In addition to successive acute stressors and ultradian pulses, longer-term changes in the neuroendocrine status or life history of an organism would be expected to influence the rapid response to CORT. There is ample evidence of this occurring for the slow, genomic CORT actions (as e.g., reviewed in Joëls et al., 2012), but there are few studies that have addressed this with respect to rapid CORT actions. A low concentration of CORT (3 nM) – that does not induce a detectable response in adrenalectomized mice – increased the mEPSC frequency in dentate granule cells in slices from adrenalectomized mice by $\sim 50\%$, which is a similar increase to that seen with 100 nM in adrenalectomized controls (Joëls et al., 2013). The increase in mEPSC frequency caused by 3 nM CORT in adrenalectomized mice was blocked by a GR but not MR antagonist. This suggests a sensitization to the rapid CORT effects in granule cells after CORT depletion by adrenalectomy; of note, the higher concentration of CORT (100 nM) that caused a strong increase in mEPSC frequency in sham-operated mice was without effect in the slices from adrenalectomized animals. Conversely, chronic restraint stress caused an increase in spontaneous GABAergic IPSCs in hippocampal CA1 neurons, but blocked or occluded the DEX-induced increase in sIPSC frequency

recorded *in vitro* in naïve animals, which could indicate either desensitization or occlusion of the GABA response by chronic stress (Hu et al., 2010). Spontaneous glutamatergic and GABAergic synaptic transmission in the PFC was also investigated in adult animals following early life stress exposure (e.g. Karst et al., 2020), but no change in fast-onset CORT effects was seen.

Finally, the sex and age of the organism are likely to impact rapid responses to CORT, similar to what has been described in the noradrenergic system response to stress and CRH (e.g. Curtis et al., 2006; Borodovitsyna et al., 2022). This, however, remains speculative at this time since nearly all studies to date have been carried out in young-adult male rodents (see Sup. Table S1).

In conclusion, fast-onset CORT actions on excitatory and inhibitory neurotransmission are plastic and can change due to i) the influence of other, earlier-onset stress mediators, ii) recent fluctuations in the CORT level due to prior stress or ultradian pulses, iii) chronic changes in CORT levels such as seen after adrenalectomy or chronic stress, and likely iv) the sex, age and genetic background of the organism. The significance of rapid CORT actions for neuroendocrine and behavioral responses should ideally, therefore, be interpreted in the context of these environmental factors, something that deserves more attention.

3. Mechanisms

3.1. Receptors

Exactly how the rapid effects of corticosteroids are mediated has been subject to much speculation (Fig. 6). There is compelling evidence that receptors that are associated with the membrane are involved. This is based mostly on the fact that the CORT actions are too rapid to be mediated by transcriptional effects of nuclear receptor activation and that membrane-impermeant conjugates of CORT or DEX with BSA evoke similar rapid actions (see Sup. Table S1). Since steroids conjugated to BSA result in molecules that are too big to pass the membrane, it has been reasoned that the receptors involved in fast-onset actions must be

accessible from the outside of the plasma membrane. These results with BSA-conjugated steroids have sometimes been challenged based on the assumption that steroid molecules can dissociate from the BSA, resulting in “free” steroid that can cross the membrane and activate the intracellular nuclear receptors. This appears unlikely, however, because i) steroids applied intracellularly via the recording pipette generally do not reproduce the rapid steroid actions (e.g. Olijslagers et al., 2008; Wang et al., 2012; Di et al., 2003), and ii) Tasker and colleagues showed that DEX-BSA is stable for long periods of time and at a range of temperatures, with very low amounts of DEX dissociating from the conjugate (Weiss et al., 2019). Denaturation of the DEX-BSA conjugate revealed that free DEX molecules are trapped in the DEX-BSA three-dimensional structure, but importantly, when purified and renatured, the DEX-BSA molecules were still able to induce the rapid response.

A critical question is whether the membrane-associated receptors are in fact the same as the intracellular nuclear receptors, GR and MR, which are translocated to the plasma membrane. Functional evidence supporting the membrane-associated receptors as a variant of the nuclear receptors includes the findings that rapid corticosteroid actions are not observed when the nuclear GR or MR are conditionally knocked down in the target neurons (Karst et al., 2005; Karst et al., 2010; Nahar et al., 2015; Solomon et al., 2015). Immunohistochemical studies have revealed the nuclear GR in the membrane fraction of hypothalamic extracts analyzed with Western blots (Nahar et al., 2016) and localized to hypothalamic, hippocampal and amygdalar neuron membranes visualized with electron microscopy (Liposits & Bohn, 1993; Liposits et al., 1987; Johnson et al., 2005). The nuclear GR is also expressed in the anterior pituitary gland associated with lipid rafts (Wehmeyer et al., 2014), where it has been observed to translocate from the cytosol to the membrane of adrenocorticotropin-secreting cells upon treatment with corticosterone (Deng et al., 2015a).

Agonists of the MR and GR have been reported to effectively mimic the fast-onset actions in many studies, while results using antagonists were more variable and dependent on the steroid receptor and the brain circuits tested (see Sup. Table S1). For instance, the effectiveness of

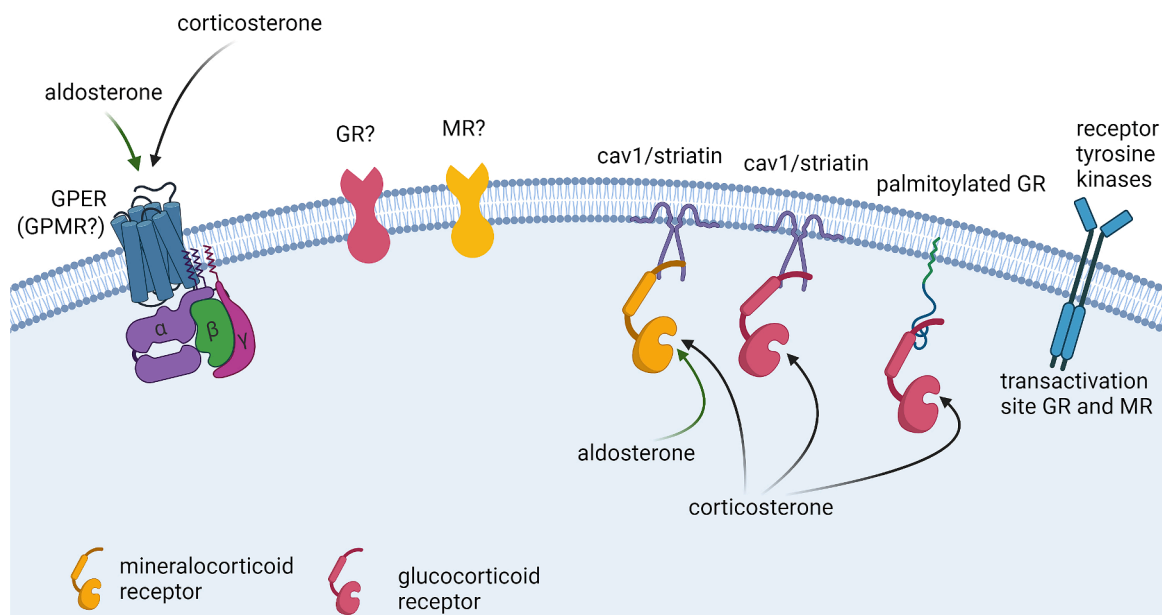


Fig. 6. Overview of potential receptors mediating non-genomic corticosteroid actions. Rapid non-genomic corticosteroid signaling is mediated by receptors associated with the plasma membrane. The nuclear glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) may be anchored to the plasma membrane via association with caveolin or striatin. The GR, but not MR, possesses a palmitoylation site that may allow it to be tethered to the membrane, although this was not seen in pituitary corticotrophs (Aguilera, 2011). The G protein-coupled estrogen receptor (GPER) was recently found to bind aldosterone with greater affinity than estrogen (Karst et al., 2022), and may therefore also be a G protein-coupled MR (GPMR). Furthermore, the existence of an unknown membrane MR and/or GR cannot be excluded (GR? and MR?). Beside binding to specific receptors, corticosterone can potentially affect signaling by non-genomic transactivation of, for example, receptor tyrosine kinases.

receptor modulators was clearly seen for the rapid corticosteroid effects thought to be mediated by MRs, with clear agonistic effects of the mineralocorticoid aldosterone and inhibitory effects of the MR antagonist spironolactone in studies on glutamate and GABA release and glutamate receptor mobility, as well as in behavioral studies (see Sup. Table S1) (for review see (Wehling, 2018)). The pharmacological evidence has been less consistent for rapid corticosteroid actions thought to be mediated by GRs. Generally, the involvement of GRs is based on the ability of the GR agonist DEX to evoke changes, although caution needs to be exercised since DEX can also bind to MR with moderate affinity (Perreau et al., 1999), comparable to aldosterone (Luttge et al., 1989), such that the high concentrations of DEX used in many studies may not be selective for GR. However, the highly selective GR agonist RU28362 also did not mimic the CORT effect in some studies (Philibert & Moguilevski, 1983).

The rapid effects of glucocorticoids at excitatory synapses on hypothalamic neuroendocrine cells (Di et al., 2003; Nahar et al., 2015), at inhibitory synapses on principal neurons of the basolateral amygdala (Di et al., 2016) and on hippocampal CA1 neurons (Hu et al., 2010) are not blocked by the GR antagonist mifepristone (RU486), which suggests i) that the membrane receptor may not be the nuclear GR, ii) that it is a structural variant of the nuclear GR, or iii) that mifepristone cannot bind the GR when it is positioned in or close to the plasma membrane. Nevertheless, some studies do report blockade of rapid glucocorticoid effects by mifepristone (Neiva et al., 2020; Zeise et al., 1992; Wang & Wang, 2009; Karst et al., 2010; Ikeda et al., 2015; Bahamonde et al., 2023), underscoring the elusive nature of the membrane receptor mechanism.

Visualization of MR and GR in the plasma membrane has, so far, been inconclusive, although electron microscopy studies have provided evidence of GR in the membranes of neurons in the lateral amygdala (Johnson et al., 2005), PVN, and CA1 (Liposits & Bohn, 1993), and of MR in the membranes of presynaptic terminals, neuronal dendrites, and dendritic spines of neurons in the lateral amygdala (Prager et al., 2010). However, other attempts have been less successful. For instance, imaging approaches in fixed hippocampal tissue as well as in live cells using a wide range of antibodies and overexpression of, for example, MR-GFP in COS7 and cultured hippocampal neurons have failed to convincingly demonstrate MRs in the plasma membrane, despite abundant intracellular MR labeling (Karst et al., 2022). These conflicting findings may possibly be due to distinct patterns of membrane MR expression in different brain areas.

The physicochemical properties of MR and GR make the integration of these receptors into the plasma membrane unlikely, despite the extracellular accessibility suggested by physiological experiments. It cannot be excluded that MR and GR are not located *within* the plasma membrane but, rather, tethered to it (see Fig. 6). Palmitoylation of receptors has been proposed as a possible mechanism (reviewed in (Treviño & Gorelick, 2021)), but appears unlikely because first, the MR, in contrast to the GR, protein lacks a palmitoylation site and second, mutation of the putative palmitoylation site in the GR did not affect the CORT-induced membrane translocation of GR in cell lines (Deng et al., 2015b). Another mechanism that has been suggested is the association of steroid receptors with caveolin-1 or striatin located within caveolae, which are enriched in membrane-associated signaling molecules like G-proteins. The binding site of MR or GR in caveolae would be located on the intracellular face of the membrane, however, the question arises as to whether the extracellular BSA-conjugated corticosteroid molecules would be capable of reaching these receptors. Also, such a mechanism would not explain why intracellularly administered corticosterone is ineffective.

The inability of MR and GR (ant)agonists to impact rapid corticosteroid actions at some synapses (Venero & Borrell, 1999; Di et al., 2003; Di et al., 2009; Di et al., 2016; Hu et al., 2010) suggests that in addition to the well-known MR and GR, corticosteroids may also bind to other hitherto unknown membrane-associated receptors. Corticosterone-

selective membrane receptors that do not bind aldosterone or dexamethasone were reported in membrane fractions from amphibian brain tissue already in the 1990 s (Orchinik et al., 1991), although similar high-affinity binding sites were not found in membranes prepared from the mammalian brain (Orchinik et al., 1997).

Other binding partners that are possible candidates for rapid effects via transactivation are receptor tyrosine kinases like EGFR, PDGFR, and IGF1R, all of which are located intracellularly. Also, receptors such as the G protein-coupled estrogen receptor (GPER), which was recently found to bind the mineralocorticoid aldosterone (Ding et al., 2022), is a membrane receptor candidate that may mediate some of the rapid MR effects. GPER is located in the plasma membrane and would presumably act downstream of MR, resembling the mGluR-ER α interaction (Mermelstein, 2009) and explaining why both the MR antagonist spironolactone and the GPER antagonist G-15 were effective in blocking the rapid CORT actions in the infralimbic PFC (Karst & Joëls, 2023).

3.2. Downstream signaling pathways

There is abundant evidence to suggest that the membrane-associated corticosteroid receptor(s) may exert their rapid actions via G protein-coupled receptor (GPCR) and G-protein signaling pathways. Early studies in the amphibian brain by Moore and colleagues identified a possible membrane glucocorticoid receptor with GPCR properties (Orchinik et al., 1992; Orchinik et al., 1991).

As described above, glucocorticoids have opposing non-genomic effects on excitatory and inhibitory synaptic transmission in hypothalamic magnocellular neuroendocrine cells via retrograde endocannabinoid suppression of glutamate release at excitatory synapses and nitric oxide facilitation of GABA release at inhibitory synapses. Cannabinoid receptors are also present at GABA synapses, but the phasic release of 2-AG induced by rapid glucocorticoid signaling is restricted spatially to glutamate synapses by astrocytic buffering, except under conditions of astrocytic withdrawal, such as in response to chronic dehydration (Di et al., 2013) (Fig. 7). The activation of the different retrograde messengers is caused by divergent G-protein signaling mechanisms downstream from the membrane receptor: signaling via a G α subunit induces 2-AG synthesis at excitatory synapses while nitric oxide synthesis at inhibitory synapses is dependent on G-protein β/γ subunits (Di et al., 2009) (Fig. 7). The G α signaling that triggers 2-AG synthesis requires cAMP/PKA activity (Di et al., 2003; Malcher-Lopes et al., 2006) as well as downstream phospholipase C, protein kinase C, ERK MAP kinase, calcium, and Src tyrosine kinase activation (Harris et al., 2019)), invoking a complex signal transduction mechanism with multiple possible entry points for transactivation by parallel signaling pathways. The nuclear GR has been associated with MEK and the tyrosine kinase Src via its interaction with HSP90 (Pratt & Toft, 2003), which suggests that these signals may be activated by GR at the membrane or via signaling from the membrane, though this sequence has not been established.

Also, β -arrestin may be involved in membrane receptor signaling. Beta-arrestin association with GPCRs has been reported to allosterically activate MEK and downstream ERK/MAP kinase (Kahsai et al., 2023) as well as Src (Pakharukova et al., 2020). The complexity of the signaling, therefore, suggests a multiplexed pathway that may incorporate β -arrestin signaling and signaling pathways both upstream and downstream from β -arrestin (Harrison and Tasker, 2022). Indeed, recent evidence in knockout mice suggests that β -arrestin is required for rapid corticosteroid actions at a membrane-associated MR (Karst et al., 2022) and may, therefore, also be in the signaling pathway of the membrane-associated GR.

Similarly, in hippocampal pyramidal neurons, rapid corticosteroid actions were reported to increase NMDA receptor surface expression by inhibiting receptor internalization via GPCR and protein kinase signaling involving multiple serine/threonine and tyrosine kinase activities (Yang et al., 2013). This rapid corticosteroid regulation of

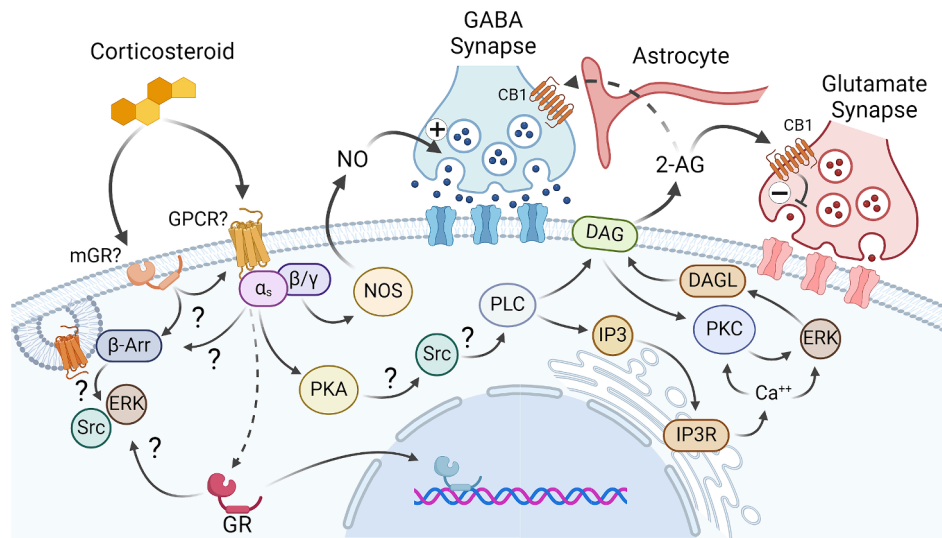


Fig. 7. Overview of putative signaling pathways of the membrane-associated glucocorticoid receptor. Activation of an unknown membrane corticosteroid receptor (mGR and/or GPCR) in PVN neuroendocrine cells induces the synthesis of the endocannabinoid 2-AG at glutamatergic excitatory synapses and nitric oxide (NO) at inhibitory synapses. The retrograde 2-AG release at excitatory synapses binds to presynaptic CB1 receptors and suppresses glutamate release and excitatory synaptic transmission in hypothalamic CRH, oxytocinergic, and vasopressinergic neurons, while the retrograde NO signal facilitates GABA release and increases inhibitory synaptic transmission in oxytocin and vasopressin neurons. Despite CB1 receptors at both glutamate and GABA synapses, and tonic anandamide regulation of GABA synapses (not shown), the glucocorticoid-induced endocannabinoid modulation is constrained spatially to glutamate synapses by astrocytic buffering. The signaling pathways downstream of the membrane-associated glucocorticoid receptors are complex, involving both α and β/γ subunits of G proteins and serine/threonine kinases (PKA, ERK), tyrosine kinases (Src), and calcium. There is also evidence for the involvement of β -arrestin (β -Arr) signaling. Additionally, membrane-associated glucocorticoid receptors can also signal to the nuclear GR (nGR) to stimulate the translocation of the unliganded nGR to the nucleus and transcriptional regulation. The nGR can also associate with ERK and Src, which provides a possible alternate rapid signaling pathway via nGR activation.

receptor trafficking in hippocampal neurons is reminiscent of the rapid corticosteroid actions in hypothalamic CRH neurons that rapidly regulate the intracellular trafficking of $\alpha 1$ adrenergic receptors, but this causes a depletion, rather than an increase, in surface receptor expression by preventing rapid recycling of the receptors (Jiang et al., 2022). These studies and others (Karst et al., 2022) support the possible role in rapid corticosteroid actions for β -arrestin signaling downstream from GPCR activation (Fig. 7), and could help explain the dependence of the rapid corticosteroid actions on both the nuclear receptors and multiple G-protein and protein-kinase signaling mechanisms.

The membrane-associated GR also signals to the nuclear GR resident in the cytosol to stimulate the translocation of the unliganded GR to the nucleus to trigger genomic regulation (Rainville et al., 2017) (Fig. 7). The transcriptional profile stimulated by the membrane receptor signaling to the unliganded nuclear GR appears to be largely distinct from that transduced by the corticosteroid-bound nuclear GR, although this will require further study to determine.

Thus, the corticosteroid receptors associated with the membrane interact with multiple biochemical signaling partners to transduce their rapid downstream effects. Whether the membrane receptor is a nuclear receptor translocated to the membrane and associated with a GPCR or itself a distinct GPCR, it nevertheless engages diverse G-protein and protein-kinase signaling mechanisms that diverge early in the signaling pathway, at the G-protein α and β/γ subunits, to regulate excitatory and inhibitory synapses. The complex signaling suggests the involvement of a multi-dimensional mechanism that invokes secondary signaling via β -arrestin activation. Rapid glucocorticoid actions extend beyond pre-synaptic and retrograde modulation of synapses to include postsynaptic adrenoreceptor trafficking, as described here, but also the synaptic trafficking of glutamate AMPA and NMDA receptors (Groc et al., 2008; Yang et al., 2013; see Harrison & Tasker, 2022 for review). Whether the multiplexed rapid corticosteroid signaling from the membrane involves more than one membrane receptor and/or divergent parallel signaling mechanisms remains to be determined.

4. Functional role of rapid corticosteroid actions

For decades, corticosteroids were considered to act mainly by regulating gene transcription, with most effects developing > 1 h after CORT levels start to rise. Experiments revealed that actions via MRs are necessary to maintain neuronal networks in a stable state, the importance of which becomes particularly evident when MR occupation is prevented (e.g., following adrenalectomy (Joëls et al., 2007)). However, there is recent evidence that genomic MR-mediated actions also play a role in the onset of the stress response (Gaudenzi et al., 2023; Mifsud & Reul, 2016). Genomic GR function that develops over a time course of > 1 hr has been studied mainly in the context of the stress response, although ultradian CORT peaks causing pulsatile genomic actions via GR were also investigated and found to be important to keep neuronal systems responsive (Sarabdjitsingh et al., 2010b; Sarabdjitsingh et al., 2010a).

The accelerated time course of rapid CORT actions suggests that the hormone may also play a prominent role in the early phase of the stress response. This has been studied in particular in the context of negative feedback effects on the HPA axis (section 4.1) and a variety of behavioral tasks (section 4.2). Obviously, in the early phase after stress exposure, other stress mediators also act on brain cells, so the contribution of CORT should be considered in combination with the actions of other stress signals (section 4.3). And rapid CORT actions after stress are inevitably followed by slow, genomic actions. Therefore, the two time-domains collectively determine the organism's ability to adequately respond to stressful conditions (section 4.4).

4.1. Rapid corticosteroid regulation of the HPA-axis

Exposure to excessive and/or sustained circulating corticosteroids (e.g., during trauma or chronic stress) can cause structural and functional damage to the brain. Well-studied examples include the loss of dendritic arbor and excitatory synaptic input in hippocampal and PFC pyramidal neurons (e.g., Watanabe et al., 1992; Radley et al., 2004) and the

suppression of neurogenesis (see e.g., Gould & Tanapat, 1999 or Joëls et al., 2004 for review), with corresponding deficits in spatial and working memory (Diamond & Rose, 1994; Kim et al., 2014). Corresponding changes to the amygdala include dendritic hypertrophy in basolateral amygdala principal cells that correlates with enhanced excitatory synaptic input and synaptic excitability, and an increase in fear and anxiety-like behaviors (Suvrathan et al., 2013; Vyas & Chattarji, 2004). It is critical, therefore, that constraint of HPA axis activation be built into the system to limit corticosteroid exposure in response to stress, which is accomplished mainly by the rapid negative feedback autoregulatory actions of corticosteroids.

Rapid corticosteroid actions to limit HPA axis activation were first described over 60 years ago (see e.g., Keller-Wood & Dallman, 1984) for review). The main site of rapid negative feedback regulation of the HPA stress response by corticosteroids appears to be in the hypothalamic PVN, where it suppresses the synaptic activation of the CRH neurons (Section 2.1.1). A short corticosteroid feedback loop also occurs at the level of the pituitary gland to control ultradian (i.e., ~ hourly) pulses of ACTH release (see Gjerstad et al., 2018 for review) (Fig. 8). This rapid ultradian corticosteroid effect at the pituitary may be mediated by the release of annexin 1 from pituitary folliculostellate cells and annexin 1 binding to pituitary corticotrophs (Buckingham et al., 2006), where it can suppress ACTH secretion via, in part, a large-conductance potassium channel-dependent mechanism (Duncan et al., 2016). As described above, negative glucocorticoid modulation of the HPA axis also occurs in the ventral hippocampus (Jacobson & Sapolsky, 1991; Cole et al., 2022) and medial PFC (Diorio et al., 1993). These higher-order sites of rapid corticosteroid actions may be engaged more to mediate the stress regulation of cognitive function and resultant descending control of HPA activation than as negative feedback relays to the HPA axis. Nevertheless, the multiple central sites of negative regulation of the HPA axis by feedback actions of corticosteroids point to the critical importance of constraining HPA activation to limit total corticosteroid exposure.

4.2. Importance of rapid effects for behavior

The evidence of a critical role of rapid nongenomic corticosteroid actions in rodent behavior has come from *in vivo* studies in which pharmacological agents were administered intracerebrally or peripherally and led to behavioral effects within 15 min and/or that were insensitive to protein synthesis inhibitors. While a broad range of different behaviors has been observed in the context of rapid corticosteroid actions, here we focus specifically on aggression, anxiety-like behavior, and memory (re)consolidation and retrieval, which have been extensively studied. For more information on this topic, we refer the reader to other reviews (Haller et al., 1998; Moore & Evans, 1999; Dallman, 2005).

For decades, it has been observed that stress can rapidly increase aggression (reviewed in Haller et al., 1998). The nongenomic nature of this stress effect was confirmed in an experiment in which CORT was administered intracerebroventricularly and was found to enhance aggression within 10 min, independent of protein synthesis, in a rat resident-intruder model (Mikics et al., 2005), an effect that was dependent on MR activation (Kruk et al., 2013).

Blocking MR bilaterally in the rat hippocampus caused an anxiolytic effect in a light–dark box test of anxiety-like behavior (Smythe et al., 1997). Low doses of CORT and CORT-BSA infused into the insular cortex rapidly (<5 min) induced an anxiety-like phenotype in the elevated plus maze and a novelty-suppressed feeding paradigm, which was blocked by a GR antagonist (Bahamonde et al., 2023). Peripheral CORT administration during the circadian active phase in rats didn't affect anxiety-like behavior, but quickly increased risk assessment behavior in a protein synthesis-independent manner (Mikics et al., 2005). Di et al. (2016) showed that anxiety-like behavior observed within 30 min after acute stress during the circadian inactive phase was suppressed by blocking the rapid CORT-induced 2-AG signaling at inhibitory synapses in the BLA.

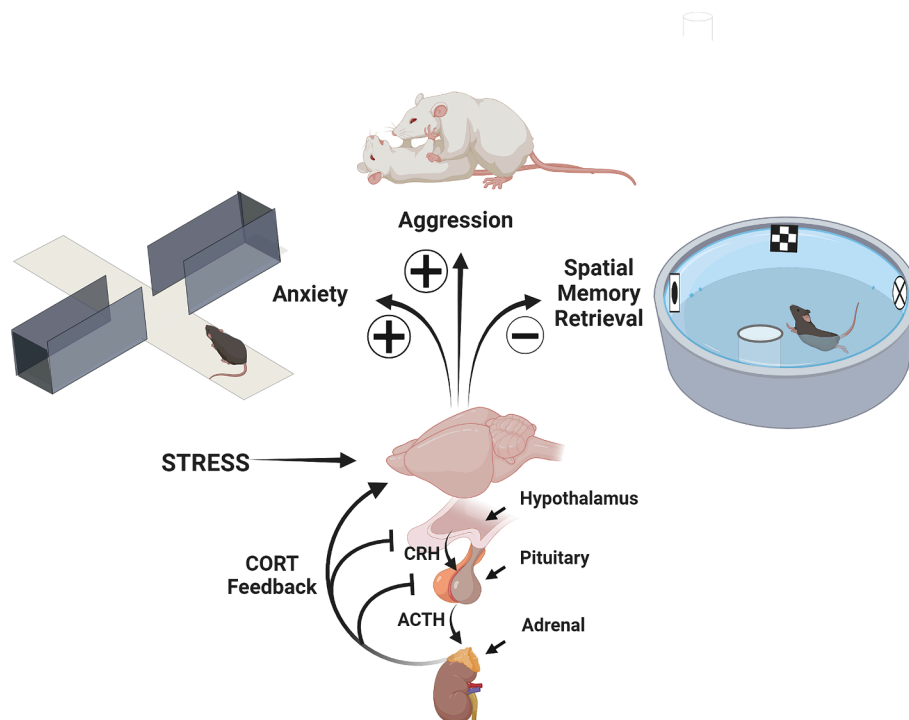


Fig. 8. Overview of the rapid neuroendocrine and behavioral effects of stress-activated corticosteroid signaling. Stress-induced activation of the hypothalamic–pituitary–adrenal (HPA) neuroendocrine axis elicits corticosteroid secretion from the adrenal glands (corticosterone, CORT), which feeds back onto the brain to 1) curtail HPA activation via inhibitory actions at the pituitary and hypothalamus, and 2) influence emotional, social, and cognitive function via actions in multiple higher order brain structures, such as the amygdala, hippocampus, and prefrontal cortex. Behaviors found to be influenced by rapid CORT actions in animal models include anxiety-like behavior, aggression, and spatial learning and memory (retrieval).

With respect to fear memory processing, application of the MR-antagonist spironolactone before, but not after, task acquisition diminished contextual fear memory retrieval 3 h later, which supports a role of MR during the learning phase (Zhou et al., 2010). Contextual aspects of learning, in particular, may be impaired: A peak in corticosterone causes (male) rodents to rapidly switch to a stimulus–response strategy in an MR-dependent manner (Schwabe et al., 2007; 2022). However, most studies have focused on the rapid role of CORT during the retrieval phase of memory formation. Thus, CORT administered into the BLA 10 min before recall of a fear memory in an inhibitory avoidance paradigm impaired the retrieval of the memory (Ali Vafaei et al., 2023). Earlier studies reported similar effects of the MR antagonist spironolactone on the retrieval and reconsolidation of contextual fear memory (Zhou et al., 2011). In a T-maze memory task, intrahippocampal infusion of CORT or CORT-BSA 15 min prior to memory retrieval was shown to impair spatial memory performance (Dorey et al., 2011), an effect that was blocked by the MR antagonist spironolactone, but not by the GR antagonist mifepristone, and was insensitive to inhibition of protein synthesis, pointing to non-genomic actions of MR. Largely consistent with these findings, mice trained in a contextual serial discrimination task showed a peak in intrahippocampal CORT level 15 min after stress, which was coincident with their disrupted retrieval performance, although spatial memory per se was unaffected (Chauveau et al., 2010). The disrupted memory retrieval did not occur when stress-induced CORT synthesis was suppressed by pretreatment with metyrapone; and intrahippocampal CORT-BSA infusion in non-stressed mice reproduced the acute stress effects.

Interestingly, similar effects on hippocampal memory were reported when CORT was administered peripherally 30–60 min prior to testing memory retention. Thus, Sajadi et al., 2006 reported impaired retrieval in the Morris water maze when CORT was administered I.P. 30 min prior to the test trial. This was unaffected by pretreatment with the protein synthesis inhibitor anisomycin, pointing to a nongenomic mechanism of CORT. Atsak and colleagues reported an impaired retrieval of contextual fear memory 1 h after peripheral CORT injection and that this involved the endocannabinoid system (Atsak et al., 2012), which has also been associated with nongenomic CORT actions (e.g., Di et al., 2003). If indeed these results with intracerebral and peripheral administration of CORT both reflect nongenomic signaling mechanisms, they indicate that, *in vivo*, the nongenomic effects in the brain may still be operational up to 30–60 min after CORT levels rise in the blood, consistent with the long-lasting effects of rapid CORT actions seen in the BLA (Di et al., 2016; Karst et al., 2010). This underscores the notion that the potential involvement of rapid nongenomic CORT actions should be accounted for when interpreting the effects of stress *in vivo*.

All in all, there is convincing evidence for nongenomic and fast-onset CORT effects on rodent behavior. In general, the available data point to a CORT-dependent i) increase in aggression against intruders, ii) increase in anxiety-like behavior, and iii) impairment of memory retrieval (Fig. 8). Where tested, MRs have emerged as the salient receptors responsible for these rapid behavioral effects of CORT, although the role of GRs has not been ruled out. This is largely consistent with behavioral studies that have revealed a sex-dependent role of MR in attention, exploratory, and searching behavior in a novel environment, and a switch to a more effective but less flexible learning strategy (Vogel et al., 2016; Schwabe et al., 2010).

4.3. Rapid CORT effects on behavior in the context of other stress signals

Many studies have shown that exogenous CORT administration *in vivo* is sufficient to rapidly change behavior. Yet, during stress, brain cells are also exposed to successive waves of various other stress signals, which raises the question as to the role of CORT in driving behavior directly after stress.

Clearly, the fact that MR and GR antagonists, and inhibition of CORT synthesis, prevent rapid stress-induced behavioral changes supports a

role for CORT under physiological conditions (Smythe et al., 1997; Dorey et al., 2011; Bahamonde et al., 2023). Nevertheless, it is likely that other stress mediators contribute significantly to rapid behavioral responses. First, neurotransmitter and neuropeptide levels in the brain peak more rapidly than CORT levels, since CORT has to be synthesized in and released from the adrenal glands, transported from the adrenals to the brain, and cross the blood–brain barrier to enter the brain parenchyma. For example, after stress, fast changes (<15 min) have been reported in the levels of GABA, acetylcholine, noradrenaline, and serotonin in the hippocampus (Aloisi et al., 1997; Peñalva et al., 2002; Hajós-Korcsok et al., 2003; de Groote & Linthorst, 2007); in acetylcholine, noradrenaline, and CRF in the amygdala (Merlo Pich et al., 1995; Quirarte et al., 1998; Hatfield & McGaugh, 1999; Kellis et al., 2020), and in acetylcholine, norepinephrine, and dopamine in the PFC (Chen et al., 2016; Del Arco et al., 2011; Feenstra et al., 2001). These stress mediators are thought to peak within a few minutes, although transmitter detection is constrained by the temporal resolution of sampling small volumes. Linthorst and collaborators elegantly demonstrated that strong stressors, such as swim and restraint stress, but not a mild novelty stress, cause the release of corticosteroid-binding globulin from the liver, which results in a delay of ~ 20 min for CORT levels to rise in the hippocampus (Droste et al., 2008; Qian et al., 2012). Accordingly, most studies report high CORT levels > 15 min after stress, e.g., in the hippocampus (Tronche et al., 2010; Garrido et al., 2012; Dorey et al., 2011; Bray et al., 2016), amygdala (Bouchez et al., 2012; Del Arco et al., 2015) and PFC (Garrido et al., 2012; Chen et al., 2016). Therefore, in the small window of time directly following stress exposure, it is likely that the actions of stress mediators other than CORT are predominant.

Secondly, the successive, albeit overlapping, waves of stress signals to which brain cells are exposed are expected to influence each other. As described above, *in vitro* experiments revealed that activation of β -adrenoceptors on BLA neurons changes the response to subsequent CORT application in a time-dependent manner (Karst & Joëls, 2016). Concurrent activation of β -adrenoceptors and CORT receptors resulted in synergistic actions on LTP in the dentate gyrus (Pu et al., 2007), whereas in the BLA, CORT slowly reversed the effects of β -adrenoceptor activation (Pu et al., 2009). This is consistent with behavioral observations on inhibitory avoidance, which showed that CORT delivered into the BLA impaired retrieval (or reconsolidation) 10 min later and that this was exacerbated by pretreatment with a β -adrenoceptor antagonist (Ali Vafaei et al., 2023). Of note, the overlapping waves of stress signals do not exclude that noradrenergic actions can occur downstream of corticosteroid actions, as was seen, for example, in a study of emotional memory formation (Atsak et al., 2012).

Taken together, multiple chemical stress signals other than corticosteroids play a role in the immediate behavioral response to stress, and they are likely to interact with and influence subsequent rapid corticosteroid actions. This interplay among stress signals merits further investigation.

4.4. Complementary rapid and delayed CORT actions

Rapid corticosteroid actions are invariably followed by slow, genomic corticosteroid effects, provided intracellular receptors are expressed in target cells, because they are caused by the same wave of hormone reaching the brain. The nature of rapid and slow actions can differ markedly, though, depending on the receptors and signaling pathways involved.

The difference between rapid and delayed corticosteroid actions is already noticeable at the single cell level. In the CA1 region of the hippocampus, for instance, CORT rapidly and reversibly increases the mEPSC frequency in CA1 pyramidal cells, but selectively increases the mEPSC amplitude > 1 h later (Karst & Joëls, 2005; Karst et al., 2005). CORT given concurrently with high-frequency stimulation of the Schaffer collaterals promotes synaptic plasticity (Wiegert et al., 2006), but when given > 1 hr in advance of the stimulation suppresses plasticity

(Diamond et al., 1992; Pavlides et al., 1993; Joëls & Krugers, 2007). The opposite effects have been reported in the BLA (Sarabdjitsingh et al., 2012; Sarabdjitsingh & Joëls, 2014; Sarabdjitsingh et al., 2014). Of note, activation of a membrane-associated glucocorticoid receptor with DEX-BSA has been reported to cause the nuclear GR to traffic to the nucleus and effect changes in gene transcription (Rainville et al., 2017), showing that delayed genomic actions can apparently also be induced by membrane receptor regulation of unliganded intracellular receptors.

Differences between the rapid and delayed effects of corticosteroids are also seen at the whole brain network level, since different circuits are activated at early and late stages following stress exposure, possibly due to the differential expression of MR, GR, or other molecules mediating fast-onset corticosteroid effects. As described in section 4.2, rapid corticosteroid actions in rodents play a role in aggression, anxiety, attention, and exploratory and searching behaviors; promote a switch to a more effective, but less flexible, learning strategy; and impair memory retrieval. This generally, but not exclusively, involves MRs and brain regions such as the hypothalamus, amygdala, and striatum. By contrast, the slow actions of corticosteroids promote higher cognitive functions that play a more future-oriented role, such as the consolidation of memory, particularly contextual memory, decision-making, and prosocial behaviors (Joëls et al., 2018; Sandi, 1998; de Kloet et al., 2018). These actions have been found to depend on GRs and require activation of, for example, the hippocampus and PFC.

We propose here, as in previous reviews (see Joëls, 2018; de Kloet & Joëls, 2023), that an optimal balance between the two time-domains of corticosteroid actions is essential for the adaptation of the organism to a changing environment. According to this model, the rapid actions are focused on the here and now and play a short-term survival role, while the delayed, long-lasting (i.e., slow) actions redress the short-term perturbations and re-equilibrate homeostatic function to confer long-term adaptation within a revised environmental context.

5. Potential importance of rapid corticosteroid actions in human health and disease

When rodent studies provided evidence for the rapid time domain, in addition to the already established slow domain, of CORT actions, several studies were initiated to determine whether rapid effects could also be discerned in humans. To demonstrate fast-onset, nongenomic cortisol actions in the human brain, one obviously cannot take advantage of the tools commonly used in rodent research, like intracerebral administration of CORT/DEX-BSA or protein synthesis inhibitors. The only index of such rapid corticosteroid effects in humans, therefore, is the relatively fast time frame in which functional changes occur after exogenous administration of hydrocortisone or exposure to stress in conjunction with pretreatment with MR or GR antagonists.

5.1. Rapid effects in healthy human subjects

5.1.1. Neuroendocrine regulation

As discussed above (Section 2.1), it has long been known that corticosteroid pretreatment or prior stress exposure can rapidly inhibit stress activation of the HPA axis, which was considered evidence for rapid corticosteroid feedback inhibition. However, most of the studies on fast feedback regulation of the HPA axis have been performed in animal models, with only a few studies on rapid corticosteroid regulation having been conducted in humans to date.

An early study performed on subjects with hypocortisolism caused by Addison's disease showed that intravenous cortisol infusions caused a rapid decrease in the elevated basal ACTH levels seen in these patients, but the corticosteroid receptor dependence was not determined (Fehm et al., 1979). A more recent investigation in healthy adult male subjects found that intravenous administration of prednisolone, a nonselective GR/MR agonist, prevented the normal circadian morning rise and accelerated the evening decline in ACTH and cortisol levels within 60

min and that this effect was blocked by a GR, but not MR, antagonist (Russell et al., 2010). This study and another (Carroll et al., 2019) also showed that prednisolone or cortisol pretreatment blocked the rise in circulating ACTH and cortisol levels induced by exogenous ovine CRH application, suggesting a pituitary site of rapid feedback steroid action. Finally, a recent study tested the sensitivity of the stress activation of the HPA axis to fast feedback regulation by administering orally either the MR antagonist spironolactone or the GR antagonist mifepristone 90 min before application of the Trier Social Stress Test, a psychosocial stress test. That study found that blocking MR, but not GR, caused a significant increase in the stress cortisol response (Deuter et al., 2024), suggesting that there is a baseline inhibition of the HPA axis by MR activation that, when lifted, disinhibits the CRH neurons and amplifies the HPA response to psychological stress.

Thus, rapid feedback effects of corticosteroids on circadian and stress activation of the HPA axis have been confirmed in human subjects, although the respective roles of the two receptors remain to be worked out.

5.1.2. Behavior

In studies directly addressing the timing of the behavioral effects of corticosteroids, three groups were compared: 1) human subjects treated with hydrocortisone several hours before behavioral testing (resulting in a cortisol peak > 1h before the test and return to baseline at the time of testing) in combination with placebo treatment 30 min before testing, which targets the slow, genomic steroid actions; 2) subjects treated with placebo several hours before the behavioral test and hydrocortisone treatment 30 min before testing, which focuses on the fast steroid actions; and 3) the placebo-placebo control group. The advantage of studies in humans is that one can combine behavioral testing with functional (f)MRI, something that is not feasible in rodents due to the inherently stressful nature of fMRI investigation in a fixed-posture constellation. Moreover, in humans, one can make use of tests that are not feasible in rodents (e.g., those based on a theory of mind), as well as receive subjective feedback on the test conditions.

By and large, compared to placebo controls and to a group in which the genomic effects of hydrocortisone were allowed to develop, human subjects receiving hydrocortisone shortly before testing i) made emotional, egocentric rather than rational choices, ii) relied less on contextual information and instead used simple stimulus-response learning strategies, and iii) made use of simple motor learning approaches (Dolfen et al., 2021) (for review, Hermans et al., 2014). By contrast, individuals tested several hours after the peak in salivary cortisol showed better working memory performance, more rational and altruistic choices, and made use of contextual learning strategies (see e.g. Joëls et al., 2018 for a review). Other human behavioral studies using a single test time point following hydrocortisone administration found generally a similar pattern of responses (Hermans et al., 2014).

Simultaneous fMRI recording revealed that in human subjects tested < 30 min after the peak in cortisol, amygdala activity is upregulated and coupled to the frontoparietal region, potentially interfering with frontoparietal cortical function (Fig. 9; Sup. Table S2) (see also Van Oort et al., 2017 for review). Striatal systems are engaged in memory tasks in an MR-dependent manner at the cost of involvement of hippocampal circuits. Also, the activity within various parts of the frontal lobe was found to be reduced. This was also found in other fMRI-based studies in which brain activity was recorded within 30 min of the cortisol peak, which in most cases was elicited by stress exposure (see Sup. Table S2 for a comprehensive literature overview) (Fig. 9).

Fewer studies have addressed human brain activity at > 60 min after the cortisol peak. Generally, these studies report that the amygdala gradually becomes uncoupled from higher brain areas, and that the activity in the dorsal PFC, insular cortex and hippocampus is upregulated (see for literature overview Sup. Table S2). Interestingly, a recent study in rodents reporting on single cell c-fos activation at various time points following foot shock showed a similar sequential activation of the

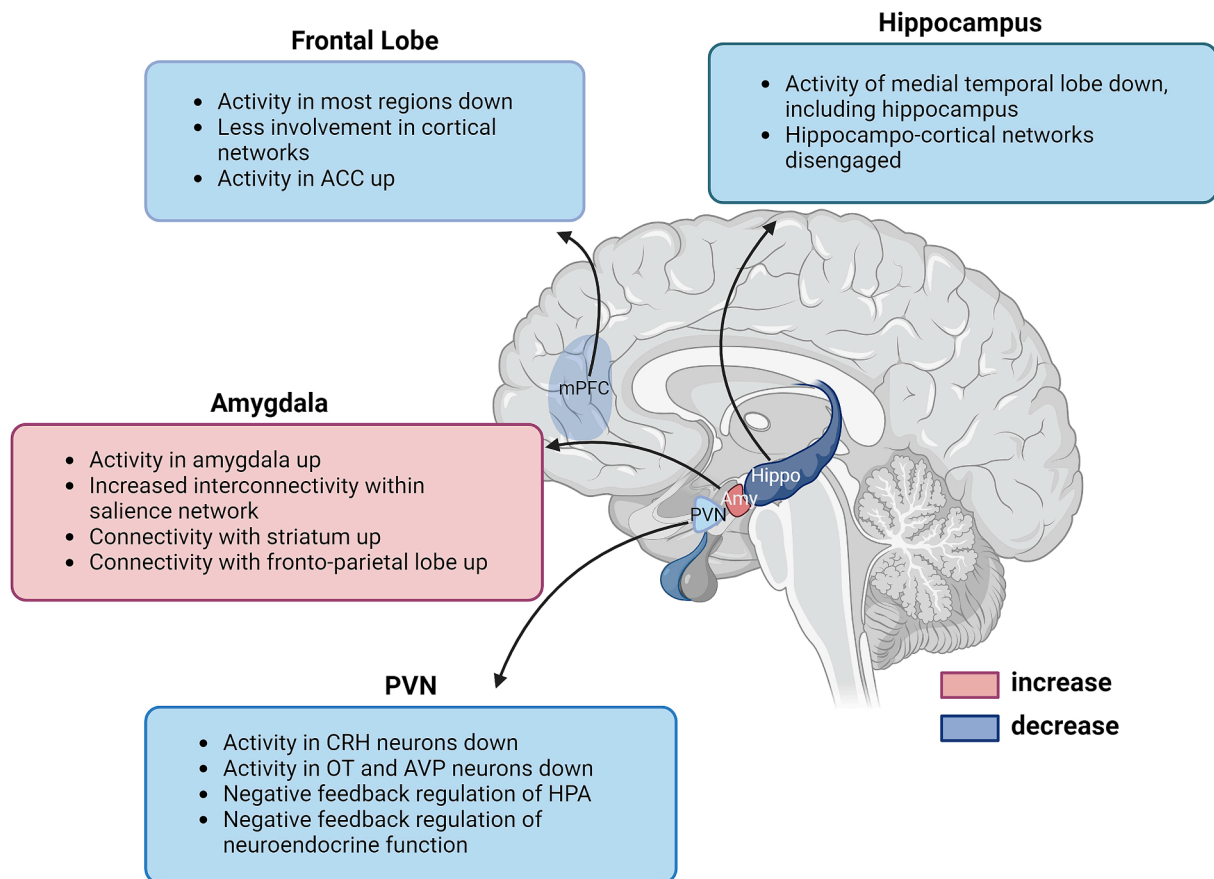


Fig. 9. Summary of rapid corticosteroid effects on human brain activity. In the short term (<30 min after the peak in cortisol), connectivity within the salience network, and particularly amygdala activity, is increased. In some behavioral tasks, the coupling of the amygdala with striatal and frontoparietal networks was found to be strengthened. Later (>60 min after the cortisol peak), the amygdala becomes uncoupled again. By contrast, shortly after the peak in cortisol, hippocampo-cortical networks are disengaged. Limbic regions, including the hippocampus and various parts of the frontal lobe (but not, for example, the anterior cingulate cortex, ACC) show reduced activity. Neuroendocrine systems in the hypothalamus, including CRH neurons as well as oxytocin (OT) and vasopressin (AVP) neurons in the PVN, are under negative feedback control. For more detailed information, see text and Sup. Table S2.

amygdala, PFC and hippocampus (Bonapersona et al., 2022).

Rapid effects after hydrocortisone administration do not prove that endogenous cortisol evokes similar fast functional changes in the brain. In fact, rapid changes in salience network activity after stress were effectively blocked by the β -adrenoreceptor antagonist propranolol (Hermans et al., 2011). However, there is also evidence for a role of cortisol. Thus, increased generosity towards socially close, but not distant, individuals was seen in subjects tested shortly after stress onset, but not in subjects tested 90 min after stress onset (Margittai et al., 2015). This early stress-induced increase in generosity was mimicked by hydrocortisone administration, suggesting a rapid corticosteroid effect on social discounting behavior. It was counteracted by administration of the α_2 adrenoreceptor antagonist yohimbine, which increases noradrenaline release but may also increase the levels of other neurotransmitters, supporting the notion that cortisol, rather than norepinephrine, causes the rapid behavioral effect of stress (Margittai et al., 2018).

This similarity in the behavioral response to stress and hydrocortisone was not always observed. For instance, hydrocortisone rapidly impaired, and then slowly improved, the contextual learning of *emotional* (but not *neutral*) information, whereas psychosocial stress rapidly impaired, and then slowly improved, contextual learning of *neutral* (but not *emotional*) information (Sep et al., 2019; van Ast et al., 2013). In the game theory intertemporal choice paradigm, subjects showed an increased preference for early smaller rewards over delayed larger rewards when tested shortly after hydrocortisone administration, but not several hours later (Riis-Vestergaard et al., 2018), whereas

psychosocial stress did not significantly affect intertemporal choice at either time point (Haushofer et al., 2013), again dissociating the behavioral effects of stress versus cortisol.

Some studies in humans examined the role of MR, which in rodents seems important for most fast-onset behavioral actions. Administration of the MR antagonist spironolactone impaired selective attention (Otte et al., 2007; Cornelisse et al., 2011) and working memory, delayed recall of visuospatial memory, and caused a trend toward reduction in mental flexibility (Otte et al., 2007). Administering the corticosteroid fludrocortisone, which binds MR with higher affinity than GR (Oelkers et al., 1994), resulted in selective attention toward sad, but not happy, faces (Schultebrasucks et al., 2016) and caused an increase in risk taking behavior (Deuter et al., 2017) in healthy men and women. Whether these presumably MR-mediated behavioral effects were due to rapid or delayed actions of the corticosteroid could not be established from the paradigms used.

5.2. Rapid corticosteroids effects in mental health patients

Experimental protocols focusing on the temporal dynamics of corticosteroid actions have rarely been applied to human subjects suffering from mental health disorders. A notable exception is a study conducted in healthy male subjects and siblings of schizophrenia patients, considered at risk for stress-induced psychopathology, who were exposed to psychosocial stress or control conditions and tested using fMRI for changes in functional connectivity in their salience and executive control networks immediately or 1.5 h after stress exposure (van Leeuwen

et al., 2019). Acute stress increased functional connectivity in the salience network in the healthy controls, but not in the siblings of schizophrenics. Functional connectivity within the salience network was reduced in both groups at a later time point following the stress, while functional connectivity between the executive network and the cerebellum was enhanced in both groups. These data suggest that the rapid, but not delayed, effects of stress are altered in individuals at risk for schizophrenia. This may explain why, in a separate study, acute but not ambient psychosocial stress impaired learning in individuals classified as high schizotypal (Walter et al., 2022).

Other studies have compared cognitive function following psychosocial stress in various groups of patients with that in healthy controls using non-specific time points (30–60 min), which prevents the designation of the observed effects as fast-onset, nongenomic effects. In most cases, no differences between patients and healthy controls were observed, e.g., in the case of free recall of earlier learned information (Duesenberg et al., 2019) or the recognition of facial emotional expressions (Graumann et al., 2021).

MR ligands have also been tested for their role in cognitive function in patient populations (see review by Wingenfeld & Otte, 2019), although the experimental design of these studies also did not allow for assignment of the observed effects to fast-onset cortisol actions. For example, spironolactone treatment of a (mixed-gender) group of major depressives and healthy controls several hours before testing revealed that depressed patients had higher cognitive empathy scores compared to controls after placebo, but not after spironolactone treatment. After spironolactone treatment, depressed patients, but not controls, showed reduced cognitive empathy (Wingenfeld et al., 2016). Conversely, fludrocortisone treatment of a (mixed-gender) group of depressed patients and healthy controls resulted in a main effect of the corticosteroid on verbal memory and executive function (an improvement), but no interaction between treatment and patient population was found (Otte et al., 2015). Individuals with depression and healthy controls did not differ concerning selective attention to emotional stimuli, emotion recognition, autobiographical memory, or spatial learning and memory performance; nor did fludrocortisone treatment affect their performance (Fleischer et al., 2015; Nowacki et al., 2021; Kaczmarczyk et al., 2022). Male and female subjects may respond differently to stress and treatment (Inoue et al., 2015), so the mixed-gender design could have obscured potential sex-dependent effects of the corticosteroid. Interestingly, women, but not men, who carried an MR haplotype that results in higher MR expression *in vitro* showed a lower prevalence of major depression (Klok et al., 2011).

It is too early at this time to conclude whether rapid cortisol actions contribute to psychopathology, possibly via MR, and, therefore, whether they could present an effective target for drug therapy.

5.3. Concluding remarks

Over the past two decades, the existence of rapid corticosteroid actions in many brain areas has been firmly established. In our overview of rapid cellular changes by corticosteroids, we concentrated on those actions that target excitatory and inhibitory synapses, since most studies to date have focused on these important synaptic systems. However, rapid corticosteroid effects are certainly not restricted exclusively to these transmitter systems (see e.g., Gasser & Lowry, 2018; Jiang et al., 2022). The nature of the rapid CORT effects is region-specific and they occur in a complementary fashion to the well-documented slow, genomic CORT actions. It is possible that a third, intermediate domain also exists, in which effects develop over 10–20 min and peak in < 1 hr (Joëls et al., 2012; Keller-Wood & Dallman, 1984), but it is difficult to distinguish between fast and intermediate time domains, especially in an *in vivo* experimental design.

Studies over the last two decades have revealed that in many, but certainly not all, cases, the “classical” corticosteroid receptors (i.e., nuclear receptors) seem indispensable for fast-onset functional changes,

but that, in contrast to the genomic pathway, these receptors appear to be associated with the plasma membrane and accessible from the external face of the membrane. Whether or not this involves MR and GR that are located at the membrane or other membrane proteins that subsequently activate cytosolic MR and GR is currently unresolved. To date, convincing evidence for unique, membrane-located receptors that mediate the fast-onset corticosteroid actions is lacking. This prevents the development of drugs selective for the membrane receptors, such as has been the case for the membrane estrogen receptor GPER (Prossnitz, 2018).

Several downstream signaling pathways have been implicated in the rapid corticosteroid effects. These are diverse pathways included in the signaling of many neurotransmitters and hormones, which seriously hampers the specific targeting of molecules important for rapid corticosteroid actions. For example, endocannabinoids are involved in some fast-onset corticosteroid effects, although this is not universally the case and is not exclusive to corticosteroid actions, such that targeting cannabinoid receptors for drug therapy would be expected to have significant off-target effects.

The lack of selective drugs targeting rapid corticosteroid signaling is a serious limitation in behavioral studies, especially in humans. In rodents, local infusion of BSA-conjugated corticosteroids has convincingly established the role of rapid nongenomic corticosteroid actions in behavior, but investigation of rapid effects in humans has depended exclusively on the timing of stress and/or corticosteroid administration relative to behavioral testing. Unfortunately, the timing after acute stress has not been rigorously accounted for in most behavioral investigations of human subjects, which makes it difficult to distinguish with any certainty the rapid effects of cortisol from intermediate or delayed effects.

Another limitation of the current body of literature is the fact that most studies have been performed on male subjects, which presents a significant gender gap in our understanding of rapid corticosteroid actions. This prevents the generalizability of the findings, as not only the HPA stress response (Kajantie & Phillips, 2006; Moisan, 2021), but also the response to stress mediators, show clear sex dependence at the cell, circuit (e.g., Bates et al., 2023), and behavioral levels (e.g., Merz & Wolf, 2017). Moreover, current evidence is based primarily on studies in healthy young adult subjects. Age and diseased states are known to alter circadian and ultradian rhythmicity as well as the setpoint for HPA responses (e.g., Upton et al., 2023), introducing significant potential variability in corticosteroid responsiveness. Each of these factors will impact the contribution of rapid corticosteroid actions to brain function.

Despite these limitations, the emerging evidence points to a clear role of rapid corticosteroid actions in the brain's response to circadian and ultradian rhythms and acute stress. The rapid, non-genomic actions of corticosteroids are generally complementary to the slow, genomic actions, and a balance between rapid and delayed corticosteroid actions appears to be critical for optimal adaptation, coping, and viability in a dynamic environment. It will be interesting going forward to determine the extent to which disruption of this balance between non-genomic and genomic corticosteroid regulation can increase an individual's vulnerability to psychopathology.

CRedit authorship contribution statement

Marian Joëls: Writing – review & editing, Writing – original draft, Conceptualization. **Henk Karst:** Writing – review & editing, Writing – original draft, Conceptualization. **Jeffrey G. Tasker:** Writing – review & editing, Writing – original draft, Conceptualization.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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