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Review

Corticosteroid hormones in the central stress response: Quick-and-slow

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Abstract

Recent evidence shows that corticosteroid hormones exert rapid non-genomic effects on neurons in the hypothalamus and the hippocampal CA1 region. The latter depend on classical mineralocorticoid receptors which are accessible from the outside of the plasma membrane and display a 10-fold lower affinity for corticosterone than the nuclear version involved in neuroprotection. Consequently, this 'membrane' receptor could play an important role while corticosteroid levels are high, i.e. during the initial phase of the stress response. We propose that during this phase corticosterone promotes hippocampal excitability and amplifies the effect of other stress hormones. These permissive non-genomic effects may contribute to fast behavioral effects and encoding of stress-related information. The fast effects are complemented by slower glucocorticoid receptor-mediated effects which facilitate suppression of temporary raised excitability, recovery from the stressful experience and storage of information for future use.

Keywords: Stress; Brain; Behavior; Electrophysiology; Feedback; Glucocorticoid receptors; Mineralocorticoid receptors; Non-genomic steroid action; Genomic steroid action; CRH

1. Introduction

Glucocorticoids are secreted from the adrenal in hourly pulses which are thought to synchronize and coordinate sleep related and daily events [42]. At any time a glucocorticoid response can be triggered by a stressor. In concert with other stress mediators, the stress-induced rise in glucocorticoid concentration facilitates adaptation to stress and restores homeostasis, (among other things) by enhancing emotional arousal and promoting motivational and cognitive processes [6,17,26]. A glucocorticoid response that is excessive, prolonged or inadequate impairs adaptation to stress and is considered a risk factor for stress-related diseases. The hormones have profound effects on brain development and are a significant factor in the aging process.

The key towards understanding these fundamental processes underlying homeostasis and health is in the receptors that mediate the action of the corticosteroids. These are the classical glucocorticoid receptors (GR), selective for naturally occurring and synthetic glucocorticoids; and the mineralocorticoid receptors (MR), which retain corticosterone and aldosterone with a very high affinity, i.e. about 10-fold higher than to the GR [6]. The MR also binds progesterone and deoxycorticosterone with relatively high affinity [3] and hence this receptor is considered promiscuous in non-epithelial cells. In epithelial cells the MR is aldosterone-selective because the naturally occurring glucocorticoids are metabolized by the 11β-steroid-dehydrogenase type 1 [13]. The MR and GR are nuclear receptors that mediate genomic actions of the naturally occurring glucocorticoids corticosterone in rodents and cortisol in man [32,43].

Our contribution to this special issue of Frontiers will focus on the MR and GR. These receptors are abundantly expressed in the limbic brain where they mediate distinct and complementary actions. While most emphasis in the past decades was on their genomic action there obviously was a problem. Thus, over the years findings were reported that showed fast effects of corticosteroids on feedback operation in the HPA axis [4]. Fast effects within minutes were also described for violent behavior propagated by a

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fast feedforward mechanism [21] which were not genomic, but obeyed the pharmacology dictated by the classical nuclear receptors. Moreover, corticosteroid effects were observed on cognitive operations in appraisal of novel situations [29,30], extinction processes [2] and more recently on retrieval processes [7,35]. Recent discoveries using an electrophysiological approach have supplied a mechanistic basis to these fast behavioral and neuroendocrine effects. We first will review these fast cellular effects, and next examine the fast effects in the chain of events that take place from the first encounter with a real or imagined stressor to its long-term outcome on cognitive performance.

2. Fast effects of corticosteroid hormones on neuronal function

Parvocellular neurons in the PVN are critically involved in the production and release of CRH. These processes are under fast and delayed negative control of corticosterone [4]. Insight in the putative neurobiological substrate of the fast negative feedback was recently provided by Tasker and co-workers [38]. They showed that glucocorticoids rapidly and non-genomically suppress the frequency (but not amplitude) of miniature excitatory postsynaptic currents (mEPSCs), which reflect the postsynaptic response to the spontaneous release of a single glutamate-containing vesicle [8]; inhibitory events were changed in magnocellular but parvocellular neurons [9,40]. It was argued that corticosterone attenuates the release probability of glutamate-containing vesicles, a presynaptic phenomenon. Interestingly, this effect was found to depend on a postsynaptic G-protein linked pathway, a process blocked by leptin [24]. This supports the involvement of retrograde messengers. In accordance, corticosteroids stimulate endocannabinoid synthesis and release from the postsynaptic compartment which subsequently via a presynaptic CB1 receptor leads to suppression of glutamate release [8,24].

The nature of the receptors mediating these fast effects of corticosteroid hormones on PVN parvocellular neurons is still unclear. Corticosterone was only active when administered on the outside of the plasma membrane. This does not congrue with a nuclear MR or GR localization. Moreover, antagonists for the classical nuclear MR and GR did not interfere with the suppression of mEPSC frequency. Possibly a so far unknown G-protein coupled receptor is responsible for these actions.

Rapid effects of corticosteroid hormones have also been seen in the hippocampus, but the characteristics differ from those seen in the hypothalamus. Thus, it was observed that rapidly after corticosterone application the frequency of mEPSCs in hippocampal CA1 neurons is *enhanced* [18]. No effect was observed on mEPSC amplitude or kinetic properties. As paired pulse facilitation was decreased, it was concluded that corticosterone rapidly increases the release probability of glutamate-containing vesicles. Enhanced release of glutamate from the hippocampus *in vivo*, shortly after administration of corticosterone, was indeed reported [39]. Preliminary evidence indicates that the rapid effect on mEPSC frequency involves a presynaptic ERK1/2 pathway, independent of retrograde messengers [31].

The corticosterone-induced enhancement of mEPSC frequency was quickly reversed upon removal of the steroid hormone [18], which points to a non-genomic mechanism. This was confirmed in follow-up experiments where the increase in mEPSC frequency with corticosterone was also demonstrated in the presence of a protein synthesis inhibitor. Moreover, nuclear localization of the hormone-receptor complex appeared not necessary, since a corticosterone-BSA conjugate evoked effects comparable to the natural hormone itself. The effects of corticosterone were seen with ~10 nM of the hormone, which is a concentration that can be reached in the hippocampus under stressful conditions.

Because the hormone concentration necessary to see changes in mEPSC frequency is closer to the Kd of the GR than of the MR it was assumed that the rapid effects involve the GR. However, application of a selective GR-agonist was ineffective. The effect of corticosterone could not be blocked by a GR-antagonist and was still present in forebrain specific GR knockouts [18]. By contrast, the mineralocorticoid aldosterone strongly increased mEPSC frequency, an effect that was fully suppressed by the MR-antagonist spironolactone. No change in mEPSC frequency was induced by corticosterone in forebrain specific MR knockouts. Collectively, these data indicate that in the hippocampus corticosterone can increase the release probability of glutamate-containing vesicles in a manner requiring the 'classical' MR, which for some reason is inserted into the membrane and has a 10-fold lower apparent affinity than the nuclear MR [18].

More recently, other rapid effects were also reported for CA1 hippocampal neurons. For instance, it has been found that corticosterone suppresses the K^+-conductance I_A, via a postsynaptic membrane MR coupled to a G-protein dependent pathway [31]. Effectively, this could mean that increased presynaptic release of glutamate is accompanied by an enhanced likelihood that action potentials are generated postsynaptically. This could contribute to the fact that long-term potentiation in the CA1 area is facilitated when corticosterone is present during high-frequency stimulation of the Schaffer collaterals, although it should be noted that this phenomenon is not sensitive to GR- as well as MR-blockers [41]. Interestingly, corticosterone was also found to rapidly facilitate the excitatory effect of β-adrenergic agonists on LTP in the dentate gyrus [34]. By contrast, if corticosterone was applied several hours before the β-agonist, so that genomic effects were allowed to develop, the steroid suppressed excitatory effects via the β-agonist on LTP [34].

3. Corticosteroid hormones in the stress response

How can these rapid cellular effects of corticosterone contribute to the central stress response?

With respect to the HPA regulation, it has been known already for a long time that rising levels of corticosterone can exert a fast negative control over the release of CRH and ACTH [4]. This effect may be short-lived, because as soon as corticosteroid levels plateau the negative influence is lost, only to re-appear some time later when gene-mediated effects kick in. This transient character of fast corticosteroid effects does not seem to hold for limbic actions. Thus, *in vitro* studies show that the enhancement of mEPSC frequency lasts as long as corticosterone concentrations are high (Karst, unpublished observation). This could signify that during the initial stage of the central stress response—i.e. when levels of corticosterone, peptides like CRH and vasopressin, and of catecholamines are high-stress-induced levels of corticosterone promote hippocampal excitability and amplify the effect of other stress hormones (Fig. 1). These permissive effects of corticosterone, which at least partly involve membrane MRs, may contribute to fast encoding of stress-related information, to appraisal processes and the selection of behavioral responses to cope with the stressor [27,29,30].

By the time that hormone levels subside, gene-mediated effects by corticosterone have developed. These slow effects are mostly mediated via nuclear GRs (reviewed in [15,17]). In the hippocampal CA1 area, activation of nuclear GRs raises the threshold for induction of LTP, so that any information reaching this area several hours after the encoding of stress-related information has started must be very salient in order to surpass the threshold for LTP induction. This may help to preserve the earlier information. Gene-mediated GR actions further slowly attenuate the transfer of excitatory information, suppress excitatory β-adrenergic actions and enhance inhibitory effects of serotonin (reviewed in [15,17]). This fits with the notion that at least 1 h after stress exposure the temporary raised excitability is reversed and normalized to pre-stress levels [16], thus preventing the hippocampal response from overshooting or persisting when no longer necessary. This can be regarded as the limbic correlate of the slow negative feedback in the hypothalamus. Gene patterns contributing to these delayed genomic effects of corticosteroids have been identified [5,28].

At last: what about the nuclear form of the MR? It has been demonstrated that nuclear MR-mediated actions are crucial for the stability of neuronal networks, survival of neurons in the hippocampus under adverse conditions as well as the threshold/sensitivity of the stress system and behavioral responses [20,23,37]. Recent studies using mouse lines where the MR was knocked out [1,12] or overexpressed [11,22,36] generally support this point of view.

4. Perspectives

While electrophysiological studies over the past years have firmly established the existence of rapid non-genomic corticosteroid effects in brain, numerous questions are still

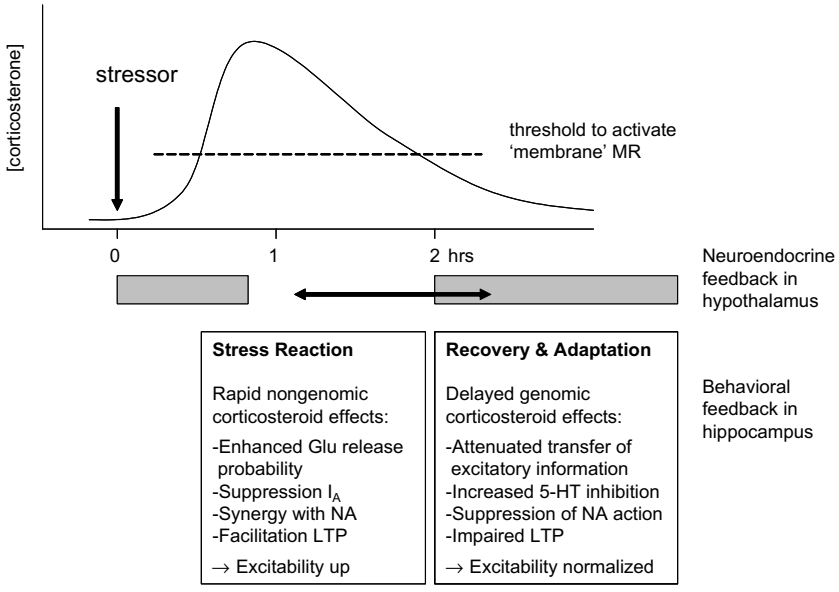

Fig. 1. Shortly after exposure to a stressor (vertical arrow), corticosteroid levels rise. Rapid as well as delayed negative feedback has been described (grey bars), the latter causing normalization of corticosteroid levels some hours after stress exposure. The onset of the delayed negative feedback varies (indicated here by horizontal arrow), depending e.g. on modulatory input to the PVN. Recently, rapid non-genomic cellular effects were described in the hypothalamus, which may provide a neurobiological substrate for the fast feedback. In the hippocampus, corticosterone can also exert a number of rapid non-genomic actions which require relatively high levels of the hormone. Hence, these will take place only when a certain threshold concentration of the hormone is surpassed (striped line). We propose that overall these rapid effects in CA1 neurons promote excitability and amplify the effects of other stress hormones. These rapid effects contribute to the overall 'central' stress reaction, comprising facets of appraisal, attention and alertness. At the same time, however, gene-mediated pathways are started [28] which some hours later (i.e. by the time that hormone levels are declining) result in attenuated neurotransmission, thus normalizing the earlier raised activity. This phase is important for recovery and adaptation.

unanswered. First and foremost it will be important to link the presently described cellular effects to the sets of behavioral and neuroendocrine observations: the cellular non-genomic effects are likely to underlie fast changes in memory formation and HPA activity, but causative evidence has not yet been provided. In addition to the rapid hormonal influences on encoding of information, there is also ample evidence for non-genomic modulation by stress hormones of retrieval of information stored in limbic regions [35]. As yet, a neurobiological substrate for this phenomenon is not available at the cellular level.

Clearly, a host of mechanistic questions are still open. The fast non-genomic effects in part require 'classical' nuclear corticosteroid receptors [18]. Are these membrane receptors identical to or variants of the ones mediating genomic effects? If they are identical, then why do they not translocate to the nucleus but instead travel towards the plasma membrane? And is the proportion of receptors in (or close to) the membrane dependent on external factors, like the availability of corticosteroid hormones over a longer period of time? In part, however, the receptors mediating fast corticosteroid receptors do not display the pharmacological profile of nuclear receptors [8,41]. Therefore, the existence of a so far unknown G-protein coupled receptor to which corticosterone binds with relatively high affinity cannot be excluded, as was described for estrogens [33].

The comparison between hypothalamus and hippocampus shows that rapid non-genomic effects of corticosteroids are regionally differentiated. It will therefore be very important to also examine rapid effects in other limbic areas important for the central stress response, like amygdalar nuclei or subareas of the prefrontal cortex [10,19,25]. Extracellular recording studies in fact support rapid effects of stress on firing patterns in the prefrontal cortex [14]. Extension of the current studies to these areas will be necessary to get a full comprehension of the role of rapid non-genomic corticosteroid effects during the initial and late phases of the central stress response.

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