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Inhibiting 11β-hydroxysteroid dehydrogenase type 1 prevents stress effects on hippocampal synaptic plasticity and impairs contextual fear conditioning

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ABSTRACT

11β-Hydroxysteroid dehydrogenase type 1 (11β–HSD1) catalyzes intracellular regeneration of corticosterone and cortisol, thereby enhancing glucocorticoid action. Inhibition of 11β–HSD1 reverses the deficits in cognition with aging, a state of elevated glucocorticoid levels. However, any impact of 11β–HSD1 inhibition during high glucocorticoid states in younger animals is unknown. Here we examined whether a single injection of the selective 11β–HSD1 inhibitor UE2316 modifies the effect of stress on hippocampal long-term potentiation and fear conditioning, a learning paradigm that is strongly modulated by glucocorticoids. We found that novelty stress suppresses hippocampal synaptic potentiation. This effect was completely prevented by administration of UE2316 one hour before stress exposure. A single injection of UE2316 also impaired contextual, but not tone-cue-fear conditioning. These observations suggest that local metabolism of glucocorticoids is relevant for the outcome of stress effects on hippocampal synaptic plasticity and contextual fear conditioning. Selective 11β–HSD1 inhibitors may be an interesting new approach to the prevention of trauma-associated psychopathology.

1. Introduction

Stressful events stimulate the hypothalamic–pituitary–adrenal (HPA) axis to release glucocorticoid hormones from the adrenal cortex (corticosterone in mice; cortisol in humans) (Joëls and Baram, 2009). Glucocorticoids enter the brain and bind to two subtypes of discretely localized intracellular receptors, i.e. the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR), which are expressed in regions that are critical for memory formation such as the hippocampus, amygdala, and prefrontal cortex (de Kloet et al., 2005). MRs are already largely occupied when hormone levels are low whereas GRs – due to their 10-fold lower affinity for corticosterone– only become substantially activated when hormone levels rise after exposure to stressful events (de Kloet et al., 2005).

Glucocorticoids, via activation of MRs and GRs, promote behavioral adaptation to fearful events (de Kloet et al., 1999, 2005; Roozendaal et al., 2009). Activation of MRs regulates appraisal and response selection during the learning process (de Kloet et al., 1999) and also the encoding of fearful events, particularly the contextual aspects (Zhou et al., 2010). Via GRs, corticosteroid hormones promote the consolidation of fearful information (e.g. Oitzl and de Kloet, 1992; Sandi and Rose, 1994; Pugh et al., 1997a,b; Oitzl et al., 2001; Roozendaal et al., 2006, 2009; Zhou et al., 2010). The mechanism by which glucocorticoids are thought to impact on storage of fearful events involves dynamic regulation of synaptic plasticity (Joëls et al., 2012). Thus, glucocorticoids enhance hippocampal synaptic transmission within minutes via activation of MRs (Karst et al., 2005). Over the same time scale, they facilitate long-term potentiation (LTP)(Wiegert et al., 2006). Some hours later, via slower processes that require gene transcription, glucocorticoids suppress the ability to induce LTP (Pavlides et al., 1996; Xu et al., 1997; Kim and Diamond, 2002; Alfarez et al., 2002; Wiegert et al., 2005), which might reflect a mechanism to preserve already stored information (Diamond et al., 2007; Krugers

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et al., 2010). Some regional specificity in corticosteroid effects may occur: in the ventral hippocampus corticosterone generally facilitates synaptic potentiation (Segal et al., 2010). In contrast to acute rises in corticosteroid level, chronic elevation, such as may occur during aging, compromizes cognitive performance (Lupien et al., 2009).

The concentration of glucocorticoids in the brain is not only dependent on adrenal secretion but also on intracellular metabolism (Holmes et al., 2003). 11β-Hydroxysteroid dehydrogenase type 1 (11β–HSD1) catalyzes intracellular regeneration of corticosterone and cortisol in the brain, thus locally amplifying glucocorticoid action (Holmes and Seckl, 2006). This is relevant for age-related cognitive deficits which are associated with chronically elevated corticosterone levels (Holmes et al., 2010; Sooy et al., 2010; Yau et al., 2011, Yau and Seckl, 2012). Thus, mice deficient in 11β–HSD1 throughout life are protected from hippocampus-dependent memory impairments associated with aging, presumably due to their lower intracellular corticosterone levels (Yau et al., 2001; Yau et al., 2007). Moreover, inhibiting intracellular regeneration of corticosterone with a selective 11β–HSD1 inhibitor for 10 days reversed age-related cognitive deficits in memory formation (Sooy et al., 2010).

It is still unknown, however, whether *brief* inhibition of 11β–HSD1 can effectively modulate brain function in young adult animals. We therefore tested the hypothesis that pharmacological inhibition of 11β–HSD1 acutely prevents the effect of stress on hippocampal synaptic plasticity and that this is reflected in reduced contextual fear conditioning, a learning paradigm that is sensitive to circulating levels of glucocorticoid hormones (Pugh et al., 1997a, b; Zhou et al., 2010).

2. Materials and methods

2.1. Animals

Male C57/BL6 mice (6–10 weeks of age, Harlan, The Netherlands) were housed (2–4 mice per cage) for at least one week before experiments started. All animals were kept on a light/dark cycle of 12 h (lights on at 8 a.m.; humidity 55% ± 15; room temperature kept at 22 °C ± 2) and food and water were given without restriction. The behavioral experiments or decapitations were performed between 8:30–11:30 a.m. and approved by the local Animal Ethics Committee of the University of Amsterdam (DED210) and University of Utrecht (DED2011.I.12.113). All efforts were made to minimize suffering of the animals.

2.2. Stress and synaptic plasticity

The novel 11β-hydroxysteroid dehydrogenase type 1 inhibitor (UE2316, 10 mg/kg), shown to be a more potent enzyme inhibitor than the previously reported UE1961 (Sooy et al., 2010) and to reduce corticosterone regeneration in CNS (Webster et al., 2011; Cobice et al., 2013), was injected intraperitoneally one hour before stress. Stress was applied by exposing the animals to a novel environment (cage) for 20 min. Control animals were left undisturbed in their home cage. Immediately after stress, the mice were decapitated. The brain was rapidly removed and placed in ice-cold aCSF containing (in mM): NaCl (120), KCl (3,5), $MgSO_4$ (1,3), NaH_2PO_4 (1.25), $CaCl_2$ (2.5), glucose (10) and $NaHCO_3$ (25), pH 7.4, and continuously gassed (mixture of 95% O_2–5% CO_2). Next, dorsal hippocampal slices (350 μm) were made using a vibratome (LEICA VT 1000S) and stored in aCSF at room temperature for >1 h. Slices were transferred into a slice chamber where they were kept submerged in aCSF at a temperature of 32 °C. The aCSF bath was refreshed at a rate of 2.5 ml/min and equilibrated with 95% O_2 and 5% CO_2. A bipolar stimulation electrode (60 μm stainless-steel wires insulated except for the tip) was placed on the Schaffer collaterals, and glass recording pipettes (filled with aCSF) were positioned in the CA1 stratum radiatum to record field Excitatory Postsynaptic Potentials (fEPSPs). At the start of the experiment, an input–output curve was established to record the slope of the fEPSP, from which maximal and half-maximal slope as well as the corresponding maximal and half-maximal stimulus intensity were determined (Wiegert et al., 2006). The half maximal stimulus intensity that was calculated was used throughout the remainder of the recording session. After establishing the input–output curve, we monitored baseline synaptic transmission using half-maximal stimulation intensity with a frequency of 0.033 Hz. In some cases, a population spike superimposed on the fEPSP was seen when stimulating at half-maximal stimulation intensity. In these cases, we slightly reduced the stimulation intensity to spike threshold level for the population spike. When signals were stable during a baseline period of 20 min, repetitive tetanic stimulations (10 Hz; 900 pulses) were applied, after which recordings proceeded for another 60 min at a frequency of 0.033 Hz; this stimulation paradigm is very sensitive to the effects of corticosterone (Wiegert et al., 2006). Two consecutive traces were averaged to represent the mean per minute. Data were acquired, stored, and analyzed using Signal 2.16 (Cambridge 159 Electronic Design, United Kingdom). In a separate series of slices, paired pulse stimulation (at stimulus intervals of 50 ms or 200 ms) was applied at half maximal stimulus intensity and fEPSPs were recorded.

2.3. Contextual fear conditioning

Animals were trained in a fear conditioning chamber (Context A, W × L × H: 30 cm × 24 cm × 26 cm) that contained a grid floor with 37 stainless steel rods and was connected to a shock generator and sound generator (Med-Farm LION-ELD) developed in-house. The 11β-hydroxysteroid dehydrogenase type 1 inhibitor (UE2316, 10 mg/kg, Cobice et al., 2013) or vehicle (Veh, propylene glycol; Zhou et al., 2010) was injected intraperitoneally one hour before training. During training, one animal at a time was placed into context A. After three minutes of free exploration, one mild footshock (2 s, 0.4 mA) was delivered. Thirty seconds after the end of the footshock, the mouse was placed back into its home cage. Freezing behavior, defined as no body movements except those related to respiration, was determined every 2 s throughout training. Twenty four hours later, one animal at a time was placed in context A for 3 min without receiving footshock and freezing behavior was scored.

2.4. Tone-cued fear conditioning

A separate group of animals was handled for three days and placed for 20 min/day in context B which has the same size as context A, but different contextual background (odor, texture and color). On the day of tone-cue training, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor (UE2316, 10 mg/kg) or vehicle (Veh, propylene glycol; Zhou et al., 2010) was injected intraperitoneally one hour before training. During training, one mouse at a time was placed into context A. After three minutes of free exploration, the mouse was exposed to a tone (100 dB, 2.8 kHz) that lasted for 30 s and co-terminated with a mild footshock (2 s, 0.4 mA). Thirty seconds later, the animal was placed back in its home cage. Twenty four hours later, one mouse at a time was placed in context B. After 3 min of free exploration, the animal was exposed to one tone for 30 s. Freezing behavior was scored during exploration, tone- exposure and 30 s after tone exposure.

2.5. Corticosterone assay

Blood samples were determined from randomly selected vehicle, stressed, UE2316-treated and UE2316-treated stress animals. Trunk blood was collected and centrifuged for 15 min at 4000 r.p.m. at 4 °C. Plasma was stored at −80 °C until processed using a commercially available radioimmunoassay according to the manufacturer's instructions (RIA; MP Biomedicals Inc., Santa Ana, CA, USA). Corticosterone levels were determined as described before (Sarabdjitsingh et al., 2010).

2.6. Statistical analyses

Plasma cortisterone levels, baseline and high-frequency induced synaptic characteristics, and paired pulse facilitation were analyzed by two-way ANOVA. In case of main or interaction effects, planned post-hoc pairwise group comparisons were carried out, corrected with Bonferroni for multiple testing. Paired pulse facilitation was expressed as [(slope of the second fEPSP/slope of the first fEPSP) * 100%] and synaptic potentiation as fEPSP slope % of baseline. In the fear conditioning paradigm, freezing was expressed as % of the time that was studied and differences between experimental groups were examined using unpaired Student's *t*-tests. *p* values <0.05 were considered significantly different.

3. Results

3.1. Plasma corticosterone levels

Plasma corticosterone levels for the four experimental groups are shown in Table 1. In all groups, corticosterone levels were above what was expected at this time of the day, indicating that the

Table 1
Plasma corticosterone levels after UE2316 and/or stress treatment.

Group	N	Corticosterone (ng/ml)
Vehicle	6	225.8 ± 31.6
Vehicle + Stress	9	324.1 ± 31.4*
UE2316	3	122.4 ± 56.1
UE2316 + Stress	8	180.7 ± 25.1#

* and # indicate $p < 0.05$ compared to Vehicle and Vehicle + Stress respectively.

injection procedure itself was probably mildly stressful. Statistically significant main effects of both stress ($F_{(1, 22)} = 5.07$; $p < 0.05$) and UE2316 treatment ($F_{(F1,22)} = 12.6$; $p < 0.01$) were found (Table 1), though there was no interaction effect. Supporting the effectiveness of the 11β-HSD type 1 inhibitor, UE2316 prevented the effect of novelty stress on plasma corticosterone levels (UE2316 + stress: 180.7 ± 25.1 ng/ml; vehicle + stress: 324.2 ± 31.4 ng/ml; $t_{(15)} = 3.52$, $p < 0.05$).

3.2. Stress and CA1 synaptic transmission

We first tested if a single injection with UE2316 prior to stress exposure affects CA1 synaptic transmission and the ability to induce LTP in hippocampal slices prepared after stress or control treatment. Baseline synaptic characteristics, i.e. baseline slope of the fEPSP (here defined as the response closest to the half-maximal response which did not show a population spike), maximum slope of the fEPSP, baseline half maximal stimulus intensity and maximal stimulus intensity, were not significantly affected by exposure to stress (Table 2). Also, treatment with UE2316 did not affect baseline synaptic characteristics, nor did we observe an interaction effect (Table 2).

To examine whether stress affected paired pulse facilitation, double pulse responses were recorded at 50 ms or 200 ms intervals. For the stimulus interval of 50 ms, a significant interaction was found between stress and treatment ($F_{(1, 31)} = 5.76$; $p < 0.05$), indicating that UE2316 treatment affected paired pulse facilitation differently in stressed versus control animals (Fig. 1). No main effect of stress or UE2316 treatment on paired pulse facilitation was observed, either at the 50 ms or 200 ms interstimulus interval. Also no interaction effect was found at 200 ms ($F_{(1, 31)} = 2.66$; $p > 0.05$).

In control mice hippocampal slices, stimulation in CA1 stratum radiatum with 900 pulses at 10 Hz yielded significant synaptic potentiation, which lasted for at least one hour (paired Student's *t*-test; mean baseline vs mean 60 min post-tetanic period, $p < 0.001$; Fig. 2A and B). Two-way ANOVA did not show a significant main effect of either stress or UE2316 treatment. However, a significant interaction was found ($F_{(1, 28)} = 19.6$; $p < 0.001$). Hippocampal CA1 synaptic potentiation in vehicle-treated animals was significantly reduced by stress ($t_{(14)} = 3.95$; $p < 0.01$; 25% reduction vs non stress; Fig. 2A and B). Treatment with UE2316 did not affect basal synaptic potentiation, but completely prevented the effect of stress on synaptic potentiation ($t_{(14)} = 4.56$; $p < 0.01$; 28% increase vs vehicle + stress; Fig. 2A and B).

3.3. Fear conditioning

We next examined if the ability of UE2316 to prevent stress-induced changes in electrical activity occurs in parallel with a (stressful) hippocampus-dependent learning paradigm such as contextual fear conditioning. During exploration in context A (before exposure to the footshock) animals did not display freezing behavior (Fig. 3A). After the footshock, animals showed low levels of freezing behavior, which were not significantly different between vehicle- and UE2316 treated animals. UE2316 treatment prior to training significantly reduced the freezing response measured during the retention test, 24 h after treatment (75% reduction compared to vehicle controls and $p < 0.01$) (Fig. 3B and C).

We also tested the cued variant of the task, which is strongly amygdala-dependent. Both vehicle-treated and UE2316-treated animals did not display freezing behavior before and during exposure to the tone in context A (Fig. 4A). After the footshock, both vehicle- and UE2316-treated animals displayed freezing behavior, which was comparable for both experimental groups. During the retention test, 24 h later, both UE2316- and vehicle-treated animals displayed low levels of freezing behavior when exposed to context B alone. However, during and after exposure to the tone in context B, freezing behavior increased significantly (~60% freezing) in both experimental groups with no effect of UE2316 treatment (Fig. 4B).

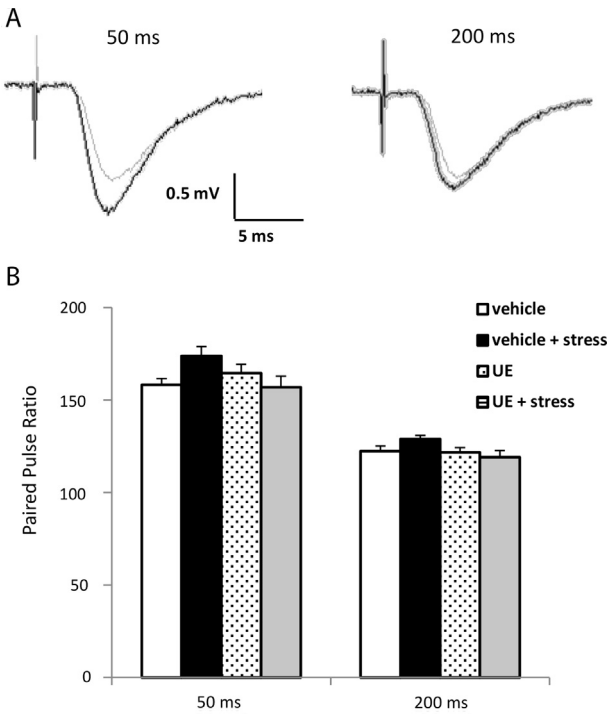

Fig. 1. Paired Pulse Ratio A) Representative fEPSP traces of the paired pulse ratio recorded in the CA1 area of a vehicle-treated mouse, at 50 ms (left) and 200 ms interval (right). To allow comparison between traces, the response to the first (gray) and second pulse (black) are here superimposed. At the 50 ms interval, the response to the second pulse is enhanced compared to the response to the second pulse. Such facilitation is not the case with the 200 ms interval. B) Paired pulse ratio (expressed as [slope second pulse/slope first pulse] * 100%) in the hippocampal CA1 area at 50 ms and 200 ms interstimulus interval. UE = UE2316. Vehicle: $n = 10$; Vehicle + Stress: $n = 10$; UE: $n = 8$; UE + Stress: $n = 7$. Data are means ± SEM.

Table 2
Baseline synaptic characteristics.

Group	N	Baseline slope	Max slope	Half Max SI	Max SI
		(mV/ms)	(mV/ms)	(mV)	(mV)
Vehicle	8	632 ± 57	1488 ± 127	1.84 ± 0.02	2.20 ± 0.08
Vehicle + Stress	8	651 ± 60	1574 ± 137	1.90 ± 0.02	2.40 ± 0.04
UE2316	8	592 ± 60	1499 ± 228	1.87 ± 0.02	2.25 ± 0.05
UE2316 + Stress	8	627 ± 42	1533 ± 87	1.84 ± 0.022	2.13 ± 0.06

4. Discussion

Previous work has shown that deficiency or inhibition of 11β-HSD1 prevents or ameliorates deficits in cognition that occur with aging, a state associated with elevated glucocorticoid levels. However, any impact of 11β-HSD1 manipulation during an acute rise in glucocorticoid levels of young animals, as occurs after a stressful event, has not been examined. Our results show that inhibiting 11β–HSD1 acutely prevents the effects of stress on hippocampal synaptic plasticity and reduces contextual fear conditioning, while leaving cue fear conditioning undisturbed.

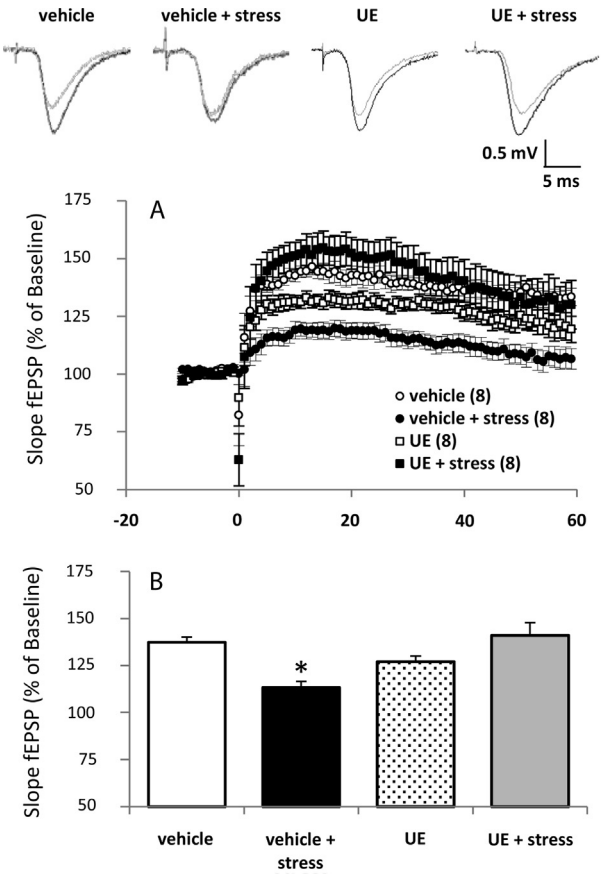

Fig. 2. Effect of stress and UE2316 on hippocampal synaptic potentiation A) Inset on top: Representative individual fEPSP traces taken from each treatment group. The gray traces represent the baseline fEPSP, the black trace was taken between 50 and 60 min after tetanic stimulation. Graph: Stimulation with 900 pulses at 10 Hz yielded synaptic potentiation in the CA1 area of hippocampal slices from control animals. Synaptic potentiation was suppressed in animals pre-exposed to novelty stress. This effect was prevented by pretreatment with UE2316 (UE). B) Synaptic potentiation over 60 min (i.e. from 0 to 60 min post-tetanus) was impaired after exposure to stress but prevented by UE2316 pretreatment. *, $p < 0.01$, vehicle compared to vehicle + stress. Vehicle: $n = 8$; Vehicle + Stress: $n = 8$; UE: $n = 8$; UE + Stress: $n = 8$. Data shown are means ± SEM.

4.1. Synaptic transmission

Exposure to stressful events or elevated corticosterone level enhances synaptic insertion of AMPA receptors (Groc et al., 2008; Martin et al., 2009; Yuen et al., 2009), thus promoting spontaneous synaptic transmission, for instance in the hippocampus (Karst and Joëls, 2005); this is a genomic GR-dependent phenomenon. The insertion of AMPA receptors may elevate the threshold for synaptic strengthening of novel input (an example of metaplasticity) and reduce the ability to elicit long-term potentiation in the dorsal hippocampus >1 h after stress, as has been reported consistently (Kim et al., 1996; Pavlides et al., 1996; Alfarez et al., 2002; Kim and Diamond, 2002; Krugers et al., 2010; Groc et al., 2008). Conversely, corticosterone facilitates the ability to elicit long term depression (LTD) (Xu et al., 1997; Xiong et al., 2004; Wong et al., 2007; Niehusmann et al., 2010). Together, these complex effects of stress hormones on synaptic function may protect information related to the stressful event: novel information reaching the same neural network hours after the initial learning event must be salient enough to overcome this threshold and be stored (Krugers et al., 2010). In this manner, corticosterone, via GR activation, could promote storage of relevant information. Our current data suggest that regeneration of corticosterone from the inert 11-keto metabolite is a critical step in this process. Whether or not this conversion takes place locally -in the hippocampus- cannot be inferred from the current experiment. Our data show that plasma corticosterone levels are lower after stress in UE2316 treated animals which could contribute to the effects of UE2316 on synaptic plasticity and behavior. The effect of UE2316 on plasma corticosterone levels might be explained by enhanced metabolic clearance rate of corticosterone. Notably, earlier studies have demonstrated that a comparable UE compound (UE1961) does reduce the conversion of the 11-keto metabolite into active corticosterone in rodent hippocampus and cortex (Sooy et al., 2010). In agreement, UE2316 does affect regional brain steroid concentrations (Cobice et al., 2013), and brain corticosterone levels are reduced by UE2316 treatment over and above any effect of the inhibitor on plasma corticosterone levels (Yau et al., unpublished data). Regardless of the site of action, we conclude that a single injection of the 11β−HSD1 inhibitor UE2316 prevents the impairing effect of stress on subsequent hippocampal synaptic plasticity, i.e. prevents the elevation in threshold for synaptic strengthening of novel input.

Preventing enzymatic regeneration of corticosterone by administering UE2316 did not significantly affect basal hippocampal transmission, implying that the enzyme (and hence the level of corticosterone under non-stressed conditions) is not crucial for basal transmission. This observation agrees with most studies examining effects of corticosterone on basal CA1 hippocampal transmission, reporting little effect of the hormone (reviewed in Joëls et al., 2012). Moreover, administration of UE2316 did not affect hippocampal synaptic plasticity in mice that were not exposed to novelty stress. This suggests that regeneration of corticosterone is not required for the ability to induce and maintain synaptic plasticity under non-stressed (or mildly stressed) conditions. Whether UE2316 prevents the effect of stress on LTD remains to be established.

4.2. Behavior

Preventing regeneration of corticosterone from the inert 11-keto metabolite interferes with stress-induced effects on synaptic

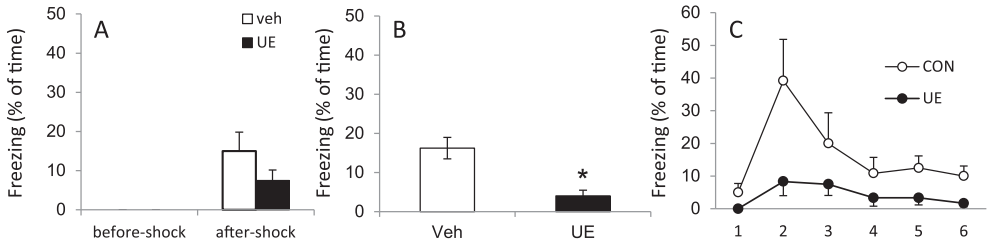

Fig. 3. Effect of UE2316 (UE) on Contextual Fear Conditioning A) Training: Freezing behavior (expressed as % of time) before and after exposure to the footshock in context A. B) Memory: Freezing behavior (expressed as % of time) 24 h after training in context A. C) Freezing behavior expressed over 6 blocks of 30 s, 24 h after training in context A. *, $p < 0.05$. Vehicle: $n = 8$; UE: $n = 8$. Data shown are means ± SEM.

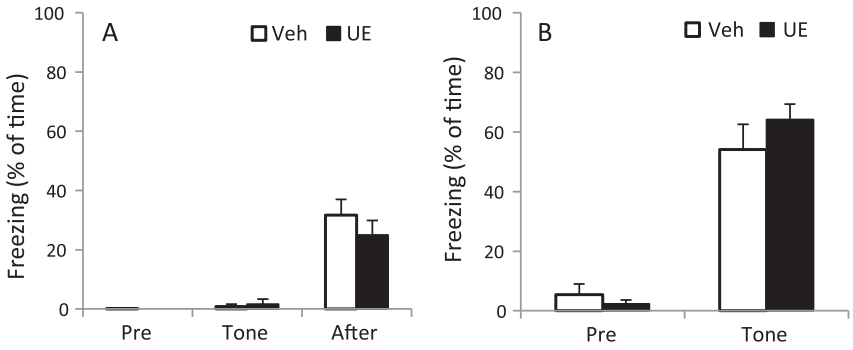

Fig. 4. Effect of UE2316 on Cued Fear Conditioning A) Training: Freezing behavior (expressed as % of time) before exposure to the tone, during exposure to the tone and after exposure to the footshock in context A. B) Memory: Freezing behavior (expressed as % of time) was measured in context B before exposure to the tone (Pre) and after exposure to the tone (Tone). Vehicle: $n = 8$; UE: $n = 8$. Data shown are means ± SEM.

plasticity. This is predicted to impair storage of contextual information gathered under stressful conditions. In a hippocampus-dependent test known to be modulated by glucocorticoids, administration of corticosterone or GR agonists promotes memory consolidation, as demonstrated in various tasks including contextual fear conditioning (e.g. Oitzl and de Kloet, 1992; Sandi and Rose, 1994; Pugh et al., 1997a,b; de Kloet et al., 1999; Oitzl et al., 2001; Joëls et al., 2006; Roozendaal et al., 2006, 2009; Zhou et al., 2010). The effects of GR activation on memory consolidation involve genomic actions (Oitzl et al., 2001) but may also involve more rapid epigenetic effects (Roozendaal et al., 2010). In addition, activation of MRs has been implicated in fearful memory formation. Genetic interference with MRs or blocking MRs using spironolactone, hampers spatial memory (Berger et al., 2006) and contextual fear conditioning (Zhou et al., 2010). Our observation that inhibition of 11β–HSD1 impairs contextual fear conditioning in a mild stimulation paradigm implies that this enzyme and its regeneration of corticosterone are indeed important for contextual fear conditioning. A likely explanation is that 11β–HSD1 inhibition interfered with stress-induced rises in intracellular corticosterone level resulting in less activation of GRs. GRs enhance memory formation for arousing events, explaining the impairment in contextual fear conditioning when the generation of corticosterone is inhibited. We here used a mild stimulation protocol, because this was earlier shown to be highly sensitive to the presence of corticosteroids, as opposed to conditions using a higher shock intensity (e.g. Zhou et al., 2010). We cannot exclude, however, that 11β–HSD1 may also be effective when using stronger stimulation paradigms.

Interestingly, inhibiting 11β–HSD1 did not affect memory formation in a cue fear conditioning paradigm, which critically depends on amygdala function. While 11β–HSD1 is present in the amygdala (Pelletier et al., 2007), GR expression in these cells is considerably lower than in the hippocampus. Possibly, local regeneration of corticosterone is only effective when high levels of GR are present to mediate the effects, such as may occur with stronger stimulation conditions. Alternatively, the lack of effect of UE2316 on cue fear conditioning might be due to relatively low expression of 11β–HSD1 in young mice since decreased cued fear conditioning has been observed in aged (but not young) 11β–HSD1 knockout mice (N. Wheelan and JLW Yau, unpublished data). Also, cued fear conditioning is a very robust learning paradigm, as evident from the substantial levels of freezing during the retention trial found in the present study. Since corticosteroid hormones subtly modulate memory formation (de Kloet et al., 1999), the cued memory trace is possibly already so strong that it is not prone to modification by inhibition of 11β–HSD1.

In summary, we show that a single peripheral injection with the 11β–HSD1 inhibitor UE2316 is sufficient to prevent stress-induced actions on hippocampal synaptic plasticity and on fear memory in young mice. While fear memory formation is beneficial under most conditions, it may be a risk factor for trauma-related psychopathology in genetically vulnerable individuals. In anticipation of traumatic events (e.g. in professionals with a high risk on trauma exposure) 11β–HSD1 inhibitors may provide an interesting tool for new strategies aimed at prevention of psychopathology.

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