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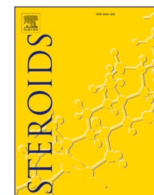

Corticosterone rapidly reduces glutamatergic but not GABAergic transmission in the infralimbic prefrontal cortex of male mice

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ABSTRACT

Rapid non-genomic effects of corticosteroid hormones, affecting glutamatergic and GABAergic transmission, have been described for many limbic structures in the rodent brain. These rapid effects appear to be region specific. It is not always clear which (or even whether) corticosteroid receptor -the glucocorticoid receptor (GR) or mineralocorticoid receptor (MR)- initiate these rapid effects. In the hippocampus and amygdala membrane-associated MR, but also membrane-associated GR (in amygdala), are involved. Other studies indicate that the rapid modulation may be induced by transactivation of kinases, or other receptors, like the G-protein coupled estrogen receptor (GPER) which was recently found to bind the mineralocorticoid aldosterone. In the current study we explored, in young adult male C57Bl6 mice, possible rapid effects of corticosterone on layer 2/3 infralimbic-prefrontal cortex (IL-PFC) neurons. We show that corticosterone, via non-genomic MR activation, reduces the mEPSC -but does not affect mIPSC- frequency; we observed no effect on mEPSC or mIPSC amplitude. As a result, overall spontaneous activity in the IL-PFC is suppressed. A potential role of GPER cannot be excluded, since G-15, an antagonist of GPER, also prevented the rapid effects of corticosterone.

1. Introduction

The prefrontal cortex (PFC) is part of the limbic system and an important relay station between the higher cognitive cortical and other limbic structures in the brain. The PFC is responsible for e.g. the regulation of emotional behavior, social behavior, decision-making, and working memory [1–4]. Stress is a major regulator of PFC function [5–7] and, as in other limbic structures, PFC neurons express corticosteroid receptors [8]. Besides the glucocorticoid receptor (GR), which is expressed throughout the whole brain, the PFC, like most other limbic structures, also contains the mineralocorticoid receptor (MR) [9,10]. These two corticosteroid stress-hormone receptors are genome binding molecules and supposed to play an important role in the long term regulation of PFC neuronal activity. Accordingly, stress has been shown to affect mPFC (medial prefrontal cortex) related behavior and physiology via activation of these corticosteroid receptors. It has, for instance, been shown that decision making in mice as well as in man is affected via the GR [11]. Yuen et al. [12,13] extensively studied the excitability of PFC primary neurons after stress or treatment with corticosterone. They showed that the glutamatergic transmission was enhanced after acute stress and that stress had a facilitating effect on working memory [12]. Repeated stress, however, caused a reduction of the glutamate receptor expression and function in the PFC [13].

In addition to these slow genomic corticosteroid actions, rapid modulation of the PFC by corticosteroids has also been postulated. The PFC is thought to switch to a minimum of activity directly after the onset of a stressful event, leading to impaired LTP (long term potentiation), impaired divided attention and impaired multitasking [14–17]. Diamond et al. [14] speculated that under these circumstances the brain only executes simple tasks.

These rapid effects can only take place if corticosterone acts via a non-genomic pathway. In previous studies, we and others [18–26] showed that corticosterone can rapidly, within minutes, affect limbic brain structure function. Rapid effects were reported in the hypothalamus, the hippocampus and the amygdala. The result of rapid corticosterone actions is not uniform but seems to be area specific. The group of Jeffrey Tasker was one of the first groups showing that corticosterone induces a rapid effect in the brain [18]. In the paraventricular nucleus (PVN) they showed that corticosterone affects the GABAergic and glutamatergic transmission [19,20]. Corticosterone and Dexamethasone, a

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GR agonist, rapidly suppressed the excitatory postsynaptic currents in CRH (corticotropin-releasing hormone) protein expressing parvocellular cells and in magnocellular neurons [19], as well as the neurons of the supraoptic nucleus (SON) [20]. This suppression could be blocked with cannabinoid CB1 receptor antagonists [18–22]. The inhibitory GABAergic input to the PVN was also affected by glucocorticoids. In magnocellular neurons, Dexamethasone elicited a rapid increase of the miniature inhibitory postsynaptic current (mIPSC) frequency. Here, the retrograde messenger nitric oxide was responsible for the increase in spontaneous GABA activity [20]. Remarkably, neither blockade of GR nor of MR antagonized corticosterone or dexamethasone effects on glutamatergic or GABAergic transmission. Di et al. 2016 [23] further described a rapid effect of corticosterone in the amygdala, where glucocorticoid stimulation rapidly reduced the spontaneous GABA transmission via a non-genomic pathway. Activation of membrane receptors stimulated the release of retrograde endocannabinoids via G-protein activation. Similar to the PVN, neither an antagonist of GR nor MR blocked rapid corticosteroid actions.

In our laboratory, we focused on rapid effects of corticosterone in the hippocampus and basolateral amygdala (BLA). In both structures, corticosterone induces a non-genomic increase in the frequency of excitatory currents (mEPSCs). We provided evidence that presynaptic membrane-associated MRs are responsible for the activation of a MEK/ERK pathway, enhancing synapsin-induced vesicle release in the hippocampus [24] and presumably also in the BLA. In addition, in the BLA, indirect evidence for the existence of postsynaptic membrane-associated GRs was found [25]: Effects of GR-activation were observed in i) stressed mice and ii) after a second surge of corticosterone during an ex vivo BLA recording. Under these circumstances membrane-associated MRs are most likely internalized [26] and not available anymore for activation. A second hit of corticosterone then activates GRs, in turn activating endocannabinoid receptors, inducing a retrograde reduction of glutamate release. These opposite effects of corticosterone, prior to an after stress respectively, are responsible for metaplasticity in the BLA [25] and may be an important mechanism for fear learning and fear extinction.

Although there is thus overwhelming evidence for rapid non-genomic corticosterone activation in the brain, until now the responsible receptors have not been visualized yet [27]. In a recent study we summarized the arguments for the (lack of) existence of a membrane MR [26]. Interestingly, recent findings indicate that, possibly, other receptors with a binding site for mineralocorticoids -and not recognized by MR antibodies- might be candidates for the mechanism underlying rapid corticosteroid effects. Especially the G-protein estrogen receptor (GPER, or GPR30) [28–30] and Acquaporin-2 [31] seem to be potential candidates. These receptors have corticosteroid binding sites, and are located on the outside of the membrane, which could explain the rapid effects induced by corticosterone conjugated to albumin (Cort-BSA) [18,32], a conjugate that cannot pass the membrane. Other candidates, like receptor tyrosine kinases, require intracellular binding and are therefore, given the effectiveness of Cort-BSA, less likely candidates.

In the PFC, rapid effects of corticosterone on glutamatergic and GABAergic transmission are less well documented. To understand the effect of stress on the mPFC, we here studied i) potential rapid effects of corticosterone on the infralimbic PFC (IL PFC) layer 2/3 neurons, ii) the role of the MR in such effects, and iii) possible interactions of mineralocorticoids with GPER.

2. Material and methods

2.1. Animals

The experiments were approved by the Dutch Central Committee Animal experiments (centrale commissie dierproeven, CCD), project # AVD11500202010585. Young adult (n = 47, 10–12 week old) male mice (C57BL/6JOlaHsd, Envigo RMS, The Netherlands) were housed at normal day-night cycle (lights on: 08:00–20:00 h), with temperature of 22 ± 2 °C and humidity of approximately 65%. Food (standard chow) and water were provided ad libitum. The described methodology adheres to the ARRIVE guidelines [33] and Gold Standard Publication Checklist [34] to improve the quality of reporting on animal studies.

2.2. Electrophysiology

2.2.1. Slice preparation

For electrophysiological experiments, animals were taken from the home cage between 8:30 and 9:00 AM (around the circadian trough of corticosterone release) and quickly decapitated, to avoid a stress-induced rise in endogenous corticosteroid levels. The brain was quickly removed from the skull and stored in ice cold slicing medium containing: 120 mM choline chloride, 3.5 mM KCl, 0.5 mM $CaCl_2$, 6 mM $MgSO_4$, 1.25 mMNaH_2PO_4, 25 mM D-glucose and 25 mM $NaHCO_3$. Coronal slices of 350 µm thickness were made with a vibratome (Leica VT 1000S) and placed in artificial cerebrospinal fluid (ACSF) containing: 120 mM NaCl, 3.5 mM KCl, 1.3 mM $MgSO_4$, 1.25 mM NaH_2PO_4, 2.5 mM $CaCl_2$, 25 mM D-glucose and 25 mM $NaHCO_3$ and heat shocked at 32 °C for 20 min. Slices were then transferred to a storage bath at room temperature and after recovery for at least 1 h, one slice at a time was used for the recordings. The slice was transferred to the recording bath, and continuous perfused with ACSF at 32 °C. Cells were visualized with an upright microscope (Zeiss Aksioskop) with infrared DIC, a 40x water immersion objective, a 10 × video lens and a microscopy camera (Qimaging, Rolera bolt). All electrophysiological recordings were made from pyramidal-shaped neurons of the infralimbic (IL) mPFC layer 2 or 3.

All chemicals were obtained from Sigma-Aldrich (USA).

2.2.2. mEPSC and mIPSC recordings

The pipette solution to record mEPSCs and mIPSCs was composed as follows: 120 mM Cs methanesulfonate, 17.5 mM CsCl, 10 mM Hepes, 5 mM BAPTA, 2 mM MgATP, 0.1 mM GTP (295 mOSM; pH 7.3 adjusted with CsOH). Miniature postsynaptic currents mediated by glutamate and GABA were recorded in neurons in the presence of 0.5 µM TTX (Latoxan, France). The mEPSCs (AMPA receptor-mediated currents) were recorded at a holding potential (Vh) of −65 mV, i.e. the reversal potential for chloride. Subsequently, in the same neuron, the GABAergic mIPSCs was recorded at Vh of + 10 mV, which is the reversal potential for glutamate. All data was stored and afterwards analyzed with Clampfit 10.7. The events were detected with a template search and then analyzed for frequency and amplitude.

After a whole cell patch formation was established, recordings of the mEPSCs and /or mIPSCs were started when the recording remained stable for at least 5 min. First, mIPSCs were recorded for 5 min, followed by a 5 min recording of mEPSCs. These recordings represented the baseline. Then, corticosterone, aldosterone, RU28362 (Roussel-Uclaf, former French pharmaceutical company), G-15 (Tocris Bioscience, UK) or vehicle (0.09% ethanol) was superfused to the recording bath for 20 min. During that time, in three time-blocks of 5 min, mEPSCs were recorded, followed by a mIPSC recording of 5 min. When the effect of the MR antagonist spironolactone was tested in the presence of corticosterone, the slices were pre-incubated with spironolactone for at least 20 min. Also in the recordings with the GPER antagonist G15, G15 was already present in the perfusion medium for at least 20 min. Of note, the control experiments in which the effect of G15 alone was tested were carried out at SILS, Amsterdam. All remaining experiments were performed at the UMC Utrecht. We cannot entirely rule out (to us unknown) influences of the environment and/or season on baseline mEPSC and mIPSC frequencies. Since the effects involved paired testing, this is unlikely to affect our overall observations.

All chemicals were obtained from Sigma-Aldrich (USA) unless otherwise specified.

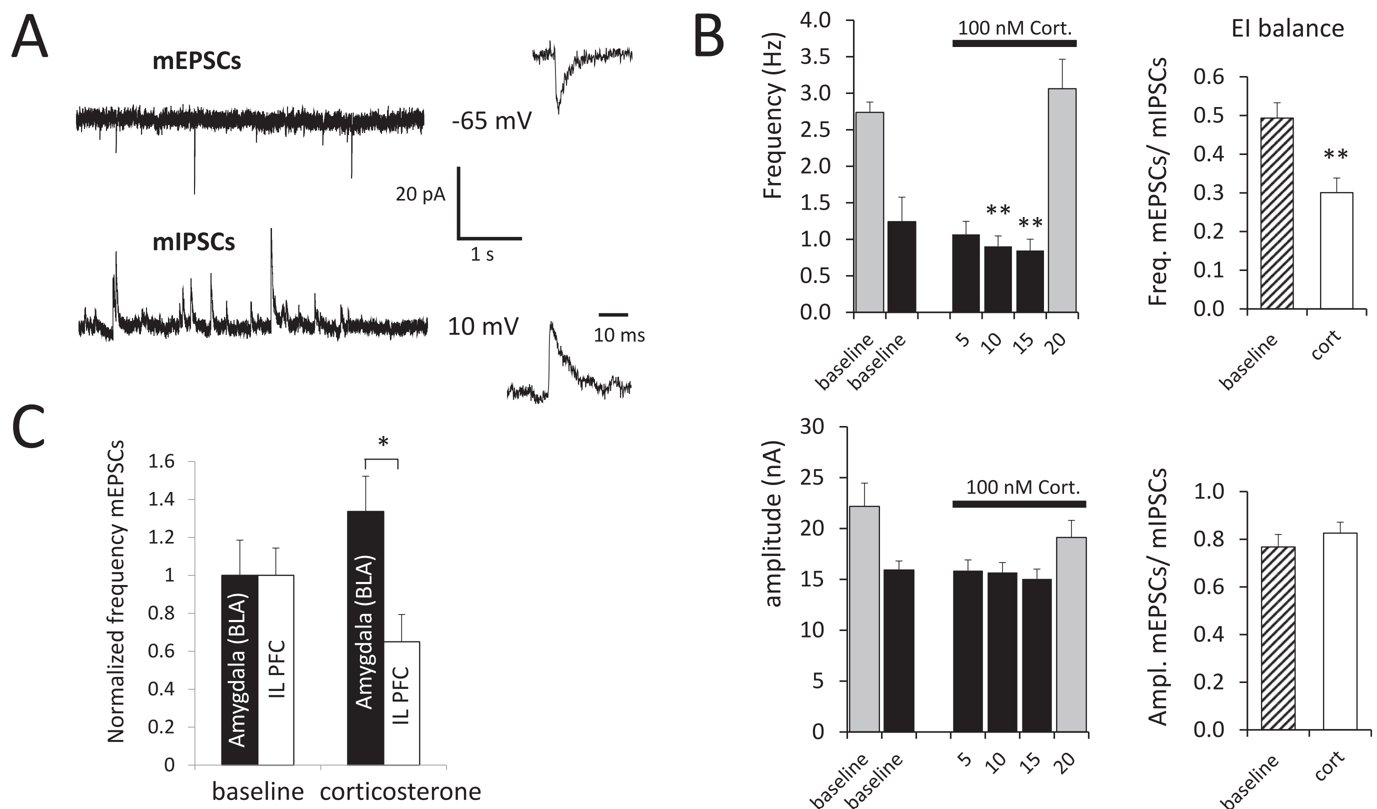

Fig. 1. At a holding potential of −65 mV (i.e. the Erev of GABA) glutamatergic mEPSCs in a mouse layer 2/3 IL-PFC neuron, and at 10 mV (Erev for glutamate) GABAergic mIPSCs can be detected in the same neuron. A typical mEPSC (top) and mIPSC (bottom) is depicted on the right. Corticosterone (100 nM) causes a decrease of the frequency of mEPSCs (black bars). From 10 to 15 min after wash-in the effect was significant, compared to baseline ($p = 0.002$, $n = 8$). The frequency of the mIPSCs (grey bars) was not affected ($p = 0.08$). The EI-balance was calculated by dividing mEPSC frequency by the mIPSC frequency. Compared to baseline (striped bar), corticosterone (white bar) causes a reduction in the EI-balance ($p = 0.006$, 15–20 min after wash-in), indicating that the network is shifted towards more inhibition. No effect of direct corticosterone application was observed on the amplitude of the mEPSCs and mIPSCs. The EI-balance calculated for the amplitude was also not affected. In slices of stressed mice, application of corticosterone induces a reduction of mEPSCs [25] in the BLA. To exclude the possibility that the observed reduction of mEPSCs in the IL-PFC neurons is due to stress prior to slice preparation, we compared the effect of corticosterone treatment in slices from the same animals on BLA neurons and PFC neurons. Because we observed an increase of the mEPSC frequency in the BLA neurons, we concluded that the mice were not stressed and that the rapid effect of corticosterone on PFC neurons indeed is opposite to that in BLA neurons ($p = 0.04$, $n = 6$). $P < 0.05$*, $p < 0.01$**.

2.3. Statistics

Statistical analysis was performed with IBM SPSS Statistics 23.0. Data are presented as mean ± SEM. Normality of data distribution was tested with the Shapiro-Wilk test. The primary question was whether corticosterone induced a rapid effect on the glutamatergic and/or GABAergic transmission. To test this, we applied a paired two tailed Students *t*-test, testing differences between the baseline and final 5-minute block of the agonist (or vehicle) application for both the mEPSCs and mIPSCs.

3. Results

3.1. Rapid effect of corticosterone

Examples of mEPSC and mIPSC recordings in IL-PFC layer 2/3 principal neurons of male mice are depicted in Fig. 1A. After baseline recordings for 5 min of mIPSCs (holding potential of + 10 mV) and subsequently of mEPSCs (holding potential −65 mV) (Fig. 1B), 100 nM corticosterone was added to the perfusion medium. Already within 15 min after the start of the perfusion, the frequency of the mEPSCs was significantly reduced ($p = 0.002$, paired Student's *t*-test, comparing baseline with 10–15 min after wash-in, $n = 8$ (i.e., 8 animals, with 1 recording per animal)). No effect of corticosterone on mIPSC frequency was observed ($p = 0.08$). The mean amplitude of mEPSCs and mIPSCs were unaffected during treatment (respectively, $p = 0.15$ and $p = 0.35$) (Fig. 1B).

The reduction of the mEPSC frequency during corticosterone treatment could, potentially, result from metaplastic changes after stress, as described for the BLA [25], despite the precautions we took to avoid stressing the mice. To test this remote possibility, in slices of a few mice we also tested the effect of corticosterone on mEPSC frequency in the BLA. Here we found an *increase* in mEPSC frequency (Fig. 1C), which was significantly different from the corticosterone effects in the IL-PFC ($p = 0.04$, unpaired Student's *t*-test, $n = 5$), indicating i) that the mice were indeed not stressed prior to slice preparation and ii) that the effect of corticosterone in the mPFC is opposite to that in the BLA.

3.1.1. Excitation-Inhibition balance

To study the excitation-inhibition balance (EI-balance), we divided the frequency of the mEPSCs by the frequency of the mIPSCs for each neuron. The same was done for the amplitude of the mEPSCs and mIPSCs. Fig. 1B shows that the mEPSC/mIPSC frequency, and hence the release of glutamate and GABA, is rapidly reduced by corticosterone ($p = 0.006$, $n = 8$). There was no effect of corticosterone on the EI-balance of the amplitudes ($p = 0.15$).

3.1.2. Which receptor, the MR or GR, is responsible for rapid effects?

Next, we used agonists for the MR and GR to test if one of the two corticosteroid receptor types is responsible for the rapid non-genomic effect of corticosterone in IL-PFC principal neurons. Therefore, we repeated the experiments, perfusing 10 nM Aldosterone (MR agonist) or

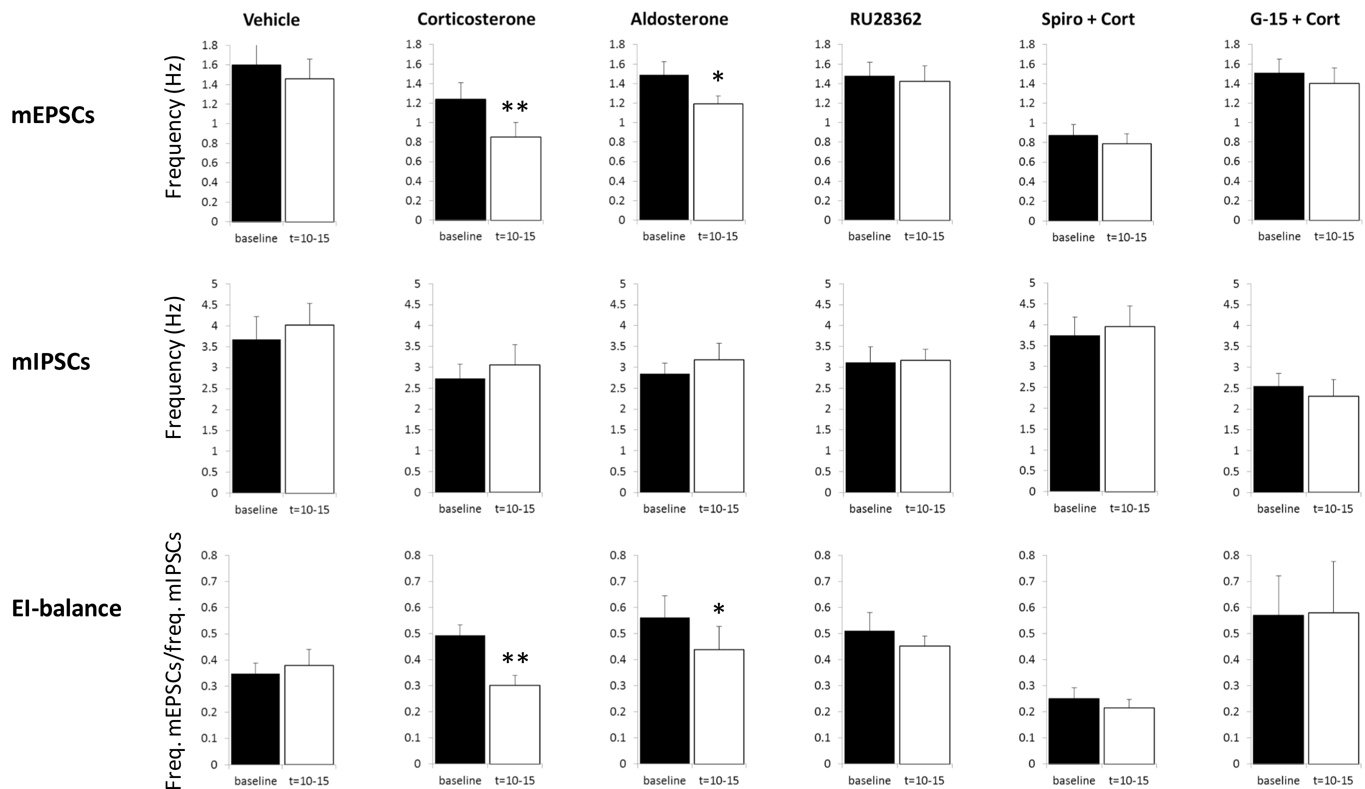

Fig. 2. The rapid effect of corticosterone in the IL-PFC is most likely mediated via MR activation. Comparable to corticosterone (n = 8), the MR agonist aldosterone (n = 8) reduces the frequency of mEPSCs within 15 min after treatment. An antagonist of MR, spironolactone (n = 7), prevents the effect of corticosterone. Both, corticosterone and aldosterone affect the EI-balance in a similar way: They rapidly reduce the excitability. GR activation via RU28362 (n = 6) does not change the mEPSC or mIPSC frequency or EI-balance. As a control, vehicle (n = 6) treatment also did not affect mEPSC- or mIPSC frequency or EI-balance. Here we show that rapid corticosteroid actions in the PFC involve MR, which may take place via binding of MR to GPER. Thus, an antagonist of GPER, G-15 (n = 6), prevented the rapid effect of corticosterone. $P < 0.05$*, $p < 0.01$**.

100 nM RU28362 (GR agonist), using concentrations that previously were found to be effective in the hippocampus [32]. Like corticosterone, perfusion with 10 nM Aldosterone reduced the frequency of the mEPSCs, with an onset after 10 min ($p = 0.02$, n = 8) (Fig. 2). Again, no effect was observed on the mIPSC frequency ($p = 0.15$). As a net result, the EI-balance was shifted towards inhibition ($p = 0.01$).

The GR agonist RU28362 did not cause any effect on the mEPSC- or mIPSC frequency (resp. $p = 0.60$ and $p = 0.82$, n = 6) and also did not change the EI-balance ($p = 0.44$). Both, aldosterone and RU28362 did not affect the amplitude of the mEPSCs and/or mIPSCs.

Given the effectiveness of the MR-agonist aldosterone, we subsequently blocked the MR with 100 nM spironolactone and then added 100 nM corticosterone, to further examine a potential involvement of the MR. This treatment prevented corticosterone to reduce the mEPSC frequency ($p = 0.09$, n = 6).

From these results, it appears that, similar to what was earlier observed in the hippocampus and amygdala, a membrane-associated MR might be responsible for a rapid non-genomic effect of corticosterone in the IL-PFC.

However, mineralocorticoids or possibly even MR molecules themselves are also thought to bind to GPER [30]. To explore the possibility that corticosterone activation via GPER may be involved in the rapid effect, we added corticosterone to the slice in the presence of G-15 (1 μM), a GPER antagonist. This completely blocked the effect of corticosterone (Fig. 2). G-15 itself did not influence the frequency of the mEPSCs (from 1.39 ± 0.22 Hz at baseline to 1.23 ± 0.17 Hz during G-15 administration, $p = 0.08$, n = 6) nor mIPSCs (5.03 ± 0.43 versus 4.79 ± 0.58 Hz respectively, $p = 0.64$).

4. Discussion

In this study we demonstrate that corticosterone exerts a rapid effect on the mEPSC-, but not mIPSC frequency of infralimbic IL-PFC layer 2/3 principal neurons, in male mice. In contrast to what was earlier observed in the hippocampus and amygdala, corticosterone causes a *reduction* of the mEPSC frequency in the mPFC. As a net result, corticosterone will cause a rapid shift of the EI balance and presumably result in a reduction of the spontaneous excitability.

The IL-PFC area mainly projects to the nucleus accumbens-shell [35] and the BLA [36,37] and is, among other things, involved in extinction of fear memories [36–39] and in social interaction [35]. The shift towards more inhibition of the PFC in the first period of a stressful event is in line with the reported effects on LTP, attention and multitasking and fits well with the hypothesis that the PFC is suppressed during the first period of a stressful event and allows simple behavioral responses favorable for immediate survival of the individual to prevail [14].

We further conclude that corticosterone specifically affects glutamate release in the IL-PFC involving a non-genomic activation of MRs. We excluded the possibility that the reduction occurred via metaplastic inhibition of glutamate release via membrane GRs, as was earlier demonstrated in the BLA of stressed mice. Thus, in slices containing the BLA and PFC from the same mice, corticosterone caused respectively an increase in the mEPSC frequency in the BLA -in line with the animals not being stressed- and a decrease in the IL-PFC. Given the opposite direction of the rapid corticosteroid actions in the PFC (compared to the hippocampus and BLA) it cannot be excluded that they may be regulated via another mechanism than the MEK-ERK pathway earlier demonstrated in the hippocampus [40].

In recent years, our attempts to visualize the receptor responsible for rapid corticosteroid effects were unsuccessful [26]. Possibly, it may involve a hitherto unknown receptor, with a binding site for corticosterone and aldosterone that is not recognized by the current MR antibodies. It has been postulated that corticosterone or aldosterone could, instead, exert their non-genomic effects, via 1) transactivation of receptor tyrosine kinases (e.g. EGFR, PDGFR and IGF1R1), 2) a CAV1 or Striatin coupled interaction, or 3) transactivation or an interaction with GPER or AT1 receptors. If, in line with the latter possibility, GPER acts downstream of MR -as has indeed been postulated [42]- this could explain why both spironolactone and G-15 in our hands effectively blocked the effect of corticosterone. However, to date, no biochemical or molecular evidence supports this notion. By contrast, there is increasing experimental data indicating that corticosterone and aldosterone act directly as an agonist of GPER. GPER (GPR30) is a G-protein coupled estrogen receptor that has been linked to rapid corticosteroid actions in the periphery and brain [29,30,40–42]. Thus, Ding et al. 2022 [28] recently described a binding site for aldosterone on the GPER molecule. Also, 4) the Aquaporin-2 receptor was suggested as a possible target for corticosteroid receptors. Mom et al. [31] reported several binding sites for the corticosteroid receptors GR and MR on the AQP-2 receptor. Both GPER and AQP-2 receptors are located on the outside of the membrane surface and can probably be reached by cort-BSA, a compound that mimicked the rapid effect of corticosterone in the hypothalamus and hippocampus [18,32]. That makes GPER and AQP-2 receptors good candidates for playing a role in the non-genomic actions of corticosterone. Recently, GPER has been implicated in rapid learning processes [43]. Treatment with G-1, a GPER agonist, resulted in very rapid (within 40 min) changes of dendritic spines in the CA1 region of the hippocampus. Similar to 17β-estradiol, in vivo administration of G-1, rapidly enhanced activation of kinases, Akt and ERK, in the hippocampal CA1 region of rats, comparable to the effect of corticosterone [40]. GPER is found in the hippocampus and also present in the IL-PFC and many other brain structures [44]. The resemblance in the mode of actions of corticosterone and GPER activation by G-1 could be explained by a recognition site for corticosterone/aldosterone on the GPER. We here showed that G-15, an antagonist of GPER, could prevent the rapid effect of corticosterone in the IL-PFC. Therefore, we conclude that GPER may be an important target for corticosterone/Aldosterone -or even MR itself- and that it is responsible, at least in part, for the rapid non-genomic modulation of IL-PFC excitability. Potential effectiveness of G-1 or other GPER (ant)agonists may be tested in future experiments. Overall, out data emphasizes that receptors other than the classical corticosteroid receptors may (also) be involved in the rapid modulation of spontaneous activity of limbic neurons by corticosterone. This may shed new light on the function of corticosteroids on e.g. the PVN, and may eventually lead to new targets of stress response related abnormalities.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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