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No effects of hydrocortisone and dexamethasone on pain sensitivity in healthy individuals

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Abstract

Background: There is some evidence that stress-induced cortisol increase leads to a decrease in pain, while lowering cortisol levels enhances pain sensitivity, but no study has yet investigated both pharmacological enhancement and reduction of cortisol levels in the same individuals.
Methods: Firstly, we tested in 16 healthy individuals whether the treatment with hydrocortisone and dexamethasone, respectively, results in altered pain thresholds. Secondly, we aimed to test whether hormone effects are different across the pain range by using ratings for pain stimuli with varying intensity; and thirdly, we tested whether cortisol levels influence the discrimination ability for painful stimuli.
Results: Despite substantial effects of dexamethasone and hydrocortisone administration on cortisol levels, no effect of these drugs was seen in terms of pain sensitivity (pain threshold, pain rating, pain discrimination ability), although comprehensively examined. However, in the placebo condition, a significant negative correlation between cortisol and pain thresholds was seen. Similarly, there were also strong negative associations between cortisol levels in the placebo condition and pain thresholds after drug treatment (especially after hydrocortisone).
Conclusion: These findings suggest that short-term variations of cortisol do not influence pain sensitivity whereas, in general, high levels of cortisol are associated with increased pain sensitivity, at least for weak to moderate stimuli.

1. Introduction

Stress is a condition with complex effects on pain sensitivity. Thus, alterations of the hypothalamus–pituitary–adrenal (HPA) axis have been found in many functional pain disorders such as fibromyalgia (Wingenfeld et al., 2008), rheumatoid arthritis (Zoli et al., 2002) and low back pain (Geiss et al., 1997). Contrary results exist with depression as mediating factor (Wingenfeld et al., 2009, 2010). However, in pain patients, cortisol and pain are likely bidirectional related and therefore difficult to study causally. Thus, experimental studies in healthy subjects have to sort out the causal relationship between cortisol and pain before pathophysiological relationships can be determined.

Some experimental studies could demonstrate an association between cortisol and pain sensitivity. A decrease in pain sensitivity after a cognitive laboratory stressor was found to be associated with a strong cortisol response (Hoeger Bement et al., 2010). Sex seems to matter because high cortisol concentrations beforehand predicted lower pain reports during and after the cold pressor test only in men (al'Absi et al., 2002). Finally and confusingly, a correlational study suggests that greater cortisol reactivity is related to greater pain severity (Goodin et al., 2012). In accord, it has been reported that cortisol leads to a decrease in pain

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What's already known about this topic?

- There is some evidence that stress-induced cortisol increase leads via central noninflammatory mechanisms to a decrease in pain, while lowering cortisol levels enhances pain sensitivity.

What does this study add?

- No study has yet investigated both, pharmacological enhancement and reduction of cortisol levels in the same individuals. We tested the effects of hydrocortisone and dexamethasone on experimental pain sensitivity comprehensively by assessing pain thresholds, numerical ratings of stimuli across the pain range and an index of the discrimination ability for painful stimuli. We found that (1) dexamethasone and hydrocortisone administration had effects on cortisol but no effect on pain sensitivity; and that (2) basal cortisol and pain thresholds are negatively correlated.

thresholds (Choi et al., 2012) as well as an enhancement of pain sensitivity in response to thermal stimuli (Crettaz et al., 2013). Thus, the association between stress, the related release of stress hormones and pain sensitivity has remained unclear.

Pharmacological studies may also be useful to investigate the effects of cortisol in humans. Schwegler et al. (2010) could show that administrating 20 mg of exogenous cortisol did not influence pain threshold and pain tolerance using heat pain stimuli. On the contrary, a dosage of 40 mg of hydrocortisone significantly attenuated capsaicin-induced pain (Michaux et al., 2012), suggesting effects either of higher dosages or on specific pains.

Cortisol levels can be lowered by dexamethasone. This manipulation was used by Kemppainen et al. (1990) while measuring dental pain thresholds in response to a cycle ergometer test. Dental pain thresholds were elevated after the stressor; this effect was significantly reversed by dexamethasone. Metyrapone induces hypocortisolism without lowering HPA axis activity (Kuehl et al., 2010). This form of hypocortisolism was found to decrease pain thresholds. However, enhanced corticotrophin releasing hormone (CRH) levels might have contributed to the effect although no analgesic effects of CRH could be revealed in our group (Lautenbacher et al., 1999).

To our knowledge, no study has yet investigated both pharmacological enhancement as well as reduction of cortisol levels in the same individuals and their effects on pain sensitivity. The aim of the study was threefold: (1) to examine differences in pain sensitivity between experimental conditions (hydrocortisone, dexamethasone); (2) to determine the correlations among all cortisol and pain sensitivity variables; and (3) to explore sex as a potential influence in addition to the experimental conditions on pain sensitivity. We used a comprehensive set of experimental pain parameters (pain threshold, suprathreshold pain ratings, discrimination ability) to not miss any possible change in pain sensitivity.

2. Materials and methods

2.1 Participants

Sixteen healthy volunteers, seven men and nine women, participated in the study. The mean age was 38.4 years [standard deviation (SD) 5.0, median 37] with a range from 31 to 50 years.

Exclusion criteria were the following: any severe disease during the prior 6 months, i.e., central nervous system relevant somatic diseases (e.g., neurological diseases), metabolic diseases (e.g., thyroid disease, diabetes), organic shift in cortisol secretion (e.g., Morbus Cushing), immune-mediated diseases, cardiovascular diseases or other current infections and hypertension. Further exclusion criteria were pregnancy, current infection, any use of medication (last 4 weeks), any current or lifetime psychiatric disorders or cognitive impairment. These criteria were assessed in a telephone interview and an anamnestic screening session just prior to the experiment.

The protocol was approved by the ethics committee of the medical faculty of the University of Marburg, Germany; all subjects gave written, informed consent and received a 125 Euro incentive. Advertisement for the study was posted in the local culture and event magazine. The study took place in the university hospital for psychiatry in Marburg, which guaranteed constant medical support. The participants were asked to report any side-effect at any time immediately to the investigator (SW).

2.2 Procedure

A double-blind randomized placebo-controlled study design was used. All participants were tested three times (within-subject design) with a minimum of 72 h between the examinations. The participants were randomly allocated to the treatments. The experimental drugs were filled into identically looking capsules by the university pharmacy. These capsules were handed over to one of the senior authors (SL) in marked compartments, who handed them in turn over to the investigator (SW) according to the randomization protocol. Therefore, the investigator was blind as regards the respective treatment condition.

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Table 1 Study protocol.

Treatment condition	First oral intake 11 p.m. (the day before)	Second oral intake 2 p.m. (0 min)	Third oral intake 3 p.m. (+60 min)	+65 min	+75 min	+175 min
High cortisol condition	Placebo	60 mg hydrocortisone	60mg hydrocortisone	Pain threshold 1	Pain threshold 2	Ratings
Cortisol suppression	4 mg dexamethasone	Placebo	Placebo	Pain threshold 1	Pain threshold 2	Ratings
Placebo condition	Placebo	Placebo	Placebo	Pain threshold 1	Pain threshold 2	Ratings

The study protocol is presented in Table 1. The day before testing, a pill containing either placebo or 4 mg dexamethasone was taken at 11 p.m. at home. The subjects were instructed how to behave properly and that misconduct would become conspicuous by the control of the hormone levels.

The day after, subjects received an intravenous catheter 1 h prior to the test. At 2 p.m., they took the second pill, containing 60 mg of hydrocortisone or placebo, respectively, which was repeated at 3 p.m. Two oral boluses were given separated by 1 h to prevent blood concentrations of hydrocortisone from decreasing too early.

The sequence of the three test conditions, namely sessions with placebo, dexamethasone and hydrocortisone, was counterbalanced. Our randomization protocol (randomization due to random tables) determined for each study entry the sequence of the three conditions in which the new subject was tested. For that purpose, sextets of sequences were set up, consisting of the sequences PLACEBO-DEX-HYDRO, PLACEBO-HYDRO-DEX, HYDRO-PLACEBO-DEX, HYDRO-DEX-PLACEBO, DEX-HYDRO-PLACEBO, DEX-PLACEBO-HYDRO. The first subject entering the sextet was randomly assigned to one of the six sequences; the second subject was randomly assigned to one of the five remaining sequences, and so on. This protocol guaranteed a complete balance of all possible sequences of treatments after completion of each sextet.

Blood samples were drawn at 30-min intervals with the first sample drawn at 2 p.m. (0 min, +30, +60, +90, +120, +150, +180, +210).

Pain sensitivity was measured at three time points (see Table 1): +65 min after second drug intake, +75 min after second drug intake and +185 min after second drug intake.

2.3 Tests of pain sensitivity

The device used for the subsequent tests was the computer-controlled stimulation unit PATH-Tester MPI100 (Phywe GmbH, Göttingen, Germany) which produces thermal stimuli by a Peltier thermode (stimulation area: 6 cm^2; contact pressure: 0.4 N/cm^2). The long edge of the thermode was attached to the right lateral dorsum pedis at a distance of about 1 cm from the toes. The study protocol was analogue to a former study of the senior author (Lautenbacher et al., 1994).

2.3.1 Pain threshold 1 – method of limits

The pain threshold was determined by having the subject stop a temperature rise of 0.7 °C/s, starting from 38 °C, as soon as the participant felt pain. There were eight trials. The threshold was computed as the mean of the peak temperatures of the last five trials.

2.3.2 Pain threshold 2 – method of adjustment

This threshold measure was designed to be free of reaction time influences. The subject had to adjust the temperature to the level of her/his pain threshold with heating and cooling buttons, starting from 38 °C. The change in temperature stopped when the subject released the buttons. Seven trials were conducted. The threshold was computed as the mean of the last six trials.

2.3.3 Pain ratings

To assess subjective pain ratings across the pain range, two series of heat pain stimuli were administered varying in steps of 1 °C from 38 °C to 48 °C (series 1) and 37 °C to 47 °C (series 2), respectively. Accordingly, 11 stimuli were administered per series. The sequence of the 11 stimuli of series 1 ranging from 38 °C to 48 °C was randomized (randomization due to random tables) with one limitation. The difference of subsequent stimuli was not allowed to be larger than 3 °C to avoid strong contrasts. The sequence of series 2 ranging from 37 °C to 47 °C was identical.

The stimuli had a sawtooth form; the rate of temperature change was 1.5 °C/s, the baseline temperature was set to 36.0 °C. Therefore, the duration of the least intense stimulus (37.0 °C) was 1.3 s whereas the duration of the most intense stimulus (48.0 °C) was 16 s. However, the subjects were asked to rate both intensity and unpleasantness always when the temperatures peaked.

The participants rated the stimuli on two horizontal visual analogue scales (VAS) with lines 10 cm long to indicate pain intensity and unpleasantness.

2.3.4 Pain discrimination ability

In the second series, each stimuli was exactly 1 °C below the related stimuli of the first series. The temperature difference between series 1 and 2, namely 1 °C on average, was scheduled to allow assessment of the discrimination ability for such a temperature difference (Lautenbacher et al., 2002). A score for discrimination ability was computed using the difference of 1 °C between stimulus series 1 (38–48 °C) and stimulus series 2 (37–47 °C). More precisely, the differences between the VAS ratings for those pairs of stimuli from series 1 and series 2 with a temperature difference of 1 °C were

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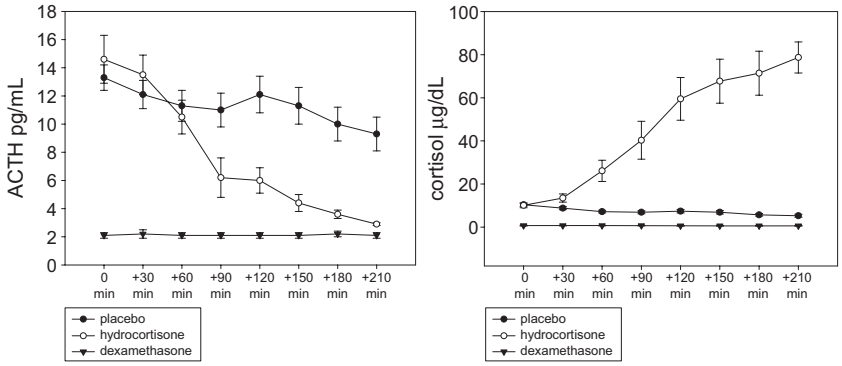

Figure 1 ACTH and cortisol levels (mean/standard error of the mean) in the three treatment conditions: dexamethasone, hydrocortisone and placebo (n = 16) (adapted from Wingenfeld et al., 2011).

determined, e.g., VAS rating 38 °C – VAS rating 37 °C, VAS rating 39 °C – VAS rating 38 °C, and so on. Then, these VAS rating differences were averaged per person for the intensity or the unpleasantness ratings to provide parameters of how well an individual can differentiate between temperature differences of 1 °C in such a temperature range [see also Lautenbacher et al. (2002) and Lautenbacher et al. (1999) for detailed description].

The rationale behind assessing pain discrimination ability was the following: Hormonal effects might have increased sensory/perceptual noise. Noise increases might not become obvious by psychophysical parameters targeting the levels of sensations but might have to be tackled by special discrimination parameters. The basic idea of our discrimination parameter is that stimuli separated by 1 °C should have been rated differently by a certain number of VAS units. An increase in sensory/perceptual noise should reduce this psychophysical differentiation and should have become obvious in the present study by a reduction of the differences in VAS ratings between the two stimulus series.

2.4 Biochemical analyses

Blood was collected in EDTA tubes, immediately centrifuged, and the plasma was stored at –80 °C until assayed. Plasma samples were assayed using commercial enzyme-immunoassay for cortisol and chemiluminiscence immunoassay for adrenocorticotropin (ACTH) (DRG, Marburg, Germany). Inter- and intra-assay coefficients of variance were below 7% for all analyses.

2.5 Statistics

Statistical analyses were performed using SPSS Version 15.0 (SPSS, Chicago, IL, USA). Cortisol levels were analysed with a 3×8 analysis of variance (ANOVA) with repeated measurements, with the two main factors being treatment condition (placebo, hydrocortisone and dexamethasone) and time (8 measurement points). As measure for total cortisol, the area under the curve (AUC) was calculated (Pruessner et al., 2003) to analyse associations between cortisol and pain sensitivity. Data from the pain threshold and pain discrimination ability tests were analysed using univariate ANOVA with repeated measurement (treatment condition). To analyse the pain ratings (VAS), two independent ANOVAs with repeated measurement were conducted with the factors treatment condition and temperature (12 measurement points varying from 37 °C to 48 °C). Pain intensity and unpleasantness ratings, respectively, served as dependent variables. To analyse sex effects, ANOVAs were also performed including sex as an additional group factor. Effect sizes for the analyses are given as η^2.

Additionally, Pearson's correlation analyses were performed to analyse the association between cortisol (AUC) and pain sensitivity.

The alpha level for significance was set to 0.05 as long as nothing else was specified.

3. Results

3.1 Cortisol and ACTH levels

These analyses have been described in detail in a publication by Wingenfeld et al. (2011). Here, we summarize only the most important results (see also Fig. 1): For cortisol levels, we found significant effects of the main factors treatment condition ($F_{df2,30} = 46.33$, $p < 0.001$, $\eta^2 = 0.75$) and time ($F_{df7,105} = 28.36$, $p < 0.001$, $\eta^2 = 0.65$), as well as a significant treatment by time interaction effect ($F_{df14,210} = 31.73$, $p < 0.001$, $\eta^2 = 0.68$). All treatment conditions differed significantly from each other (all $p < 0.001$). Similar effects occurred for ACTH ($\eta^2 = 0.51$ –0.81). Thus, the intended manipulation was successful: after dexamethasone administration, cortisol levels were suppressed at the time of testing, and after hydrocortisone administration, cortisol was markedly enhanced.

3.2 Pain sensitivity: treatment induced changes

3.2.1 Pain threshold 1

Using univariate ANOVA with repeated measurement, there was no effect of treatment condition on pain threshold 1 ($F_{2,30} = 0.29$, $p = 0.75$, $\eta^2 = 0.02$).

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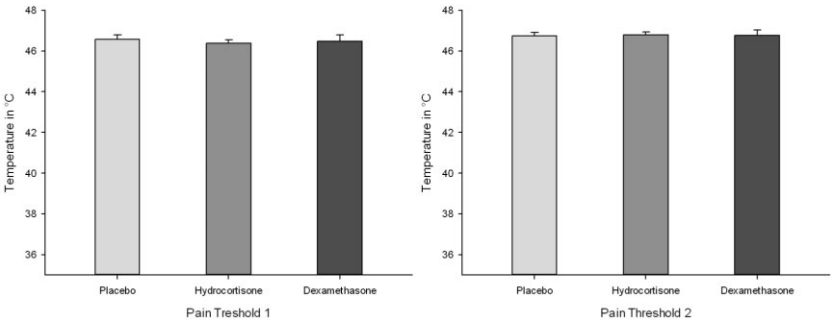

Figure 2 Pain threshold 1 and 2 (mean/standard error of the mean) in the three treatment conditions: dexamethasone, hydrocortisone and placebo (n = 16).

3.2.2 Pain threshold 2

There was also no effect of treatment condition on pain threshold 2 ($F_{2,30} = 0.02$, $p = 0.98$, $\eta^2 < 0.01$).

The results are presented in Fig. 2.

3.2.3 Pain ratings

For pain intensity, there was no effect of treatment condition ($F_{2,30} = 0.21$, $p = 0.81$, $\eta^2 = 0.01$) nor a treatment condition by temperature interaction effect ($F_{22,330} = 1.70$, $p = 0.14$, $\eta^2 = 0.10$). Means (SD) are presented in Table 2. There was a significant effect of temperature ($F_{11,165} = 132.72$, $p < 0.001$, $\eta^2 = 0.89$), showing higher intensity ratings for higher temperatures. The same picture emerged when analysing the rating of unpleasantness: main effect of treatment condition ($F_{2,30} = 0.20$, $p = 0.90$, $\eta^2 < 0.01$), treatment condition by temperature interaction effect ($F_{22,330} = 0.85$, $p = 0.66$, $\eta^2 = 0.03$) and main effect of temperature ($F_{11,165} = 119.12$, $p < 0.001$, $\eta^2 = 0.88$).

3.2.4 Pain discrimination ability

The treatment conditions did also not influence the discrimination ability for temperature difference of 1 °C, neither concerning intensity ($F_{2,90} < 0.01$, $p = 0.99$, $\eta^2 < 0.01$ nor unpleasantness ($F_{2,90} = 0.02$, $p = 0.97$, $\eta^2 < 0.01$) ratings.

Table 2 Ratings of the intensity and unpleasantness of heat pain stimuli [mean (standard deviation)].

Ratings – visual analogue scale		Placebo	Hydrocortisone	Dexamethasone
37 °C	Intensity	2.00 (0.6)	3.81 (0.9)	5.80 (1.9)
	Unpleasantness	0.00 (0.00)	1.25 (0.4)	1.38 (0.3)
38 °C	Intensity	6.69 (1.6)	7.03 (1.5)	6.19 (1.5)
	Unpleasantness	2.63 (0.8)	2.16 (0.6)	1.72 (0.5)
39 °C	Intensity	7.45 (1.7)	7.38 (1.4)	7.88 (1.6)
	Unpleasantness	2.60 (0.8)	2.13 (0.5)	2.22 (0.5)
40 °C	Intensity	11.75 (1.9)	8.91 (1.7)	10.66 (2.1)
	Unpleasantness	5.72 (1.8)	3.28 (1.2)	2.72 (0.7)
41 °C	Intensity	17.66 (3.1)	12.91 (1.6)	12.38 (2.3)
	Unpleasantness	5.56 (1.9)	3.38 (0.7)	2.88 (0.7)
42 °C	Intensity	20.94 (2.7)	21.19 (2.4)	18.31 (1.9)
	Unpleasantness	6.78 (1.8)	9.25 (1.9)	4.34 (0.9)
43 °C	Intensity	24.91 (2.7)	26.66 (3.1)	28.91 (4.1)
	Unpleasantness	12.84 (2.9)	12.22 (3.2)	8.78 (2.2)
44 °C	Intensity	22.75 (2.5)	22.06 (2.5)	24.38 (2.6)
	Unpleasantness	15.28 (3.1)	17.38 (3.3)	17.00 (3.6)
45 °C	Intensity	34.69 (4.1)	34.06 (3.8)	32.09 (3.7)
	Unpleasantness	31.25 (4.8)	32.13 (4.1)	29.00 (4.9)
46 °C	Intensity	68.44 (5.2)	66.63 (4.8)	70.53 (4.5)
	Unpleasantness	60.81 (6.9)	61.25 (5.9)	62.75 (5.9)
47 °C	Intensity	71.63 (5.1)	68.66 (4.8)	71.38 (4.3)
	Unpleasantness	63.53 (6.5)	63.41 (5.4)	64.63 (5.9)
48 °C	Intensity	82.00 (4.8)	81.56 (4.6)	83.38 (4.8)
	Unpleasantness	76.81 (6.1)	78.94 (5.5)	80.69 (5.7)

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Thus, neither enhancing nor reducing cortisol levels affected pain sensitivity in healthy volunteers.

3.3 Pain sensitivity: correlation with cortisol

Pearson's correlation analyses were performed to analyse the association between cortisol (AUC) and pain sensitivity for each treatment condition. When correcting alpha values for multiple testing within each treatment conditions, alpha has to be set to <0.01.

There were negative associations between cortisol and pain sensitivity in the placebo condition. However, results were only marginally significant: pain threshold 1: r = −0.51, $p = 0.05$; pain threshold 2: r = −0.55, $p = 0.03$. Thus, higher cortisol levels were related to reduced pain thresholds.

Furthermore, cortisol levels in the placebo condition were also marginally significantly correlated with pain threshold measurements after hydrocortisone administration (pain threshold 1: r = −0.51, $p = 0.04$; pain threshold 2: r = −0.53, $p = 0.03$), i.e., the higher the cortisol levels the lower were the pain thresholds. The association between cortisol in the placebo condition and pain measurements after dexamethasone failed significance (pain threshold 1: r = −0.47, $p = 0.06$; pain threshold 2: r = −0.35, $p = 0.18$).

Furthermore, pain thresholds after placebo were strongly associated with the pain thresholds after drug administration (pain threshold 1: hydrocortisone r = 0.65, $p = 0.006$; dexamethasone: r = 0.59, $p = 0.02$; pain threshold 2: hydrocortisone r = 0.73, $p = 0.001$; dexamethasone: r = 0.67, $p = 0.004$). Thus, participants with higher pain thresholds in the one condition also showed higher pain thresholds in the other conditions.

3.4 Effects of sex: an exploratory analysis

As sex might have influenced the results, we rerun our analyses including sex as an additional group factor (seven men, nine women). As tested with Kolmogorov–Smirnov test, the dependent variables were mostly normally distributed [men all $p > 0.05$; women all $p > 0.05$ apart from pain threshold 1 ($p = 0.02$) and pain threshold 2 after dexamethasone ($p = 0.03$)].

Concerning pain threshold 1, no main effect of sex, main effect of treatment condition or treatment condition by sex interaction effect could be revealed. The 2 × 3 ANOVA on pain threshold 2 revealed no main effect of sex or main effect of treatment condition. However, a trend significant treatment condition by sex interaction effect ($F_{df2,28} = 3.269$; $p = 0.06$, Huynh-Feldt corrected, $\eta^2 = 0.19$) occurred. While there were no differences between men and women in the placebo and the hydrocortisone condition, groups differed in the dexamethasone condition with higher pain threshold in the male participants [mean (SD) males: 46.24 (0.9), females: 45.59 (1.3)]. Concerning pain ratings, there was no effect by sex.

4. Discussion

Despite substantial effects of dexamethasone and hydrocortisone administration on cortisol levels, no effect of these drugs was seen in terms of pain sensitivity (pain threshold, suprathreshold pain ratings, discrimination ability) although comprehensively examined. However, in the placebo condition, a significant negative correlation between cortisol and pain thresholds was seen. Similarly, there were also strong negative associations between cortisol levels in the placebo condition and pain thresholds after drug treatment, especially after hydrocortisone.

Thus, our hypotheses that altering cortisol level by administration of hydrocortisone or dexamethasone, respectively, results in altered pain sensitivity could not be confirmed. Even in ratings of stronger heat stimuli, which might be closer to clinical pain conditions as regards subjective intensity, no effects of these agents were seen, suggesting no dependency of the algesic action of cortisol on pain severity. Due to the fact that we used relatively high drug dosages, it is unlikely that ineffective treatment produced the little effects. Of note, in terms of peripheral cortisol and ACTH levels, we saw significant changes in response to the drug administration.

These results are in line with several studies which could not unequivocally confirm an association between short-term variations of cortisol levels and pain sensitivity (al'Absi and Petersen, 2003; Schwegler et al., 2010). A study which used public speaking to induce stress and, thus, an increase in cortisol release failed to find an influence of cortisol release on the pain produced by the cold pressor test (al'Absi and Petersen, 2003) while others found increased pain sensitivity in response to psychosocial stress (Choi et al., 2012; Crettaz et al., 2013). Another study performed a more mental stressor, i.e., mental math tasks, and found an opposite association between high cortisol and low pain sensitivity (Hoeger Bement et al., 2010). These contradicting findings suggest that activation of other physiological stress systems than the HPA axis seems to contribute to pain sensitivity. In line with this assumption, al'Absi and Petersen found that

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systolic blood pressure changes during stress mediate pain sensitivity, suggesting the baroreceptors and vagal afferents to play an important role (al'Absi and Petersen, 2003). Considering our findings, it is alternatively likely that psychosocial stress induction leads to stronger influence on pain sensitivity compared with pharmacological manipulation. In future studies, it should be investigated whether the appraisal during stress, varying the perceived threat, influences the association between the physiological stress reaction and pain.

Using drug administration to investigate the effects of cortisol on pain has – not surprisingly – also yielded mixed results. While it has been shown that enhancing cortisol levels via administrating 20 mg of exogenous cortisol did not influence pain threshold and pain tolerance (Schwegler et al., 2010), others found an association between cortisol administration and reduced pain (Michaux et al., 2012). In accord, lowering cortisol levels by administrating dexamethasone resulted in lower pain threshold (Kemppainen et al., 1990). Dexamethasone administration leads not only to lower cortisol release but also to affect the HPA axis at higher levels with reduced ACTH levels. Thus, increased pain sensitivity after dexamethasone might be associated also with lower levels of ACTH or CRH. An alternative is the use of metyrapone, which leads to reduced circulating cortisol but increased ACTH and CRH levels. Metyrapone-induced hypocortisolism was found to decrease pain thresholds (Kuehl et al., 2010). In the present study, it is not possible to distinguish the effect of reduced cortisol levels from those of enhanced CRH levels. Of note, CRH has been shown to play an important role in pain and analgesia under certain conditions (Lariviere and Melzack, 2000). However, in one of our own studies (Lautenbacher et al., 1999), CRH administration alone or after pretreatment with dexamethasone produced – compared with placebo – no analgesic effects, neither with high nor with low cortisol levels.

In sum, the association between short-term release of HPA axis hormones and pain sensitivity is still far from clear. Future studies should combine psychosocial stress and pharmacological methods to investigate related interactions. On the side of pain assessment, a systematic evaluation of the differences between inflammatory and noninflammatory experimental pain (Sunil Kumar Reddy et al., 2012) is mandatory. By doing that, different levels of action can be distinguished, including peripheral and central forms of analgesia. Our noninflammatory heat pain paradigm is likely to mainly target the central forms.

One result of our study should still be discussed in more detail, namely the negative correlation between cortisol and pain thresholds in the placebo condition, while cortisol levels after dexamethasone or hydrocortisone, respectively, were not correlated with pain thresholds in the related conditions. However, these correlations were only marginally significant and relatively small. At first view, the negative association, which is paralleled by similar findings for the pain thresholds after the drug administration when related to basal cortisol levels, might be surprising, but this is not the only study showing a relationship in this direction. Another study suggests also greater cortisol reactivity to be related to greater pain sensitivity in general (Goodin et al., 2012). It may well be that acute and chronic stress differentially modulate the association between stress hormones and pain sensitivity (Culman et al., 1991; Cristea et al., 1994), which might help to explain some of the puzzling findings. The basal cortisol levels may indicate an innate or acquired hormonal trait, which plays an important role in pain sensitivity. Possibly, this trait might be more influential than short-living hormonal effects. Associations between cortisol release and personality traits have been shown, e.g., for hopelessness (van Santen et al., 2011), harm avoidance (Tyrka et al., 2008), novelty seeking (Tyrka et al., 2007), cognitive appraisal (Gaab et al., 2005), locus of control and social dominance (Pruessner et al., 1997), pointing to the relevance of long-lasting interactions between stress hormones and psychological functioning.

A side result of our study was that men had higher pain thresholds compared with women but only in the low cortisol condition. It is known that heat pain stimuli produce small and unstable gender differences at threshold level (Racine et al., 2012), with men being – in case of any differences – always less sensitive than women. It might well be that women experienced our experimental pain procedure as more stressful, the analgesic effect of which was reversed by dexamethasone and led to a small gender difference just in this condition (Kemppainen et al., 1990).

There are some limitations of the current study to discuss: The investigated sample is relatively small, even when considering the number of repeated measurements. To verify the results, replication in a larger cohort is required. Furthermore, it would be of interest to apply stronger pain stimuli simulating better clinical conditions or to investigate long-term effects of glucocorticoid treatment; however, beside methodological problems, there are also ethical considerations speaking against implementation. Psychological traits variables relating to cortisol release have also not been considered in the present context. Lastly, is would be interesting to collect data on central CRH levels

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driving cortisol release, which was not possible to be measured in the present study.

In sum, agents (hydrocortisone, dexamethasone) of a dosage sufficient to manipulate cortisol levels in both directions did not show any impact on pain sensitivity (pain threshold, suprathreshold pain ratings, discrimination ability) when assessed experimentally by use of brief heat stimuli.

Author contributions

K.W. was responsible for data analyses and writing the manuscript. S.W. was responsible for doing the examinations. M.K. was responsible for running statistical analyses. J.-C.K. was responsible for inspiring study and providing facilities. S.L. was responsible for designing study and writing the manuscript.

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