Corticosterone Slowly Enhances Miniature Excitatory Postsynaptic Current Amplitude in Mice CA1 Hippocampal Cells

Henk Karst and Marian Joëls

Center for Neuroscience, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands

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Karst, Henk and Marian Joëls. Corticosterone slowly enhances miniature excitatory postsynaptic current amplitude in mice CA1 hippocampal cells. J Neurophysiol 94: 3479–3486, 2005. First published July 20, 2005; doi:10.1152/jn.00143.2005. Corticosteroid hormones are released in high amounts after stress and bind to intracellular receptors in the brain, which in activated form function as transcription factors. We here tested the effect of a high dose of corticosterone on AMPA-receptor–mediated transmission in the CA1 hippocampal area, which is enriched in corticosteroid receptors. To focus on slow gene-mediated effects of the hormone, excitatory postsynaptic currents were measured at least 1 h after a brief application of 100 nM corticosterone to slices from adrenally intact adult mice. The amplitude but not frequency of miniature postsynaptic excitatory currents was found to be significantly enhanced. These effects were mimicked by 100 nM RU 28362, a selective agonist for intracellular glucocorticoid receptors. Evoked AMPA responses at the single cell were significantly enhanced when measured 2–4 h after application of 100 nM corticosterone, but not at earlier moments nor with a longer delay. In summary, the present results show that activation of hippocampal glucocorticoid receptors induces a slow enhancement of AMPA-receptor–mediated responses, at the single-cell level.

INTRODUCTION

Adrenal corticosteroid hormones (cortisol in humans, corticosterone in rats) are released into the circulation in high amounts after a stressful event. Hormone levels peak within 15–30 min and gradually normalize within 2 h, arising from a negative feedback regulation by the hypothalamus and pituitary gland (Dallman et al. 1987; Makino et al. 2002). Corticosteroids enter the brain and bind to discretely localized high-affinity mineralocorticoid receptors (MRs) as well as lower-affinity glucocorticoid receptors (GRs) (reviewed by de Kloet et al. 1998; McEwen et al. 1986). Hippocampal CA1 pyramidal neurons coexpress both receptor subtypes (Van Steensel et al. 1996). Because of the difference in affinity, basal levels of corticosterone under resting conditions will predominantly activate MRs; when steroid levels rise, such as after a stress, GRs will also become substantially activated (reviewed by de Kloet et al. 1998). Activation of corticosteroid receptors is known to regulate transcription of responsive genes (Aranda and Pascual 2001; Datson et al. 2001).

Earlier studies have shown that functional properties of CA1 pyramidal neurons are slowly but persistently changed through these genomic actions, after a temporary rise in hormone level (for review see Joëls 2001). Thus voltage-dependent calcium currents of CA1 neurons were found to be enhanced in amplitude with a considerable delay in time, i.e., 1–4 h after a brief (20-min) application of high doses of corticosterone (30–100 nM; Karst et al. 1994, 2000; Kerr et al. 1992) or after stress (Joëls et al. 2003). It was shown that this is indeed a gene-mediated process, involving DNA-binding of GR homodimers (Karst et al. 2000) and protein synthesis (Kerr et al. 1992). Other voltage-dependent currents were found to be less sensitive to GR activation (for review see Joëls 2001). G-protein–coupled signal transduction also appears to be a target for steroid modulation. For instance, CA1 pyramidal hyperpolarizations mediated by the serotonin-1A receptor are small with low levels of corticosterone (1 nM) that will predominantly activate MRs (Beck et al. 1996; Joëls et al. 1991) but increased 1–4 h after an acute stress or GR activation in vitro (Hesen and Joëls 1996; Joëls et al. 1991), again requiring GR-homodimer binding to the DNA (Karst et al. 2000) and protein synthesis (Karst and Joëls 1991).

Surprisingly, to date little is known about slow GR-mediated effects on transmission by hippocampal ionotropic receptors, in particular by the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which mediates the main basal excitatory flow of information in the CA1 area (Meng et al. 2003). In the present study we therefore examined whether brief application of corticosterone to hippocampal slices slowly changes functional properties of AMPA receptors involved in excitatory projections onto the CA1 area. We examined miniature excitatory postsynaptic potentials (mEPSCs) as well as evoked (e)EPSCs in CA1 pyramidal neurons, before and several hours after a 20-min application of 100 nM corticosterone in vitro. To specifically investigate the role of the GR, slices were also exposed to 100 nM of the highly selective GR agonist RU 28362 (Philibert and Moguilevski 1983).

METHODS

Animals and slice preparation

C57Bl/6 mice, 6 wk of age, were group-housed in cages with a light/dark cycle of 12 h (lights on at 0800 h). Food and water were given without restriction. The experiments were carried out with permission of the local Animal Committee (DED 91). The mice were decapitated under rest, around 0930 h, i.e., when plasma corticosterone levels are low (see e.g., Alfarez et al. 2002; Karst et al. 2000). Thus decapitation was always done within 2 min after taking the animal from its home cage, which is too short a time to induce any discernible rise in plasma corticosterone concentration. Accordingly,

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the plasma corticosterone levels of animals decapitated under such circumstances are very low, i.e., 2–3 μg/dl (Alfarez et al. 2002; Karst et al. 2000). The brain was removed from the skull and stored in continuously gassed (mixture of 95% O2-5% CO2) artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 3.5 KCl, 1.25 NaH2PO4, 1.5 MgSO4, 2 CaCl, 25 NaHCO3, and 10 glucose; pH 7.4, at room temperature. The osmolarity (300 mosm) of this ACSF was adjusted with a Wescor 5100C vapor pressure osmometer. Transverse slices of the hippocampus were made with a tissue chopper. The slices were stored at room temperature. After a 1-h delay, some of the slices were treated with 100 nM corticosterone (Sigma) or 100 nM RU 28362 for 20 min in ACSF at 32°C. After this treatment, the slices were moved to a storage bath with normal ACSF at room temperature and left undisturbed for at least another 40 min. The same procedure was carried out for the vehicle-treated controls.

Electrophysiology

One slice at a time was placed in a recording chamber mounted on an upright microscope (Nikon Optiphot-2). Slices were continuously perfused with ACSF (32°C, 2–3 ml/s) and kept fully submerged. Bicuculline methiodide (20 μM, Sigma) was added to the buffer to prevent γ-aminobutyric acid type A (GABA<sub>A</sub>)–receptor-mediated inhibition that could be activated by pathway stimulation. GABA<sub>A</sub>-receptor–mediated components were blocked by QX-314, which was added to the pipette solution (see following text; Perkins and Wong 1996). Debris on the surface of the CA1 cell layer was removed with a cleaning pipette. Whole cell patch-clamp recordings were made with an Axopatch 200B amplifier (Axon Instruments, Union City, CA) using electrodes from borosilicate glass (1.5 mm outer diameter; Hilgenberg, Malsfeld, Germany) with an impedance of approximately 3–6 MΩ. The electrodes were pulled on a Sutter micropipette puller. Biphasic stimuli (250 μs) were applied through a Neurolog stimulus isolator (NL 800) driven by PClamp 8.2. Input–output curves of EPSCs evoked in CA1 neurons were made at holding potential (−70 mV) by increasing stimulus intensities from 16 to 500 μA, given once every 10 s. Evoked (e)EPSCs were recorded with a sampling frequency of 10 kHz. Signals were stored and corrected off-line for leak. Input–output curves were fit with a Boltzmann equation: \( R(t) = R_{\text{max}} \left( 1 + \exp\left( (i - i_0)/I_c \right) \right) \), where \( R_{\text{max}} \) is the maximal evoked current, \( i_0 \) the half-maximal stimulus intensity, and \( I_c \) is proportional to the slope. Based on this curve the half-maximal stimulus intensity was determined. This intensity was used to determine voltage-dependent properties by evoking EPSCs at holding potentials between −80 to +50 mV, increasing the voltage in subsequent steps by 10 mV and using 10-s intervals. During these recordings 2-amino-5-phosphonovaleric acid (APV, 50 μM; Sigma) was perfused to block the N-methyl-d-aspartate (NMDA) receptor. We also studied possible changes in the AMPA versus NMDA responses after corticosterone treatment, by applying a protocol described by Saal et al. (2003). In brief, AMPA-receptor–mediated responses were determined by the (peak) signal at +40 mV in the presence of APV. By subtracting this signal from the overall response, the NMDA-receptor–mediated component could be obtained.

Miniature EPSCs

Miniature (m)EPSCs were recorded either after the recording of eEPSCs or without prior recording of eEPSCs, by adding tetrodotoxin (0.5 μM, Latoxan, Rosans, France) to the perfusate. At a holding potential of −70 mV, mEPSCs were recorded for 5 min. During some recordings the non–NMDA-receptor blocker 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 10 μM, Tocris) or the selective AMPA receptor blocker GYKI 53655 (50 μM; Bleakman et al. 1996; Vignes and Collingridge 1997; LY300168, obtained through M. Eder, Munich, Germany) was perfused to confirm that the mEPSCs were indeed mediated by AMPA receptors. The digitized data (stored on PC by Digidata interface) were analyzed off-line using Strathclyde software with detection threshold levels set >5 pA. The currents were identified as mEPSCs when the rise time was faster than the decay time. Of all cells measured, the following mEPSC characteristics were determined: inter-mEPSC interval, the frequency, rise amplitude, and tau (τ) of decay. The decay of each mEPSC was fitted with a mono- and biexponential curve in WCP. This program uses the Levenberg–Marquardt algorithm to iteratively minimize the sum of the squared differences between the theoretical curve and data curve. As a criterion for the goodness of the fit the residual SD should be <0.3. Fitting with a biexponential instead of a monoexponential curve did not increase the goodness of the fit (data not shown).

Statistics

Delayed effects (examined in different sets of cells) were analyzed with a two-tailed unpaired Student’s t-test. The distribution of mEPSC amplitudes between control and treatment conditions was performed with a Kolmogorov–Smirnov test. Input–output curves for eEPSCs were tested with an ANOVA for repeated measures (MANOVA). In all cases, significance was set at \( P < 0.05 \).

Results

Miniature excitatory postsynaptic potentials (mEPSCs) were recorded in CA1 neurons under conditions that GABA<sub>A</sub> receptors were blocked by bicuculline and spontaneous release was prevented by the addition of tetrodotoxin. Typical mEPSCs are shown in the trace of Fig. 1A. These mEPSCs are mediated by AMPA receptors because of the following reasons. 1) All recordings (unless stated otherwise) were carried out at a holding potential of −70 mV, when NMDA receptors are blocked by Mg ions (Nowak et al. 1984). 2) Introduction of the...
FIG. 1. Miniature excitatory postsynaptic potentials (mEPSCs) recorded at −70 mV in CA1 hippocampal neurons are mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. A: typical trace showing the frequency and kinetic properties (inset) of mEPSCs in a CA1 neuron. B: mEPSCs recorded at −70 mV were blocked by the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 10 μM). Numbers (1 through 6) indicate the order of the consecutive traces. Application of CNQX is indicated by the stippled line. C: AMPA-receptor blocker GYKI 53655 (50 μM) rapidly blocked mEPSCs. Numbers (1 through 6) indicate the order of the consecutive traces. Application of GYKI 53655 is indicated by the stippled line.

non–NMDA-receptor antagonist CNQX (n = 4) or the specific AMPA-receptor blocker GYKI 53655 (n = 3) completely abolished the mEPSCs (Fig. 1, B and C). Removal of the antagonists reversed the blockage of the receptors (67.5 ± 1.5%, data not shown).

In cells recorded at least 1 h after a brief (20-min) treatment with 100 nM corticosterone in vitro, the amplitude but not the frequency of mEPSCs was significantly (P = 0.0001) enhanced (see Table 1). Typical traces are shown in Fig. 2A. Figure 2B furthermore shows the normalized frequency histogram of the mEPSC amplitude and ln (amplitude), in cells from corticosterone- and vehicle-treated slices. The corticosterone-induced shift of the distribution to larger amplitudes is also very clear from the cumulative frequency distribution of the amplitudes (Fig. 2C). The delayed effect of the hormone on mEPSC amplitude was clearly mediated by the GR. As shown in Fig. 3, the highly selective GR-agonist RU 28362 induced very similar, delayed effects on the mEPSC amplitude. Especially in the case of the ln (amplitude), the distribution of both experimental groups was not different from a normal distribution and could be well fitted with a single Gaussian. Neither corticosterone nor RU 28362 affected the kinetic properties of the mEPSCs (Table 1). That is, no significant GR-dependent changes were observed in the mean rise time and the time constant of the decay for the mEPSCs.

The increased mEPSC amplitude in combination with a lack of effect on the frequency suggests that the delayed effects of corticosterone involve postsynaptic aspects of glutamatergic transmission. In subsequent experiments we examined the putative changes in synaptically evoked EPSCs and the ratio between AMPA- and NMDA-receptor–mediated responses. In Fig. 4A, averaged input–output curves of the eEPSCs are depicted for the control group and cells recorded ≥1 h after a 20-min administration of 100 nM corticosterone. All data were obtained at a holding potential of −70 mV and therefore presumably represent AMPA-receptor–mediated responses. The data show that, particularly with strong stimulation intensities, corticosterone induced a nearly 25% increase in the maximal eEPSC amplitude compared with the control amplitudes. Over the stimulation range of 300–500 μA, a significant (P = 0.04) enhancement was seen after corticosterone treatment (n = 22), compared with control (n = 26). The responses induced by half-maximal stimulus intensity, however, were not different between the vehicle- and corticosterone-treated slices. Interestingly, maximal eEPSC amplitudes seemed to change with time (Fig. 4B). The largest increase in amplitude was observed between 2 and 4 h after steroid treatment, when the corticosterone-treated cells responded significantly stronger to high-intensity stimulation than the control cells recorded in the same time interval (means ± SE; corticosterone: −1.75 ± 0.12 nA, n = 17; control: −1.26 ± 0.15 nA, n = 15; P = 0.02). Relatively small amplitudes were observed at short (<2 h) intervals after corticosterone treatment and particularly after long intervals (>4 h, see Fig. 4B). In the control group,

![Diagram](https://via.placeholder.com/150)

**FIG. 2.** Miniature excitatory postsynaptic potentials (mEPSCs) recorded at −70 mV in CA1 hippocampal neurons are mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. A: typical trace showing the frequency and kinetic properties (inset) of mEPSCs in a CA1 neuron. B: mEPSCs recorded at −70 mV were blocked by the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 10 μM). Numbers (1 through 6) indicate the order of the consecutive traces. Application of CNQX is indicated by the stippled line. C: AMPA-receptor blocker GYKI 53655 (50 μM) rapidly blocked mEPSCs. Numbers (1 through 6) indicate the order of the consecutive traces. Application of GYKI 53655 is indicated by the stippled line.

**TABLE 1.** mEPSC amplitude, frequency, rise time, and time constant of decay in the control group and in cells treated with either 100 nM corticosterone (CORT) or RU 28362 for 20 min

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 15)</th>
<th>CORT (n = 19)</th>
<th>RU 28362 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEPSC amplitude</td>
<td>21.5 ± 1.6</td>
<td>29.5 ± 1.0*</td>
<td>30.8 ± 2.2*</td>
</tr>
<tr>
<td>mEPSC frequency</td>
<td>0.69 ± 0.1</td>
<td>0.80 ± 0.14</td>
<td>0.87 ± 0.13</td>
</tr>
<tr>
<td>mEPSC rise time</td>
<td>1.52 ± 0.09</td>
<td>1.53 ± 0.04</td>
<td>1.57 ± 0.05</td>
</tr>
<tr>
<td>mEPSC τ of decay</td>
<td>13.8 ± 0.8</td>
<td>10.8 ± 0.6</td>
<td>12.7 ± 0.3</td>
</tr>
</tbody>
</table>

Values are averaged means ± SE. Cells were treated 1–4 h before recording. Data were tested with a Student’s t-test *P < 0.05.
such an obvious decline after long intervals was not observed (means ± SE: 2–4 h: −1.26 ± 0.15 nA, n = 15; >4 h: 
−1.14 ± 0.22 nA, n = 7).

We also investigated the voltage dependency of the eEPSCs. To this end, eEPSCs were recorded at various potentials in the presence of APV, thus isolating AMPA-receptor–mediated events. Current–voltage relationships of the eEPSCs (normalized to the response obtained at −70 mV) were comparable for the two experimental groups in the voltage range from −70 to +50 mV, indicating that voltage dependency was not changed by corticosteroid treatment (Fig. 4C). The paired-pulse response ratio was also not changed after corticosterone treatment (Fig. 4D).

In this study we focused on AMPA-receptor–mediated responses. To get a first impression about the selectivity of the corticosteroid effects we examined to what extent the hormone affected NMDA-receptor–mediated synaptic events. For each cell, AMPA responses were analyzed as the peak response evoked by synaptic stimulation at −40 mV, in the presence of APV (example in Fig. 5A). NMDA-receptor–mediated responses were determined by subtracting this signal from the overall response before APV treatment. As shown in Fig. 5B, the NMDA-receptor–mediated component of the synaptic responses was nearly identical in vehicle- and corticosterone-treated cells. By contrast, AMPA-receptor–mediated components recorded in the same set of cells were significantly enhanced. A similar lack of effect on NMDA-receptor–mediated responses was also inferred from the overall response at +40 mV, at 100 ms after stimulation. Earlier studies showed (Karst and Joëls 2003; Otmakova et al. 2002) that at this time point AMPA responses are in general completely inactivated, so that the recorded currents are nearly exclusively mediated by NMDA receptors. Thus analyzed signals showed no difference between the vehicle-treated cells (0.16 ± 0.02 nA) and corticosterone-treated cells (0.17 ± 0.01 nA).

**DISCUSSION**

Over the past decade several groups have shown that glucocorticoids have slow but persistent effects on the function of various voltage-dependent ion channels as well as G-protein–coupled receptor signaling pathways in the CA1 hippocampal area (for review see Joëls 2001). Surprisingly little is known, at the cellular level, about corticosteroid actions on transmission mediated by glutamate, one of the major excitatory transmitters in the hippocampus. We here show that glutamate transmission can be consistently changed by temporary activation of the glucocorticoid receptor.

Thus several hours after a brief (20-min) corticosterone treatment, the amplitude of AMPA-receptor–mediated mEPSCs was significantly enhanced. The mEPSC frequency and kinetic properties remained unaltered. Moreover, an increase in the amplitude of eEPSCs was observed, particularly between 2 and 4 h after corticosteroid treatment. This contrasts to earlier findings in the dentate gyrus, where eEPSC amplitude was unaffected by 100 nM of corticosterone in control rats, al-

![Fig. 2. Corticosterone induces a delayed enhancement of the mEPSC amplitude. A: typical traces illustrating that mEPSC amplitude was enhanced at >1 h after a 20-min corticosterone application to hippocampal slices. B: frequency histogram for the distribution of the amplitude (left) or ln (amplitude) of mEPSCs in CA1 pyramidal neurons after control treatment (gray bars) or treatment with 100 nM corticosterone (open bars, fat lines). A shift toward larger amplitudes was observed after hormone treatment. Histograms are based on 3,960 events in cells from vehicle (n = 10) and 4,216 events in cells (n = 10) from corticosterone-treated slices. C: cumulative frequency histogram shows a marked shift toward larger amplitude mEPSCs after corticosterone treatment.](image-url)
though similarly enhanced as in CA1 cells in granule cells from chronically stressed animals (Karst and Joëls 2003). A similar dichotomy between effects of corticosterone in CA1 and dentate cells was also observed earlier for field potential responses (Stienstra et al. 2000) as well as responses mediated by the serotonin-1A receptor (Karten et al. 2001).

The corticosterone-induced increase in synaptic responses presently seen in the CA1 area was restricted to the AMPA-receptor–mediated component, whereas the NMDA-receptor–mediated component appeared to be unaffected. The latter was determined by subtracting the APV-insensitive eEPSC from the overall response. Because not all NMDA-receptor–mediated effects seem equally sensitive to APV blockade (Rosenblum et al. 1997) such putative APV-insensitive NMDA currents could have escaped our attention when using this subtraction approach. However, the second method of analysis for NMDA currents, determining currents 100 ms after depolarization to $-40$ mV, by which time AMPA currents are inactivated (Karst and Joëls 2003; Otmakova et al. 2002), yielded similar results, i.e., that the NMDA-receptor–mediated component of the eEPSC is not affected by corticosterone. The paired-pulse response ratio was also unchanged. Collectively, the data indicate that corticosterone slowly increases the responses mediated by AMPA receptors in the postsynaptic density.

The presently observed effects seen several hours after corticosterone application are probably accomplished by the intracellular GR, given the effectiveness of the highly selective GR agonist RU 28362 (Philibert and Moguilevsky 1983). Incidentally, the fact that RU 28362 yielded highly comparable results as seen with corticosterone in a different (independently recorded) population of CA1 neurons supports that variations introduced by the nonhomogeneity of the CA1 pyramidal cells did not confound our results. The influence of this presumed nonhomogeneity was also limited by recording from a relatively large number of cells per group ($\geq 15$ cells in the control and corticosterone-treated groups). The time course and involvement of the GR are compatible with a gene-mediated process, much like the effects on calcium current amplitude and 5-HT-1A–receptor-mediated responses described earlier (Joëls et al. 1991; Karst and Joëls 1991; Karst et al. 1994; Kerr et al. 1992). The effects on calcium currents and 5-HT-1A–receptor-mediated responses, using the same experimental protocol, were found to involve DNA binding of GR homodimers (Karst et al. 2000). This may also be the case for the present actions on AMPA receptors, although protein–protein interactions of the GR with other transcription factors cannot be ruled out. Transcriptional regulation may be targeted directly at AMPA-receptor subunit genes, but also at proteins that are involved in the recruitment of AMPA receptors in the postsynaptic density, such as Homer-1a/Vesl-1S (Hennou et al. 2003). Interestingly, very recently swim stress was shown to induce a GR-dependent increase in AMPA-receptor–mediated synaptic responses of dopaminergic neurons in ventral tegmental area slices, prepared 24 h after the stress (Saal et al. 2003). It was demonstrated that this effect of stress in midbrain neurons requires the presence of GluR1 receptors (Dong et al. 2004). Possibly, GR activation leads to insertion of GluR1 subunit containing receptors in the postsynaptic density. If so, this did
FIG. 4. Corticosteroid effects on AMPA-receptor–mediated evoked (e)EPSC. A: averaged input–output curve constructed at a holding potential of −70 mV shows increased amplitude of eEPSCs 1–4 h after corticosterone treatment (n = 22) compared with the control situation (n = 26). Over the range of 278 to 498 μA, the difference attained statistical significance (P = 0.04). B: as shown in the scatter plot, a time-dependent change in eEPSC amplitude seemed to occur after corticosterone treatment. Relatively large responses were observed between 2 and 4 h after corticosterone administration (individual data represented by a closed square), whereas responses recorded at earlier time points but particularly at a longer delay were small. Average of the control responses, which did not display such a time dependency (see text), is indicated by the striped line. C: voltage dependency of the evoked AMPA-receptor–mediated currents was not affected by corticosteroid treatment (vehicle: n = 13; corticosterone: n = 14). A small rectification at depolarized membrane potentials was seen in both the control and hormone-treated groups. Responses were induced by half-maximal stimulus intensity. Currents were normalized to the response obtained at −70 mV. D: ratio of the response amplitude induced by the second stimulus divided by the response to the first stimulus in a double-pulse stimulation protocol with half-maximal intensity (interval 100 ms, typical example on top) was comparable in corticosterone-treated cells (n = 11) and vehicle-treated cells (n = 11). We selected a 100-ms interval, so that the first synaptic response was normalized before the second stimulation was delivered.

FIG. 5. Glucocorticoid effects on glutamate transmission are selective for the AMPA receptor. A: AMPA-receptor–mediated responses were determined by the peak amplitude of the response evoked at +40 mV in the presence of 2-amino-5-phosphonovaleric acid (APV). By subtracting this signal from the overall response before APV administration the NMDA-receptor–mediated responses were obtained. B: AMPA-receptor–mediated responses were enhanced (P = 0.004) at >1 h after corticosterone treatment (n = 10 cells; left), compared with the control group (n = 10 cells). By contrast, no change was observed for the NMDA-receptor–mediated responses (right).
not lead to discernable changes in rectification properties (Lerma et al. 1994) under the present recording conditions.

By this delayed action, corticosterone could potentially enhance postsynaptic aspects of glutamatergic transmission in the CA1 area in a slow manner. We observed, however, that the eEPSC amplitude associated with maximal stimulus intensity was enhanced within a time window of only 2–4 h after a brief corticosterone administration. Thus within the first hours responses were somewhat variable and no consistent enhancement was observed. Probably, at these early time points gene-mediated events are not yet fully developed. Nongenomic actions, however, may take place at this time point, particularly when one applies very high concentrations of corticosterone; this may be one of the explanations why some earlier studies observed a fast and rapidly reversible change in the field EPSP response while applying a high concentration of corticosterone to the slice (e.g., Vidal et al. 1986). At later moments (>4 h) the eEPSC amplitude was also not enhanced and even showed a tendency toward a decrease. Indeed, earlier field potential studies reported either no effect or even a decline of the maximal field response after corticosterone treatment (e.g., Alfarez et al. 2002).

It should be noted that these data were often based on recordings obtained with a relatively long delay (>3 h) after corticosterone treatment. We speculate that fibers cut by the slicing procedure and synaptic terminals as well as distal dendrites slowly deteriorate and become dysfunctional in our preparation (Schurr et al. 1984). This effect may be exacerbated by corticosterone treatment. Also, GR activation may slowly lead to dendritic retraction, which could influence our present recordings. Three observations support this speculation. First, slices subjected to GR activation showed a gradual decline in synaptic responses with repeated stimulation, suggesting a stronger decline in synaptic machinery after glucocorticoid exposure (Joëls and de Kloet 1993). Second, ionic currents that are generated in distal dendrites of CA1 neurons slowly decline after glucocorticoid treatment or stress (but not control conditions), as does the membrane capacitance that forms an indicator for the total cellular membrane surface (Joëls et al. 2003). Finally, preliminary data in organotypic hippocampal slice cultures show that corticosterone through a GR-dependent mechanism reduces the apical dendritic surface of CA1 pyramidal neurons (Alfarez et al. 2004). Alternatively, other differences between the present and earlier recording situations (such as the blockade of GABA_A receptors applied in the present series) may explain the discrepancies with respect to glucocorticoid actions. To allow a better comparison between whole cell patch-clamp and field-potential recordings with regard to corticosteroid effects, it will be helpful to study the effect of corticosterone on field potentials in the presence of bicuculline, in future investigations.

In summary, the present study shows that postsynaptic aspects of AMPA-receptor-mediated synaptic responses in CA1 hippocampal neurons are slowly increased after a brief activation of glucocorticoid receptors through a delayed, presumably gene-mediated mechanism. This effect lasts for several hours in the slice preparation but, at least in vitro, seems to decline with longer intervals. In this way, stress may—for a restricted period of time—affect the overall output of the hippocampal formation, including the transynaptic inhibition of the hypothalamic feedback site (Herman and Cullinan 1997), as well as behavioral processes, which critically depend on glutamatergic transmission in the hippocampus such as learning and memory.

REFERENCES


