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Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic–pituitary–adrenal axis

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Abstract

Stress activation of the hypothalamic–pituitary–adrenal (HPA) axis culminates in increased circulating corticosteroid concentrations. Stress-induced corticosteroids exert diverse actions in multiple target tissues over a broad range of timescales, ranging from rapid actions, which are induced within seconds to minutes and gene transcription independent, to slow actions, which are delayed, long lasting, and transcription dependent. Rapid corticosteroid actions in the brain include, among others, a fast negative feedback mechanism responsible for shutting down the activated HPA axis centrally. We provide a brief review of the cellular mechanisms responsible for rapid corticosteroid actions in different brain structures of the rat, including the hypothalamus, hippocampus, amygdala, and in the anterior pituitary. We propose a model for the direct feedback inhibition of the HPA axis by glucocorticoids in the hypothalamus. According to this model, glucocorticoids activate membrane glucocorticoid receptors to induce endocannabinoid synthesis in the hypothalamic paraventricular nucleus (PVN) and retrograde cannabinoid type I receptor-mediated suppression of the excitatory synaptic drive to PVN neuroendocrine cells. Rapid corticosteroid actions in the hippocampus, amygdala, and pituitary are mediated by diverse cellular mechanisms and may also contribute to the rapid negative feedback regulation of the HPA neuroendocrine axis as well as to the stress regulation of emotional and spatial memory formation.

Keywords

Corticosterone; cortisol; endocannabinoid; hypothalamus; nongenomic; paraventricular nucleus

All stressors, whether physiological or psychological in nature, elicit a generalized stress response (Selye 1936), which, simplified, consists of the activation of a neuroendocrine reflex arc, triggered by the secretion of hypothalamic-releasing hormones, and an autonomic reflex arc, triggered by the stimulation of hypothalamic presympathetic neurons. The neuroendocrine branch of the reflex is characterized mainly by the activation of the

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hypothalamic–pituitary–adrenocortical (HPA) axis, whereas the autonomic branch consists of the activation of the hypothalamic–sympathetic–adrenomedullary axis. Interestingly, both the neuroendocrine and the autonomic efferent arcs of the generalized stress response converge on the adrenal glands, albeit on different timescales and with different final endpoints: the autonomic response occurs rapidly, triggered by sympathetic neural outputs that stimulate the secretion of adrenomedullary catecholamines, and the neuroendocrine response occurs on a slower timescale, triggered by hypothalamic–pituitary hormone output and resulting in adrenocortical glucocorticoid secretion. Mineralocorticoids are also released by stress, although at much lower levels (>1000-fold), and as a consequence are not considered to be critical in the acute systemic stress response. The primary neural and hormonal adrenal outputs, rapid catecholamine secretion and delayed glucocorticoid secretion, define to a large degree (although not exclusively) the hormonal milieu of the organism over a time frame that defines the acute stress response, starting with the onset of the stressor and usually lasting for several minutes following the initiation of the stressor, and this ultimately promotes the survival of the organism under threatening internal or external environmental conditions. Because of its rapid neural component, the sympathetic leg of the stress response contributes directly to the fight or flight response, with an acute preservative impact on survival. The survival value of the neuroendocrine response that results in corticosteroid secretion is less obvious, given that its relatively slow timescale (i.e. on the order of minutes) is too slow to contribute directly to the fight or flight response. The neuroendocrine response is thought therefore, to provide a support function to the stress response, which, for example mobilizes glucose in muscle and liver to replenish energy supplies, and inhibits inflammation to prevent the diversion of valuable energy away from survival-critical function following a stress insult. Nonetheless, it is the comparatively slow neuroendocrine response that is responsible for mediating, in addition to the classical delayed transcriptional regulatory effects of the glucocorticoids, the “rapid,” nongenomic glucocorticoid actions. These are considered to result from the activation of a membrane-associated receptor and to occur on a timescale that is closely coupled to the temporal dynamics of the circulating hormone (i.e. of the order of seconds to minutes). They are considered to be rapid actions in comparison to the classical glucocorticoid effects on transcriptional regulation, but are not so fast when considered in the context of responding to and surviving a threatening stimulus. Although one can readily appreciate the selective value of these rapid glucocorticoid actions in peripheral tissues (e.g. glucose mobilization, immune suppression) for supporting the survival of the organism in the minutes during and following an acute stress response, the functions of these same rapid glucocorticoid actions in the brain are less clear. Nevertheless, one of the main functions attributed to the rapid actions of glucocorticoids in the brain is the termination of the neuroendocrine stress response, i.e. the feedback inhibition of the HPA axis, with the primary purpose, it is postulated, of preventing the depletion of stress hormones in order to maintain levels in the hypothalamus and pituitary sufficient to allow the organism to mount successive stress responses (Sapolsky et al. 2000). Another function of glucocorticoid feedback in the brain is the facilitation of acquisition of emotional and spatial memories that are salient to the specific stress stimulus (McGaugh and Roozendaal 2002).

Here, we focus on recent evidence from findings in the rodent brain for a rapid feedback inhibition of the HPA axis by glucocorticoids which is mediated by glucocorticoid-induced endocannabinoid synthesis in the hypothalamic paraventricular nucleus (PVN). Although this may represent a rapid negative feedback mechanism that prevents stress hormone depletion during the stress response, the rapid nature of the glucocorticoid signaling, the endocannabinoid involvement, and the universality of the glucocorticoid signaling mechanism among neuroendocrine systems, as well as possibly in other limbic and autonomic systems, suggest a much broader, more complicated role for the rapid glucocorticoid actions in the brain (Tasker 2006). Indeed, evidence for rapid corticosteroid effects on pre- and postsynaptic mechanisms in the hippocampus, amygdala, and hypothalamus signifies that these rapid actions may serve other functions than that of simply shutting down the HPA axis (Di et al. 2003, 2005; Roozendaal et al. 2004, 2006; Karst et al. 2005, 2010). Although we touch upon evidence for rapid corticosteroid actions in synaptic transmission in the hippocampus and amygdala, the reader is referred to recent reviews (de Kloet et al. 2008; Joëls 2008; Joëls and Baram 2009; Roozendaal et al. 2009) for further discussion of some of these corticosteroid actions and their possible roles in learning, memory formation, and fear conditioning.

***In vitro* demonstration of rapid glucocorticoid modulation of synaptic transmission**

We have recently shown with patch clamp recordings in acute *in vitro* slices of rat hypothalamus that corticosterone, the endogenous rodent corticosteroid, and dexamethasone, a synthetic corticosteroid selective for the intracellular glucocorticoid receptor (GR) over the mineralocorticoid receptor (MR), cause a rapid, concentration-dependent suppression of excitatory synaptic inputs to neuroendocrine cells of the PVN and supraoptic nucleus (Figure 1) (Di et al. 2003, 2005). This glucocorticoid-induced suppression of excitation (GSE) is nonreversible, but is not dependent on transcriptional regulation by the steroid. Glucocorticoid-induced suppression of excitation is found in the corticotropin-releasing hormone (CRH) neurons of the PVN, which are responsible for triggering the activation of the HPA axis (and represent, therefore, the predicted hypothalamic target for glucocorticoid negative feedback actions), but it is also found in the other neuroendocrine cell populations of the PVN, including in the parvocellular thyrotropin-releasing hormone cells and in the magnocellular oxytocin- and vasopressin-secreting cells, as well as in the magnocellular neuroendocrine cells of the supraoptic nucleus (Di et al. 2003, 2005, 2009). Preliminary evidence for a form of GSE has also been found recently in preautonomic neurons of the PVN that project to the stomach (Zsombok et al. 2007). Glucocorticoid-induced suppression of excitation does not appear to be mediated by the activation of the classical intracellular GR or MR signaling pathways, as it is insensitive to blockade by the GR and MR antagonists, RU486 and spironolactone, and is mediated by the activation of a membrane-associated receptor (Di et al. 2003). However, the failure to activate the genomic GR signaling pathway does not preclude the involvement of the classical GR in the membrane receptor-mediated nongenomic glucocorticoid effects and the rapid corticosteroid feedback, as we have recently acquired preliminary data in a conditional GR knockout mouse model which indicate that the GSE in the PVN may be dependent on the GR (Haam et al. 2010).

Corticosteroids also appear to exert negative feedback effects on HPA activation via actions in the hippocampus (Sapolsky et al. 1984; Jacobson and Sapolski 1991; Furay et al. 2008) and to modulate hippocampus-dependent memory formation (De Kloet et al. 1998; McGaugh and Roozendaal 2002; Kim et al. 2006). Interestingly, compared to their rapid actions in the hypothalamus, corticosteroids exert the opposite acute modulatory effect on glutamatergic excitatory synapses onto hippocampal CA1 pyramidal neurons in the rat (Karst et al. 2005). Thus, CA1 neurons respond to corticosterone with a rapid *facilitation* of glutamate release, causing an increase, rather than a decrease, in excitatory synaptic input to these neurons (Figure 1). This rapid corticosteroid effect is mediated by the direct activation of a presynaptic membrane-associated MR, since the rapid steroid effect is eliminated by blocking MR pharmacologically and is lost in mice in which the MR, but not the GR, is knocked out conditionally in the forebrain (Karst et al. 2005; Olijslagers et al. 2008). This rapid excitatory corticosteroid action in hippocampal neurons may also contribute to the fast glucocorticoid feedback, or feedforward, inhibition of the HPA axis, since a glucocorticoid-induced synaptic activation of hippocampal efferents to the hypothalamus would be expected to relay to PVN neuroendocrine cells via a peri-PVN GABAergic inhibitory relay, which would invert the excitatory hippocampal output to an inhibitory PVN input (Boudaba et al. 1996; Herman et al. 2002; Herman and Mueller 2006). The glucocorticoid effects on hippocampal outputs to the PVN have been implicated in the negative feedback regulation of the HPA axis specifically during psychological stress activation (Furay et al. 2008).

A recent study revealed a quite different rapid effect of glucocorticoids on GABAergic synaptic transmission in hippocampal CA1 neurons (Hu et al. 2010). Dexamethasone elicited a rapid synthesis and retrograde release of nitric oxide (NO) from CA1 neurons, which led to the activation of presynaptic GABA neurons and an increase in GABAergic synaptic inputs to the CA1 neurons that was action potential dependent (Figure 1). Interestingly, this effect is similar to the rapid glucocorticoid effect on GABAergic inputs to magnocellular neuroendocrine cells of the hypothalamic PVN and supraoptic nucleus which also show a rapid glucocorticoid-induced, NO-dependent increase in GABAergic inputs, albeit one that is action potential independent and mediated by a direct presynaptic modulation of GABA release (Di et al. 2009).

The amygdala is another upstream limbic structure that exerts a significant regulatory influence over the HPA axis, although rather than a feedback inhibitory influence like the hippocampus, it is considered to provide an excitatory feedforward input to the PVN that is mediated by projections from the central and medial nuclei of the amygdala to intermediate structures in the stress neural circuit, including the bed nucleus of the stria terminalis, the nucleus of the solitary tract, and the peri-PVN hypothalamus (LeDoux 2007; Rodrigues et al. 2009; Roozendaal et al. 2009; Ulrich-Lai and Herman 2009). Activation of an inhibitory GABAergic output from the central nucleus and/or medial nucleus of the amygdala (Swanson and Petrovich 1998) appears to suppress a tonic inhibition exerted on the HPA axis by peri-PVN or bed nucleus GABAergic relay neurons, leading to a disinhibition, or an activation, of the HPA axis (Herman et al. 2005; Ulrich-Lai and Herman 2009). Based on its afferent and efferent organization, the basolateral nucleus of the amygdala (BLA) represents a gateway for sensory inputs transmitted to the amygdala from the thalamus, and it relays

through the central and medial nuclei to mediate amygdaloid outputs that regulate HPA and autonomic activation (Rodrigues et al. 2009). As in the hypothalamus and hippocampus, corticosteroids trigger a rapid modulatory effect on excitatory synaptic transmission in the principal neurons of the BLA, but not in neurons of the central nucleus (Karst et al. 2010). These effects appear to be more complex than those reported in the hippocampus or hypothalamus by virtue of their changing nature under different baseline conditions of circulating corticosteroids (Karst et al. 2010). Thus, BLA neurons recorded in slices of amygdala from unstressed rats show a facilitation of glutamate release that is similar to that seen in CA1 pyramidal neurons, in that it is mediated by the direct activation of a putative presynaptic membrane MR (Figure 1). However, unlike in the hippocampus, the rapid steroid effect is nonreversible, and whereas the onset of the response is nongenomic and MR dependent, the sustained (i.e. nonreversible) component of the response is dependent on GR-induced transcriptional effects of the steroid. Interestingly, the rapid response changes its valence from excitatory to inhibitory, from increasing synaptic excitation to decreasing synaptic excitation, in BLA neurons that have been “primed” *in vitro* with a previous application of corticosteroid or *in vivo* by previous exposure of the rat to an acute restraint stress. The rapid suppressive effect of corticosteroids on glutamate release in primed amygdala slices is mediated by a nongenomic, GR-dependent mechanism, as it was lost in mice in which the classical GR was knocked out, and it depends on cannabinoid receptor activation (Karst et al. 2010) (Figure 1). The cannabinoid dependence of this rapid corticosteroid action in the BLA is similar to that implicated in the GSE in the hypothalamus (see below). Thus, the rapid corticosteroid actions in the BLA appear to be mediated by a combination of the mechanisms found in the hypothalamus and hippocampus. Whether the rapid action of corticosteroids increases (as in the hippocampus) or decreases (as in the hypothalamus) synaptic excitation in BLA neurons depends on the prior corticosteroid history of the BLA neurons, such that the rapid effects of corticosteroids in the BLA are stress–state dependent.

Endocannabinoid dependence of rapid glucocorticoid-induced suppression of synaptic excitation

Studies in the hypothalamus showed that, rather than being caused by the corticosteroid activation of receptors on presynaptic excitatory synaptic terminals, as in the hippocampus (Karst et al. 2005), GSE is mediated by the activation of postsynaptic receptors and the dendritic synthesis and release of a retrograde messenger that suppresses excitatory synaptic inputs by feeding back onto glutamatergic synaptic terminals in a retrograde fashion (Di et al. 2003). The dendritic retrograde messenger produced in rapid response to glucocorticoids and responsible for GSE is an endogenous cannabinoid (Figure 1), which was revealed both by pharmacological blockade (Di et al. 2003, 2005) and recently by genetic knockdown of the cannabinoid type I (CB1) receptor (Glatzer et al. 2008), as well as by mass spectrometric measurement of glucocorticoid-induced endocannabinoid release (Malcher-Lopes et al. 2006). Endocannabinoids are arachidonic acid-based molecules that are synthesized from lipid precursors in the neuronal membrane (see Malcher-Lopes et al. 2008; Matias and Di Marzo 2009) and act primarily as retrograde messengers at CB1 receptors at synapses in the brain (Breivogel and Childers 1998; Alger 2002; Wilson and Nicoll 2002). Both of the two

main endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are produced in the PVN in response to rapid glucocorticoid actions (Malcher-Lopes et al. 2006). Surprisingly, repeated immobilization stress exposure leads to desensitization of PVN parvocellular neurons to cannabinoids and glucocorticoid-induced endocannabinoid actions in young animals, but not adults (Wamsteeker et al. 2010), a phenomenon that may contribute to the impairment of the glucocorticoid negative feedback regulation of the HPA axis seen in adolescence during chronic stress (Romeo et al. 2006). As mentioned above, the rapid corticosteroid modulation of synaptic excitation in BLA neurons also has been shown to be partially dependent on endocannabinoid actions (Karst et al. 2010).

Interestingly, glucocorticoids also have been shown to stimulate the rapid production and dendritic release of NO by PVN neurons, although this effect is synapse specific and limited to inhibitory synapses under normal conditions, and is only detected in magno-cellular neuroendocrine cells (i.e. oxytocin and vasopressin neurons) and not in the parvocellular neuroendocrine cells (Di et al. 2005, 2009). Like in hippocampal CA1 neurons (Hu et al. 2010), the glucocorticoid-induced dendritic production of NO has a facilitatory, rather than inhibitory, effect on GABA release at inhibitory synapses onto hypothalamic magnocellular neurons, providing an additional rapid inhibitory mechanism of fast glucocorticoid action in these cells.

G protein and protein kinase dependence of rapid glucocorticoid suppression of synaptic excitation in the hypothalamus

The insensitivity of GSE to blockade by the GR antagonist RU486 and its dependence on the activation of a membrane-associated receptor suggested that it is mediated either by a novel membrane receptor or by an isoform of the classical GR that is located at the membrane and insensitive to the classical GR antagonist RU486. Several studies have been conducted in various primary neuronal cultures and in cell lines that showed rapid corticosteroid actions that depended on G protein and protein kinase activation (Ffrench-Mullen 1995; Qiu et al. 2001, 2005). A first indication of the signaling pathway engaged by the putative membrane GR in hypothalamic neuroendocrine cells came from the observation that GSE was blocked by leptin, and that this was mediated by the leptin activation of the cAMP-degrading enzyme phosphodiesterase 3B (Malcher-Lopes et al. 2006). This indicated that the membrane GR actions might be mediated by a cAMP/cAMP-dependent protein kinase A (PKA) signaling mechanism. This was borne out by the finding that the GSE and glucocorticoid-induced increase in endocannabinoids were blocked completely by inhibiting the stimulatory G protein α subunit (G_{α_s}) and PKA activity, confirming the dependence of the phenomenon on Gs/cAMP/PKA signaling. However, much like rapid corticosteroid actions in other cellular models (Chen and Qiu 1999), recent evidence indicates that the putative membrane GR signaling mechanism that stimulates endocannabinoid synthesis in PVN and supraoptic neurons is, instead, dependent on multiple kinases in addition to PKA, including protein kinase C and extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) (Di et al. 2003; Harris and Tasker 2009). Thus, the membrane-associated GR appears to signal via a complex network of different protein kinase signaling pathways. In support of the complexity of the rapid glucocorticoid signaling mechanism, we

have recently shown that the membrane-associated GR activates separate subunits of the G protein trimer, the α and $\beta\gamma$ subunits, to stimulate divergent pathways leading to the synthesis of endocannabinoids and NO, respectively, in magnocellular neuroendocrine cells (Di et al. 2009). Despite the G protein–protein kinase dependence of the rapid glucocorticoid actions in hypothalamic neuroendocrine cells, which indicates that the membrane-associated GR is a G protein-coupled receptor, we have acquired preliminary evidence in GR knockout mice that indicates that the rapid glucocorticoid actions may instead be mediated by, or at least dependent on, the intracellular GR localized to the membrane (Haam et al. 2010).

Thus, *in vitro* studies in the hypothalamus showed a rapid suppression of excitatory synaptic input to neuroendocrine cells of the PVN, including CRH neurons, by the G protein- and protein kinase-dependent induction of endocannabinoid synthesis and retrograde release, hence providing a potential mechanism for the rapid feedback inhibition of the HPA axis directly at the level of the PVN (Figure 1). We have recently tested this putative mechanism for the rapid feedback regulation of the HPA axis *in vivo* using peripheral and intra-PVN administration of glucocorticoids and cannabinoid analogs.

Endocannabinoid dependence of negative glucocorticoid feedback in the PVN

Endocannabinoids have been implicated in the regulation of the HPA axis by converging evidence in a number of recent studies (Cota 2008; Hill et al. 2010c). Thus, mice treated with CB1 receptor antagonists and CB1 knockout mice display an elevated level of CRH expression in the PVN and increased basal adrenocorticotrophic hormone (ACTH) and corticosterone concentrations in the blood (Patel et al. 2004; Cota et al. 2007; Cota 2008), and CB1 knockout mice show an enhanced HPA response to forced swim and tail suspension stress (Aso et al. 2008; Steiner et al. 2008a,b), indicating a tonic endocannabinoid inhibition of the HPA axis. The CB1 receptor knockout mouse also shows a diminished suppression of the HPA response by a low concentration of corticosteroid, although this is overcome with the administration of a higher corticosteroid concentration (Cota et al. 2007). Cultured pituitary cells from CB1 knockout mice show an elevation in the ACTH response to CRH, indicating endocannabinoids may also negatively regulate the sensitivity of the pituitary adrenocorticotrophs to CRH (Cota et al. 2007).

Acute stress and systemic corticosteroids have been shown to cause a rapid increase in endocannabinoid levels in several different stress-related brain areas, including the hippocampus, the amygdala, and the hypothalamus, although different patterns of stress-induced endocannabinoid release have been found in each of these structures (Patel et al. 2009; Hill et al. 2010a). Although both AEA and 2-AG production are induced in the hypothalamus by peripheral corticosteroids (Hill et al. 2010b) and by direct glucocorticoid actions in the PVN (Malcher-Lopes et al. 2006), acute restraint stress was shown to elicit a rapid rise specifically in the 2-AG level in the PVN (Evanson et al. 2010). The corticosteroid-induced endocannabinoid response occurs rapidly, within 10 min, suggesting that it is mediated by nongenomic corticosteroid actions. Although *in vitro* glucocorticoid administration elicited an increase in both the AEA and 2-AG content in the hypothalamic PVN (Malcher-Lopes et al. 2006), electrophysiological data indicate that it may be the 2-AG

that is responsible for the synaptic modulatory effects of glucocorticoids in PVN neuroendocrine cells, since recent experiments showed that this is prevented by blocking the activity of the 2-AG synthetic enzyme diacylglycerol lipase (Harris and Tasker, unpublished observation). The primary role of 2-AG in GSE in the hypothalamus is consistent with studies in the hippocampus and cerebellum demonstrating the 2-AG dependence on depolarization-induced suppression of synaptic excitation and inhibition (Kano et al. 2009).

Systemic glucocorticoid application causes a rapid suppression of HPA axis activation (Dallman and Yates 1969; Keller-Wood and Dallman 1984). To test whether rapid glucocorticoid feedback inhibition of the HPA axis occurs within the PVN, glucocorticoids were injected locally bilaterally into the PVN, which resulted in suppression of acute stress-induced HPA activation (Evanson et al. 2010). An identical suppression of HPA axis activation was also seen with local PVN injection of dexamethasone conjugated to bovine serum albumin, which should prevent the steroid from crossing cell membranes and restrict its actions to the extracellular compartment. This revealed a direct inhibitory effect of glucocorticoids on stress-induced HPA activation at the level of the PVN that is mediated by the activation of a putative membrane-associated GR. The glucocorticoid suppression of stress-induced HPA activation was blocked by co-application of the steroid with the CB1 receptor inverse agonist AM251 (Evanson et al. 2010). These findings indicate, therefore, that the rapid glucocorticoid suppression of HPA activity at the level of the PVN is dependent on cannabinoid receptor activation, and provide an *in vivo* physiological demonstration of glucocorticoid-induced endocannabinoid production as a main mechanism involved in the rapid feedback inhibition of the HPA axis by corticosteroids, as postulated from our previous *in vitro* electrophysiological findings. Surprisingly, although systemic application of a CB1 receptor antagonist just prior to systemic glucocorticoid administration blocked the glucocorticoid suppression of stress-induced HPA activation (Evanson et al. 2010), systemic CB1 antagonist an hour prior to glucocorticoid administration and restraint stress failed to block the glucocorticoid suppression of the HPA response (Ginsberg et al. 2010). This may be due to the finding that glucocorticoids induce an increase in endocannabinoids at multiple levels in the stress circuitry, including in limbic structures (Hill et al. 2010a), some of which may give rise to opposing effects on HPA activation via trans-synaptic mechanisms.

The hypothalamus represents a major target of glucocorticoid negative feedback regulation of the HPA axis (Jones et al. 1977), but upstream and downstream sites also contribute to the rapid glucocorticoid suppression of HPA activation. As discussed above, the rapid glucocorticoid actions in the hippocampus (Karst et al. 2005; Oligslagers et al. 2008) and the hippocampal trans-synaptic inhibitory output to the PVN (Herman et al. 2002) indicate that the hippocampus may occupy a key position in the rapid glucocorticoid feedback inhibition of the HPA (Jacobson and Sapolsky 1991). The amygdala is another upstream limbic structure that has been shown to mount a rapid response to corticosteroids and this response may, in part, be mediated by corticosteroid-induced endocannabinoid actions (Campolongo et al. 2009; Karst et al. 2010). The amygdala exerts an excitatory influence on the HPA axis (Hill et al. 2009), which is considered to be mediated by GABAergic efferents from the central nucleus (LeDoux 2007) that send an indirect projection to the PVN via an inhibitory

relay in order to achieve an excitation (i.e. disinhibition) of the PVN CRH neurons (Dong et al. 2001; Ulrich-Lai and Herman 2009). Therefore, the rapid effect(s) of corticosteroid in the BLA is/are likely to be inhibitory, since the BLA is comprised primarily of glutamatergic principal neurons that send an intra-amygdalar excitatory projection to the central nucleus (LeDoux 2007), mediated either by an increase in the inhibition or a decrease in the excitation of the BLA neurons. As discussed above, recent evidence indicates that the rapid corticosteroid effect on BLA neurons is dependent on the previous corticosteroid history of the neurons, such that corticosteroids elicit an increase in synaptic excitation in naïve BLA neurons and a decrease in synaptic excitation in BLA neurons exposed previously to stress levels of corticosteroids (Karst et al. 2010). It has been reported recently that glucocorticoids facilitate the long-term consolidation of fear memories (McGaugh and Roozendaal 2002) via a mechanism that is dependent on the endocannabinoid activation of CB1 receptors in the BLA (Campolongo et al. 2009). Endocannabinoids in the amygdala have also been shown to contribute to fear memory consolidation and to be critically implicated in the extinction of fear memories through actions in the BLA (Bucherelli et al. 2006; Ganon-Elazar and Akirav 2009). The rapid response to corticosteroids in “primed” BLA neurons (i.e. neurons previously exposed to corticosteroid) involves an endocannabinoid-dependent suppression of afferent excitatory synaptic input (Karst et al. 2010), which would be expected to diminish BLA activity and output and may underlie some of the observed effects of corticosteroids on fear memory processing. Although 2-AG levels did not change, AEA levels in the amygdala were found in a recent study to increase in response to an acute psychological stress exposure (Hill et al. 2010b), although they decreased in another study (Patel et al. 2005). Interestingly, repeated homotypic stress exposure diminished the AEA response and led to an emergent increase in 2-AG levels in the amygdala (Patel et al. 2005, 2009; Hill et al. 2010b). The decreasing AEA and increasing 2-AG levels with repeated stress exposure were implicated, respectively, in the increase in baseline HPA activity and in the desensitization to homotypic stress application that are seen following chronic homotypic stress (Hill et al. 2010b). The cellular “memory” by BLA neurons of previous corticosteroid exposure and adaptation in the rapid corticosteroid response involving endocannabinoid suppression of synaptic excitation (Karst et al. 2010) may represent an endocannabinoid-dependent cellular mechanism of stress habituation.

In addition to these upstream sites of rapid corticosteroid actions, there is also rapid HPA regulation by glucocorticoids targeting sites downstream from the hypothalamus, namely the anterior pituitary gland (Mahmoud et al. 1984; Cole et al. 2000). The HPA activation caused by a CRH challenge has been shown to be rapidly abolished by a previous administration of glucocorticoids via GR activation (Cole et al. 2000; Russell et al. 2010). The calcium-binding protein annexin A1 has been implicated in the rapid glucocorticoid inhibition of ACTH release from the pituitary through its actions on formyl peptide receptors (John et al. 2008). Interestingly, annexin A1 is expressed in nonendocrine cells of the pituitary, the folliculo-stellate cells, and is thought to be released from these cells and to act on the pituitary corticotrophs via paracrine actions within the pituitary gland. Annexin A1 and formyl peptide receptors are also expressed in the hypothalamus and may also be involved in glucocorticoid feedback at the hypothalamic level (John et al. 2008).

Thus, there is the potential for rapid glucocorticoid negative feedback regulation of the HPA axis at multiple levels of the stress neural circuit, including in the hippocampus, amygdala, hypothalamus, and anterior pituitary gland. While it is likely that the rapid glucocorticoid actions are mediated by membrane-associated corticosteroid receptors in each of the potential targets of fast feedback, the receptors responsible for, and the cellular mechanisms of the rapid corticosteroid inhibitory actions appear to differ in the various target structures. Although rapid corticosteroid actions in the hypothalamus appear to be mediated largely by glucocorticoid-induced endocannabinoid regulation of excitatory synaptic inputs to PVN neuroendocrine cells, the rapid corticosteroid modulation of synaptic excitation is independent of endocannabinoid production in the hippocampus (Olijslagers et al. 2008), is mediated by a combination of endocannabinoid-dependent and endocannabinoid-independent mechanisms in the BLA (Karst et al. 2010), and is clearly not mediated by synaptic modulatory mechanisms in the anterior pituitary (Buckingham et al. 2003). The challenge going forward will be to assign these rapid corticosteroid effects to feedback vs. feedforward physiological functions and to integrate the diverse rapid signals into a coordinated feedback regulation of the HPA axis. Moreover, it is clearly imperative for the future design and clinical use of corticosteroid analogs that target the nongenomic vs. genomic actions of glucocorticoids to identify the membrane receptor or receptors responsible for the rapid glucocorticoid effects in the brain and the pituitary.

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Figure 1.

Cellular mechanisms of rapid corticosteroid feedback modulation of principal neurons in the hypothalamus, hippocampus, and amygdala involved in the stress regulatory circuit. The main neuroendocrine branch of the stress response is characterized by CRH release from PVN neuroendocrine cells in the hypothalamus, which stimulates ACTH release from the anterior lobe of the pituitary, which leads to corticosteroid secretion from the adrenal glands into the systemic circulation. The circulating corticosteroid feeds back onto several target structures in the brain, including the hypothalamic PVN, hippocampus, and amygdala, as well as onto the pituitary. The CRH neurons (and oxytocin [OT] and vasopressin [VP] neurons) in the PVN respond rapidly to glucocorticoids with retrograde endocannabinoid (eCB) release and CB1-mediated suppression of glutamate release (Glu) from presynaptic excitatory synapses (Di et al. 2003). Magnocellular OT and VP neurons also release nitric oxide (NO) in rapid response to glucocorticoids, which facilitates GABA release at inhibitory synapses (Di et al. 2009). The CORTs in the hippocampus elicit a presynaptic facilitation of glutamate release from excitatory synapses onto CA1 pyramidal neurons (Karst et al. 2005) and a retrograde NO release that triggers a spike-dependent increase in GABA release from inhibitory synapses onto CA1 neurons (Hu et al. 2010). In the BLA, corticosteroids elicit a rapid increase in glutamate release onto BLA neurons that lack a recent exposure to corticosteroid (unprimed) or a rapid suppression of glutamate release mediated by retrograde endocannabinoids in BLA neurons that have experienced a recent exposure to corticosteroid (primed) (Karst et al. 2010).