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## Experimental characterization of the effects of acute stresslike doses of hydrocortisone in human neurogenic hyperalgesia models

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### ABSTRACT

Relative hypothalamic-pituitary-adrenal axis dysfunction has been described as a common feature of several dysfunctional pain syndromes, and its end hormone cortisol may thus constitute a protective factor against the development of chronic pain. We investigated the potential influence of experimentally induced stresslike hypercortisolism on the induction of neurogenic hyperalgesia using 2 human surrogate models: secondary hyperalgesia after intradermal capsaicin injection into the volar forearm, and perceptual windup in normal skin. In a double-blind, placebo-controlled, randomized, crossover study, a psychophysical study was performed in 10 healthy subjects (median age 23 years) examining the effects of 40 mg orally administered hydrocortisone. Numeric pain ratings were assessed for punctate pinprick and light touch stimuli applied to the zone of secondary hyperalgesia adjacent to the capsaicin injection and to the contralateral control side. In addition, visual analog ratings were assessed for repetitive pinprick stimulation of the noninjected arm. Hydrocortisone significantly attenuated the late phase of capsaicin-induced pain by nearly 50%, and hyperalgesia to pinprick stimuli by 33% (both  $P < .05$ ). Baseline mechanical pain and dynamic mechanical allodynia remained unaltered. Temporal summation (windup) to mechanical pain stimuli and electrically induced windup of second pain (tested in an independent cohort of 10 other subjects) were also unchanged. The selective effects of hydrocortisone on pinprick hyperalgesia but not pinprick pain suggest an antihyperalgesic rather than analgesic effect. The findings suggest that hypothalamic-pituitary-adrenal axis reactivity might be an important mechanism in resilience to dysfunctional pain syndromes.

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### 1. Introduction

Dysfunctional pain disorders such as fibromyalgia have been shown to be associated with a blunting of the hypothalamic-pituitary-adrenal axis, although inferring a causal relationship is precluded by the correlative and retrospective nature of the clinical studies [77]. In a recent randomized, controlled study, we were able to demonstrate that experimentally induced relative hypocortisolism has the potential to augment temporal summation of pressure pain and decrease mechanical pain detection thresholds, thus supporting the assumption of a causal involvement of the hypothalamic-pituitary-adrenal axis in modulation of pain sensitivity [38].

Consequently, cortisol might be considered a protective factor and hypercortisolemia be assumed to delay or prevent pathological pain processes. Interestingly, in diabetes mellitus, in which cortisol levels considerably exceed the normal value (roughly 2 times), the

prevalence of painful diabetic neuropathy is intriguingly low despite peripheral neuropathy with negative symptoms such as numbness as a major complication [2,50,65]. Although the exact mechanisms of painful diabetic neuropathy are not fully understood, spinal sensitization associated with increased inflammatory mediator levels possibly promoted by local hyperglycemia and induced by aldose reductase has been put forward, and could be inhibited by the anti-inflammatory actions of cortisol [8]. Additionally, painful diabetic neuropathy is characterized by a nocturnal aggravation of pain, which would fit the circadian rhythm of cortisol secretion [16].

To test whether neuroendocrinologic disturbances associated with psychological distress are a risk factor for chronic pain, we chose an indirect approach evaluating the protective effects of a mild dose of hydrocortisone (synthetic cortisol) in a human surrogate model of neurogenic hyperalgesia induced by intradermal capsaicin injection, and perceptual correlates of electrical and mechanical windup [23,40]. Those models were specifically chosen because they induce sensory signs that are frequently observed in

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both neuropathic and dysfunctional pain states (dynamic mechanical allodynia, pinprick hyperalgesia, windup) and are supposed to reflect some of the underlying mechanisms such as small-fiber activation and central sensitization [4,27,36,47]. We gave healthy volunteers either placebo or low-dose oral cortisol 90 min before intradermal capsaicin injection. The cortisol dose was calculated to mimic the cortisol response after, for example, major surgery in previously healthy people. Thus, the placebo treatment in healthy volunteers represents patients with dysfunctional reactivity of the hypothalamic-pituitary-adrenal axis (no additional cortisol).

## 2. Methods

Here we report on 2 separate double-blind, placebo-controlled, randomized, crossover trials analyzing the effects of hydrocortisone treatment on pain processing realized in 2 completely distinct subject samples undergoing different provocations (ie, the capsaicin model and mechanically induced windup in study 1, and electrically induced windup in study 2). In study 1, the influence of a supraphysiological but intermediate therapeutic dose of hydrocortisone (40 mg orally) on changes of nociceptive sensibility (secondary hyperalgesia and dynamic mechanical allodynia) induced by the selective C-fiber excitant capsaicin, as well as on perceptual windup evoked by repeated punctate mechanical stimulation was assessed [46,81]. In study 2, hydrocortisone effects on temporal summation of electrically induced and C-afferent-mediated second pain were examined in supplementary experiments [55].

### 2.1. Subjects

Experiments of study 1 were performed on 10 healthy volunteers (median age 23 years; range 20–42 years); those of study 2 were performed on 10 other participants aged between 19 and 22 years (median age 20 years). All participants of study 1 were right-handed, whereas in study 2, 3 participants showed left-handedness or ambidexterity (assessed with the Edinburgh Handedness Inventory) [51]. Subjects were free of dermatological disorders or skin lesions. Persons with diabetic syndromes or gastroenteropathies, or with renal, hepatic, or cardiovascular dysfunction were excluded. In addition, predefined exclusion criteria comprised pregnancy, chronic pain, and immunological disorders. No analgesics or antibiotics were administered 24 h before the start of each session. Each subject participated in 2 experimental sessions (placebo and hydrocortisone condition in a balanced order) with random assignment to treatment order and had previously provided informed consent. There were no dropouts. The experimental procedures, which are in accordance with the ethical guidelines of International Association for the Study of Pain, were approved by the local ethics committees [9].

### 2.2. Treatment

To mimic an acute physiological cortisol increase, a single dose of 40 mg synthetic cortisol (Hydrocortisone; Hoechst) was administered orally. This dose is the most commonly used in human psychosocial stress research [56]. For comparison, average daily cortisol production is approximately 10 mg in healthy subjects, and rises to roughly 50 mg/d in minor surgery and 75–150 mg/d in major surgery, multiple trauma, or severe sepsis, with maximal secretion amounting up to 400 mg in severe stress syndromes [17,31,39,60]. The placebo consisted of coated lactose powder.

### 2.3. Induction and monitoring of hyperalgesia

In study 1, neurogenic hyperalgesia was triggered by intradermal injection of 40 µg capsaicin (Sigma-Aldrich) dissolved in

12.5 µL of 0.16% polyoxyethylene-sorbitan-monostearate (Tween 80; Fluka, Munich, Germany) in normal saline according to the protocol of Simone et al. [63], and sterilized by filtration with Sartopure GF2 filters (pore size 0.2 µm; Sartorius, Göttingen, Germany). The sterilized capsaicin solution was prepared by a medical technical assistant and injected into the right volar forearm on half the distance between wrist and cubital fossa (Fig. 1A). For injection, sterile and pyrogen-free syringes were used, with a 30-gauge cannula introduced as horizontally and as superficially as possible into the skin. Before injection, the skin was cleaned with a 70% isopropanol pad.

The subjective pain sensation elicited by capsaicin was estimated on a visual analog scale (VAS; length 100 mm), with verbal anchoring of the endpoints ("no pain" and "maximum pain imaginable"). Ratings were collected upon injection until 5 min after injection (in intervals of 10 s for the first minute, and of 30 s from the second through the last minute).

Ten minutes after injection, the area of capsaicin-induced erythema (flare) was visually inspected and marked with a dermatologically tested marker pen. The surface boundaries were transcribed onto a transparent sheet of acetate paper at the end of the experimental session. For exact quantification of the outlined area size, a digital polar planimeter (accuracy 0.2%) was used.

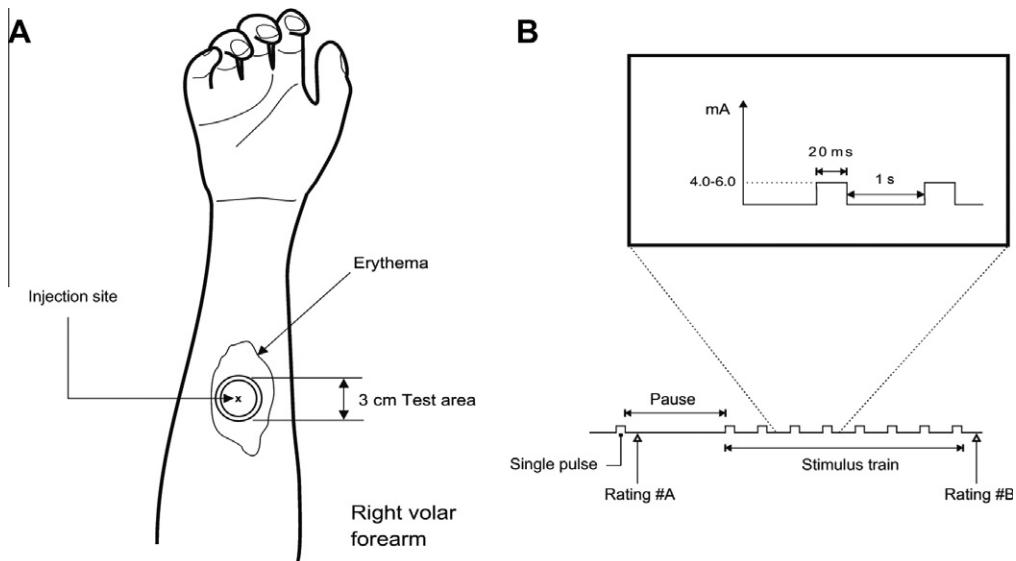
Secondary hyperalgesia to punctate stimuli was tested by applying a series of 7 probes consisting of cylindrical stainless steel wires (tip diameter 0.25 mm) mounted on plastic rods of different weights (exerting pressure forces of 8, 16, 32, 64, 128, 256, or 512 mN; MRC Systems, Heidelberg, Germany), which could slide freely within a handheld metal tube. Wire tips were flattened to avoid skin penetration. Quantitative sensory testing of dynamic mechanical allodynia relied on light touch stimulation evoked by short and gentle stroking at constant velocity (stroke length ~1 cm) with a cotton wisp, a Q-tip, and a soft brush. Ziegler et al. [81] provide further details and stimulus calibration.

The sensory testing was performed within a ring-shaped area at a distance of 15 mm from the injection site (Fig. 1A) to avoid stimulation at the zone of primary hyperalgesia. The corresponding skin region of the contralateral arm served as control area. Throughout the experimental session, the test and the control arm were comfortably laid on an armrest. The subjective sensations resulting from pricking and touch stimulation were evaluated on a numeric rating scale (NRS; 0 ≈ no pain, 100 ≈ maximal pain imaginable).

Sensory testing was organized in blocks (approximate duration 30 min), each consisting of 5 test runs (duration 5 ± 1 min) comprising 10 stimulus presentations (7 pinprick stimuli and 3 light touch stimuli), allowing for all of the stimuli described above to be applied 5 times in quasirandomized sequence during a single test block. Stimulus duration was approximately 1 s, with an interstimulus interval of approximately 10 s. Except for light touch stimuli, and in order to preclude primary afferent sensitization or fatigue effects, restimulation of an already stimulated spot was avoided [40].

### 2.4. Induction and assessment of windup

In study 1, mechanically induced windup of pain sensation was characterized on randomly assigned spots of the nondominant volar forearm. The testing for mechanical windup was performed during the pauses between the hyperalgesia testing blocks and consisted of 5 trains of 10 repeated pinprick stimuli at constant intensity (256-mN probe) with a repetition frequency of 1 Hz. For accurate repetition timing, the experimenters followed audiometronome tact beats. Subjects were asked to provide a separate pain rating for every single stimulus presentation on a VAS identical to the one for the assessment of capsaicin-evoked pain.



**Fig. 1.** Schematic representations of experimental setup (study 1) and design (study 2). (A) Injection site for capsaicin (X), area for testing of secondary hyperalgesia and dynamic mechanical allodynia (concentric circles), and schematized axon reflex flare. Mechanical (punctate/tactile) stimuli were applied along the circumference of a circle (radius 15 mm) surrounding the injection site. (B) Single test trial for the assessment of temporal summation induced by repetitive application of electrical stimuli consisting of an initial single electric (rectangular waveform) pulse followed after a certain evaluation pause (interpulse interval <45 s) by a train of 8 identical shocks delivered at a frequency of 1 Hz. VAS ratings were provided at the end of the single pulse (rating #A) and after termination of the pulse series (#B).

Pinpricks were repeated in a small skin area of  $\sim 1 \text{ cm}^2$ , which approximately corresponds to the average size of receptive fields of nociceptors [76].

In study 2, repetitive intracutaneous electric shocks (rectangular wave pulses; duration 20 ms) were delivered via a pulse generator connected to a constant current isolator to induce windup [55]. For this purpose 2 sterilized 30-gauge needle electrodes were inserted in parallel (distance  $\sim 5 \text{ mm}$ ) into the thenar eminence of the nondominant hand at half the distance between hypothenar and wrist base. Before electrode penetration, the skin was cleaned with an isopropanol pad. Subjects were grounded via wrist strap electrodes.

Test trials consisted of an initial single electric pulse followed after complete disappearance of aftersensations (interpulse interval <45 s) by a series of 8 shocks delivered at a frequency of 1 Hz (Fig. 1B). At the end of the single pulse and after termination of the pulse series, subjects rated the respective pain intensities on a handheld mechanical VAS (with graduated linear scale, 0–100 units) [54]. Depending on current intensity, this stimulation method induces an initial pricking pain experience, followed  $\sim 1.5 \text{ s}$  later by a second burning pain sensation. Estimates for both types of sensation were obtained on separate test runs, with the subjects being instructed to selectively attend either to first or second pain sensation.

To compensate for intersubject variability, the amplitude of the electric rectangular pulses was adjusted at the beginning of each session to a value where a distinct second pain sensation was identified and rated as approximately  $20 \pm 5$  on the 0–100 VAS. The adjusted current level (range 4.0–6.0 mA) was then used throughout the different testing conditions for a given experimental session.

## 2.5. Experimental protocol

Both studies consisted of 2 experimental sessions separated by at least 6 days. A given experimental session in study 1 involved 5 sensibility testing and windup assessment blocks as described before (30 min duration each). The first assessment period began 30 min before medication (premedication baseline; BL1). After completion of BL1 testing, either hydrocortisone or placebo was

administered with 200 mL of water. The second testing period (postdrug/precapsaicin baseline; BL2) began 90 min after medication. It was instantly followed by estimation of spontaneous pain and flare induced by capsaicin (ie, 2 h after medication). Three further blocks of sensibility testing followed at 30, 60, and 90 min after injection (T1–3). The resorption time frame chosen here was derived from pharmacokinetic analyses revealing that maximum concentrations are generally attained 1–1.4 h after oral hydrocortisone administration [12,14,75].

The experimental sessions of the second study consisted of baseline testing of electrically induced perceptual windup followed by ingestion of hydrocortisone or placebo with 200 mL of water. A second identical testing protocol was performed after a resorption pause of 90 min. Baseline and postmedication testing comprised 8 trials each, corresponding to 4 test runs both for first and for second pain presented in alternating order and with an intertrial interval of 3 min. Experimental factors were completely counterbalanced across subjects, who were assigned at random to a specific treatment order, to control for potential carryover and position effects related to pharmacodynamics and sensitization procedures.

## 2.6. Data evaluation and statistical analysis

For statistical analysis the Statistica for Windows package (Statsoft; Hamburg, Germany) was used. Data were analyzed with repeated measures analysis of variance (ANOVA) and *t* test for paired samples. For magnitude of effect estimation, Hays's  $\omega^2$  and Cohen's *d* were calculated, respectively. Alpha level was set at  $P = .05$ . All data graphs were created with SigmaPlot (SPSS). Data are represented as arithmetic mean (mean)  $\pm$  standard error of the mean (SEM). Sensitivity of the capsaicin model in our hands is such that a 23% change in pain is detected at  $P < .01$  and a 23% change in hyperalgesia is detected at  $P < .05$  with  $n = 10$  (data from Ziegler et al. [81], confirmed by data from Magerl et al. [46], where a 32% change in pain was significant at  $P < .005$ ).

For capsaicin-induced pain, 3 parameters were extracted, namely pain upon injection (peak capsaicin-induced pain), time constant of pain decline, and average pain during the fourth and

fifth minute (late phase capsaicin-induced pain). Time constants for capsaicin-induced pain were calculated as the time to reach a level of  $e^{-1}$  (ie, 36.8%) of peak pain rating, which was linearly interpolated from the last pain rating just above and the first pain rating just below  $e^{-1}$  level.

Pain ratings of suprathreshold pinprick stimuli were logarithmically transformed, with the purpose of normalizing and linearizing the data. In order to avoid a loss of zero values due to log transformation, a constant of 0.1 was added to all raw data (ie, zero and nonzero values) [3]. Stimulus-response (S/R) functions were derived for punctate stimuli, with the corresponding slope computation based on the estimates of linear functions derived from regression analysis.

For estimating the amount of temporal summation of pinprick pain in study 1, windup data were normalized to the rating for the initial stimulus in each train and were analyzed by 2-way repeated measures ANOVA with stimulus repetition and treatment as factors. Additionally, perceptual windup ratios were calculated for each test block as average NRS rating across fifth to 10th stimulus divided by the first stimulus rating within a given stimulus train. In study 2, temporal summation of first and second pain elicited by brief electrical stimulation was calculated as the ratio of NRS<sub>8</sub> to NRS<sub>1</sub>, wherein NRS<sub>1</sub> refers to the rating in response to the single pulse preceding each train and NRS<sub>8</sub> to the last pulse of the train of 8 electric shocks.

### 3. Results

#### 3.1. Capsaicin-evoked pain and erythema

Capsaicin injection induced a strong pain sensation with a burning character. Pain ratings reached a maximum immediately after injection and steadily decreased thereafter in an exponential fashion that could be fitted linearly in a semilogarithmic plot (Fig. 2A). The peak pain rating after hydrocortisone treatment (95.5%) was nearly identical to that after placebo (96.7%), and mean VAS ratings arithmetically averaged over the whole testing period (0–5 min) were highly correlated between both treatments ( $r = .96$ ;  $P < .05$ ). However, mean capsaicin pain ratings were reduced by 15% from 41.8% to 35.6% by hydrocortisone ( $P < .05$ , Table 1). Statistical analysis of the time course of pain ratings revealed a significant main effect of treatment ( $F_{1,9} = 5.27$ ;  $P < .05$ ; effect size  $\omega^2 = 0.18$ ). As can be seen in Figure 2A, this reduction became only apparent after a certain latency (significant time  $\times$  treatment interaction,

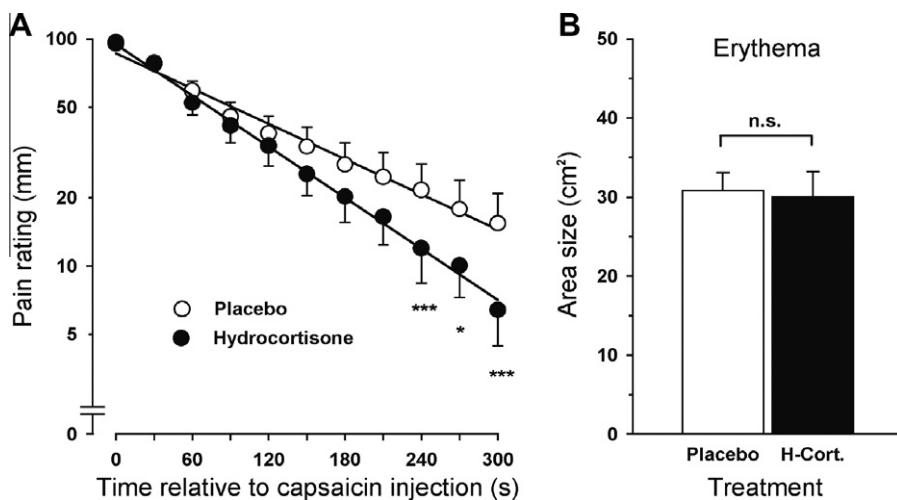
$F_{10,90} = 3.91$ ;  $P < .001$ ). Post hoc comparisons (Newman-Keuls test) confirmed that the pain reduction became significant at 4 min after the injection. Late phase ratings (average 4–5 min) were reduced by approximately 50% by hydrocortisone ( $t_{1,9} = 2.53$ ;  $P < .03$ ; effect size  $d = 0.79$ ; Table 1). Additionally, under hydrocortisone the time constant of the pain rating time course was significantly shortened compared to placebo ( $113 \pm 19$  vs  $151 \pm 30$  s,  $P < .05$ ). In all subjects pain was still present at 5 min after injection but had completely disappeared before the sensibility testing for hyperalgesia and allodynia was initiated.

Capsaicin evoked a substantial erythema surrounding the injection site as a consequence of axon reflex-induced vasodilatation [69]. Examination of the flare size (Fig. 2B; Table 1) did not show any difference between the placebo ( $30.8 \pm 2.2$  cm<sup>2</sup>) and hydrocortisone conditions ( $30.0 \pm 3.2$  cm<sup>2</sup>;  $P = .65$ ). Capsaicin-induced pain (area under the receiver-operating characteristic curve) and areas of flare were not significantly correlated ( $r = .13$ ;  $P = .72$ ).

#### 3.2. Hyperalgesia

S/R functions for pinprick pain for the test site before and after drug administration and after capsaicin injection are shown in Fig. 3. The psychometric functions for the postdrug precapsaicin period were best fitted by a power function and did not differ between the 2 treatment conditions, as the slopes of the regression functions plotted in double logarithmic space were nearly identical (power function exponents/slopes  $0.72 \pm 0.06$  vs  $0.71 \pm 0.04$  for placebo and hydrocortisone, respectively). After the capsaicin injection, an upward shift of the corresponding S/R curves in comparison to the power functions for normal skin was observed, indicating that capsaicin-induced pinprick hyperalgesia occurred under both placebo and hydrocortisone treatment.

Hydrocortisone treatment, however, significantly reduced postcapsaicin pain ratings compared to placebo ( $F_{1,9} = 7.84$ ;  $P < .04$ ;  $\omega^2 = 0.26$ ), with an average reduction of about 26% (Table 1, range 8–31%). Post hoc tests (Newman-Keuls) revealed that this antihyperalgesic effect only occurred at low to medium force levels. This finding was confirmed by an analysis of the slopes of the double logarithmic regression functions. In the placebo condition, the slope after capsaicin was much less than before because mostly ratings to lower stimulus intensities were facilitated. This reduction in slope was significantly less under hydrocortisone treatment (from  $0.71 \pm 0.04$  to  $0.63 \pm 0.06$ ;  $\Delta\% = 10 \pm 7\%$ ) than under placebo (from  $0.72 \pm 0.06$  to  $0.54 \pm 0.07$ ;  $\Delta\% = 26 \pm 7\%$ ;  $F_{1,9} = 2.77$ ;  $P < .02$ ;



**Fig. 2.** Capsaicin-evoked pain and erythema. (A) Time course of pain sensation (estimated on paper form VAS; mean  $\pm$  SEM;  $n = 10$ ) elicited by intradermal injection of 40 µg capsaicin. Hydrocortisone administration significantly reduced the area under the time course curve ( $P = .01$ ) in average by 15%. (B) In contrast, area of neurogenic erythema (mean  $\pm$  SEM;  $n = 10$ ) estimated 10 min after injection was not affected by the glucocorticoid.

**Table 1**

Summary of parameters (postdrug values) assessed in studies 1 and 2 and averaged hydrocortisone effect (as percentage change compared to placebo).

Parameter	Placebo, mean ± SEM	Hydrocortisone, mean ± SEM	Change (Δ%)	$P^a$
<i>Capsaicin-induced pain</i>				
Mean rating (mm)	41.8 ± 6.4	35.6 ± 7.2	-15%	<.05 A*
Peak rating (mm)	96.7 ± 1.2	95.5 ± 1.6	-1%	.92 NK
Late phase average rating (mm)	18.5 ± 4.6	9.5 ± 2.1	-49%	.03 T*
Decay time constant (s)	151 ± 30	113 ± 19	-25.0%	.04 T*
Capsaicin-induced flare (cm <sup>2</sup> )	30.8 ± 2.2	30.0 ± 3.2	-2.5%	.65 T
<i>Pinprick-evoked pain (0–100)</i>				
Control site				
Before capsaicin	1.5 ± 0.4	1.6 ± 0.6	+7%	.97 NK
After capsaicin	1.6 ± 0.4	1.5 ± 0.6	-7%	.92 NK
Test site				
Before capsaicin	1.7 ± 0.4	1.7 ± 0.6	0%	.99 NK
After capsaicin	4.9 ± 0.9	3.6 ± 0.9	-26%	.04 NK
Test/control				
Before capsaicin	1.1 ± 0.1	1.1 ± 0.0	0%	.88 NK
After capsaicin	3.7 ± 0.5	3.1 ± 0.4	-16%	.02 NK
Hyperalgesia (% of baseline) <sup>b</sup>	424 ± 73	316 ± 42	-25.5%	.02 T*
Hyperalgesia (% increase vs baseline) <sup>b</sup>	324 ± 73	216 ± 42	-33.3%	.02 T*
Allodynia (incidence rate)	35%	34.7%	-0.3%	
<i>Mechanical windup (% of predrug baseline)</i>				
Initial stimulus in train <sup>c</sup>	121 ± 21	118 ± 14	-2.5%	.44 T
Plateau (fifth–10th stimulus) <sup>c</sup>	247 ± 52	243 ± 42	-1.5%	.45 T
Ratio (train final/single)	2.2 ± 0.3	2.5 ± 0.5	+14%	.37 T
<i>Electrical windup (% of predrug baseline)</i>				
Single stimulus <sup>c</sup>	99 ± 7	104 ± 8	+5.5%	.56 T
Final stimulus in train <sup>c</sup>	149 ± 14	153 ± 13	+3%	.64 T
Ratio (train final/single)	1.5 ± 0.1	1.5 ± 0.1	0%	

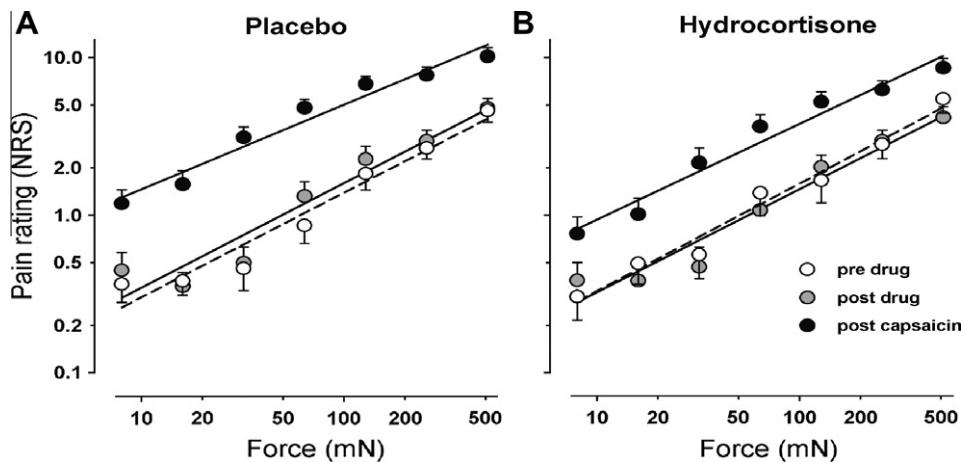
<sup>a</sup> Statistical test is indicated as follows:

A, repeated measures ANOVA (main effect analysis); NK, repeated measures ANOVA (post hoc analysis; Newman-Keuls test); T, t test for paired samples.

<sup>b</sup> Normalized to postdrug/precapsaicin values.

<sup>c</sup> Normalized to predrug values (indicated in %).

\*  $P < .05$ .



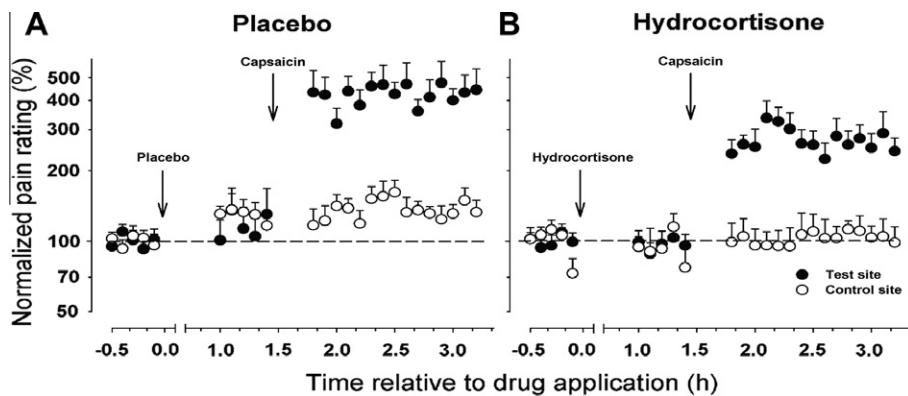
**Fig. 3.** S/R function for pinprick-evoked pain (mean ± SEM;  $n = 10$ ). The S/R functions of pinprick pain were best fitted by a power function (linearized in double logarithmic coordinate system). Dashed lines refer to predrug and solid lines to postdrug measurements. Under placebo treatment (A), a substantial capsaicin-induced upward shift of the S/R function (ie, hyperalgesia; fourfold increase) could be observed with a reduction in slope, whereas under hydrocortisone treatment (B), this upward shift was less pronounced (ie, antihyperalgesia; increase by only a factor of 3.1) and the slope was unchanged (parallel shift). These findings suggest that the antihyperalgesic effect of hydrocortisone predominated at low stimulus intensities.

$\omega^2 = 0.25$ ), indicating that ratings were reduced by hydrocortisone predominantly for those stimulus intensities that were most strongly facilitated by capsaicin. This observation suggests a specific antihyperalgesic effect.

For analysis of the time course of pinprick-evoked pain, ratings for all stimulus intensities were aggregated over each test run (ie, over a  $5 \pm 1$  min time window) and normalized to predrug values (Fig. 4A,B; corresponding nonnormalized data are presented in Table 1). Pain ratings to pinprick stimulation underwent a step increase after capsaicin injection that was stable for the entire

observation period. Hydrocortisone attenuated pain ratings to pin pricks in the capsaicin-induced secondary hyperalgesia zone by 26% vs placebo (averaged over the 90 min assessment period;  $F_{1,9} = 2.59$ ;  $P = .015$ ;  $\omega^2 = 0.15$ ). This corresponded to a 33% reduction of hyperalgesia assessed as pain rating increase over baseline (hydrocortisone  $216 \pm 42\%$ ; placebo  $324 \pm 73\%$ ,  $P < .05$ ); thus, the extent of hyperalgesia reduction by hydrocortisone is within the range that is considered clinically meaningful [18].

In contrast, we did not detect any purely analgesic hydrocortisone effects on pinprick pain because pain ratings for the test site



**Fig. 4.** Time course of pinprick-evoked pain for the control and test site. Each dot (mean  $\pm$  SEM;  $n = 10$ ) represents pain ratings aggregated over a  $5 \pm 1$  min time window (ratings were normalized to predrug values). (A) Under placebo treatment, pain ratings were slightly raised from the second testing point on, which may be attributed to sensitization elicited by the repeated pinprick application. (B) Hydrocortisone treatment prevented this sensitizing effect and substantially attenuated secondary irritant-induced hyperalgesia.

before capsaicin injection did not differ between placebo and hydrocortisone (Table 1). Moreover, pain ratings in the control area did not differ between treatments at any point in time with differences between treatments ranging between  $-7\%$  and  $+7\%$ ; all  $P > .80$ ; Table 1).

### 3.3. Dynamic mechanical allodynia

Applying light tactile stimuli to normal skin never elicited a perceptible pain sensation. In contrast, dynamic mechanical allodynia was seen in 7 out of 10 subjects and it was significant in 4 subjects (single subject statistic). For the other 3 of the 7 subjects, there was only 1 painful rating per 45 tactile stimuli. However, manifestation of allodynia was similar under both treatment conditions, with an incidence of 35% for the placebo and 34.7% for the hydrocortisone condition.

### 3.4. Perceptual windup

The analysis of the VAS ratings for repetitive pinprick stimulation (Fig. 5A,B) by repeated measures ANOVA showed a significant stimulus repetition related increase of pain sensation under both treatment conditions ( $F_{9,81} = 15.28$ ;  $P < .0001$ ;  $\omega^2 = 0.87$ ), but no significant treatment effect ( $P = .22$ ), nor any interaction between treatment condition and stimulus repetition ( $P = .26$ ). Similarly, temporal summation estimated as windup ratio did not differ between both conditions (Fig. 5C,D; Table 1). Windup ratios were quasi identical before and after medication, namely with a factor of  $2.2 \pm 0.3$  vs  $2.2 \pm 0.3$  for the placebo and  $2.4 \pm 0.3$  vs  $2.5 \pm 0.5$  for the hydrocortisone condition.

In study 2 in another group of subjects, intracutaneous electrical shock presentation reliably produced pinprick-like first and burning-like second pain, with a retest reliability of  $r = .81$  ( $P < .05$ ) and an intraindividual variation coefficient of 3% of the mean (4.6 mA) for second pain thresholds. Descriptive analysis of the data did not reveal any analgesic effect of hydrocortisone administration because VAS ratings for second pain evoked by the first stimulus in each train did not vary between hydrocortisone and placebo treatment (Table 1). Likewise, no diminution of slow temporal summation relative to baseline could be observed, as the mean ratios were very similar under the corresponding placebo and treatment conditions. On average, the postdrug temporal summation was slightly increased, but did not differ between hydrocortisone and placebo treatment (Fig. 5E,F; Table 1). In agreement with the findings for second pain, no hydrocortisone effect could be observed for first pain (data not shown).

## 4. Discussion

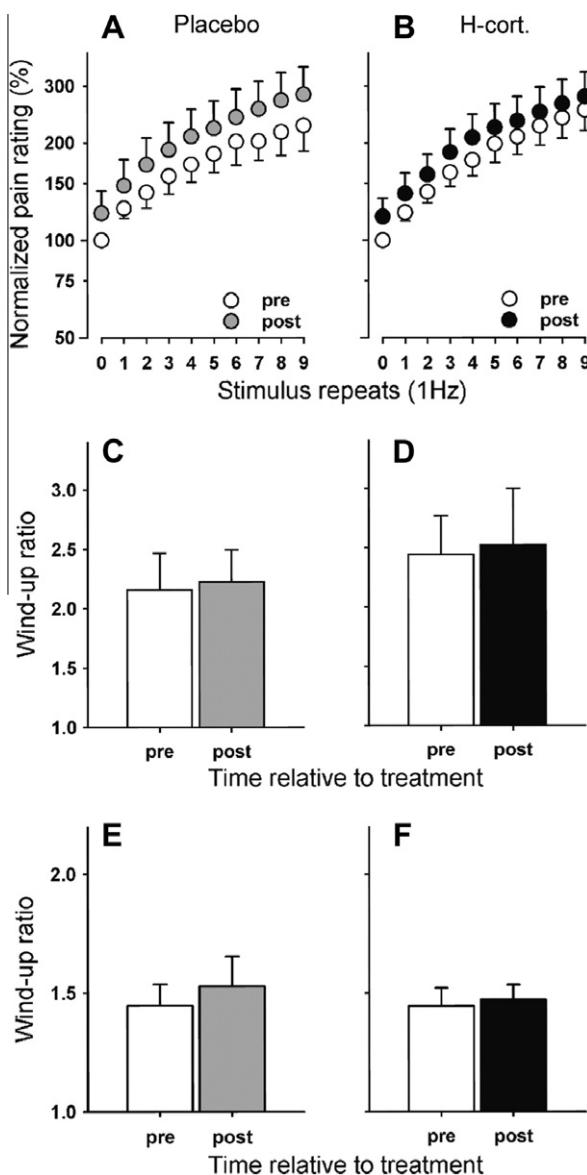
We observed an abbreviated time course and a reduction in the late phase of capsaicin-induced pain by a mild dose of hydrocortisone without any effects on the peak pain upon injection. Pinprick pain was not influenced in normal skin, but pinprick hyperalgesia after capsaicin was strongly attenuated to a degree that can be considered clinically meaningful. There was no effect on dynamic mechanical allodynia nor on windup for mechanical or electrical stimuli.

### 4.1. Antihyperalgesic, analgesic, or anti-inflammatory effects of hydrocortisone

Previously, elevated cortisol levels during stress were found to be associated with lower capsaicin-induced pain [44]. In the rodent paw formalin test, systemic corticosterone led to suppression of formalin-induced pain behavior specifically occurring during the late phase implying a role in control of central sensitization [26,62]. It is thus tempting to interpret our finding of a specific attenuation of the late phase of capsaicin-induced pain also as indicating an effect on central sensitization. The absence of an effect on peak pain, however, may also either mean that a possible analgesic efficacy of hydrocortisone may be overcome by very strong stimuli or simply be due to ceiling effects because pain ratings at capsaicin injection were near maximal imaginable pain (96 of 100).

Efficacy of corticosterone in the late phase of the formalin test may also reflect inhibition of inflammatory mediators [73]. The human capsaicin injection model also reflects some aspects of inflammatory pain, namely TRPV1-mediated pain and neurogenic inflammation [36]. The capsaicin-induced erythema, however, was not reduced in our study, making it unlikely that peripheral anti-inflammatory actions of hydrocortisone were responsible for the observed effects. Other studies have shown that reductions of capsaicin-induced erythema in humans and plasma extravasation in animals occur only with much longer duration of topical glucocorticoid treatment [34,71].

In the first-degree burn model of secondary hyperalgesia, systemic dexamethasone reduced the size of the secondary hyperalgesia area (assessed with a stiff v. Frey probe) from  $35 \text{ cm}^2$  to  $23 \text{ cm}^2$ , without any effect on perceived pain during the initiating burn [78]. Likewise, methylprednisolone led to a significant reduction of the area of secondary hyperalgesia, but no effect on pressure pain threshold [68]. Topically applied glucocorticoids did not induce any antihyperalgesic effects in the same model, suggesting a predominantly central site of glucocorticoid action, consistent



**Fig. 5.** Mechanically and electrically induced windup of pain sensation in normal skin. (A, B) VAS ratings (mean  $\pm$  SEM;  $n = 10$ ) for the estimation of the repeated pinprick stimulation in normal skin (weight force 256 mN; repetition rate 1 Hz). Postdrug values were slightly raised in comparison to the predrug reference values, but did not differ between placebo and hydrocortisone treatment. Ratings were normalized to the initial predrug VAS rating. (C, D) Pain summation estimated as windup ratio for pinprick (defined as the ratio of the first to the average across the 6 last ratings; mean  $\pm$  SEM;  $n = 10$ ) was unaffected by glucocorticoid treatment. (E, F) Similarly, temporal summation of second pain in response to trains of repeated constant intensity electric shocks (repetition rate 1 Hz; mean  $\pm$  SEM;  $n = 10$ ) was not altered by hydrocortisone pretreatment (see text for details on data aggregation).

with the concept of secondary hyperalgesia being due to central sensitization [1,46,52,74].

The hypothesis that antihyperalgesic effects of glucocorticoids may be due to an action within the CNS is further supported by data from animal neuropathic pain models, where systemic or epidural/intrathecal glucocorticoid application inhibited the development and maintenance of mechanical hyperalgesia/allodynia related to peripheral nerve injury [72,80]. Even in a classical inflammatory pain model (carrageenan-induced inflammation), there is evidence that reversal of muscle hyperalgesia by exogenous glucocorticoids might be related to spinal glucocorticoid

receptor activation leading to prolonged GABA<sub>A</sub> receptor-mediated synaptic currents [32,53].

Our finding of a predominant antihyperalgesic effect of hydrocortisone on pinprick hyperalgesia is reminiscent of the differential effectiveness of corticotropin-releasing hormone (CRH), which may at least partly be mediated by endogenous glucocorticoids [42]. Intravenous CRH application reduced pain affect and pain intensity in a clinical model with peripheral and central sensitization (postsurgical dental pain), but had no effect on heat pain thresholds and on ratings to suprathreshold thermal stimuli in normal nonsensitized skin [22,43].

#### 4.2. Possible mechanisms of antihyperalgesic action of glucocorticoids

The rapid onset of action in the present study (90 min) may be explained by nongenomic mechanisms, which have recently been identified in the nervous system [45,48,82]. Nongenomic action of glucocorticoids can operate within minutes and is mediated by binding to specific glucocorticoid membrane receptors, and may lead to rapid suppression of intracellular signal cascades—for example, mediated via phospholipase A2 [11]. Recently, low-dose hydrocortisone inhibited a different measure of central nervous plasticity, prepulse inhibition in a fast onset and rapidly declining time course, which could not be explained by genomic effects [58]. Generally, however, genomic effects can not be fully excluded because they also start already within 10–30 min and may suppress, for example, the NF-κB complex [66].

As glucocorticoid receptors have been localized on nerve cells in dorsal root and trigeminal ganglia, it may thus be hypothesized that hydrocortisone exerted a suppressive effect via glucocorticoid receptors on dorsal root ganglion neurons or presynaptic endings [10,13]. Concordant with this speculation, synthetic corticosteroids were found to suppress ectopic discharges from experimental neuromas as well as the neurotransmission in C fibers [15,28].

Suppression of secondary hyperalgesia was only assessed 30–90 min after its induction. This time window may already suffice to allow for a potential contribution of glial activation because in another model of injury-induced hyperalgesia (ie, subcutaneous formalin injection in rats), it has been shown that the expression of the microglial MAP kinase isoform p38 $\beta$ , which mediated this form of hyperalgesia, already peaked at 15 min after injection [57,61,70]. Thus, antihyperalgesia due to hydrocortisone in our study may also reflect a glucocorticoid action on immune cells within the CNS. Such a mode of action would be particularly interesting because in the same human surrogate model, the NMDA receptor antagonist neramexane exerted analgesic effects in both normal and hyperalgesic skin, thus lacking specific antihyperalgesic efficacy [35]. The lack of effect of hydrocortisone on windup suggests that the mechanisms of that short-term plasticity in the spinal cord have little in common with the more prolonged sensitization responsible for secondary hyperalgesia [79].

Intriguingly, reducing effects on detection and discrimination thresholds by exogenous hydrocortisone have been observed for other exteroceptive sensory systems (audition and gustatory sense) with comparable or even lower dosage than used in our study as well as with enhanced cortisol secretion provoked by experimental psychological stress [5,7,19,20]. In contrast to other sensory systems, a small rise in cortisol levels as during stress thus seems to selectively inhibit pathophysiological processes involved in the enhancement of pain sensitivity, while conserving normal signaling capacity of the nociceptive system. Analgesic efficacy of glucocorticoids seems to require higher cortisol levels, as has been proven in several acute surgery pain forms [59,64].

### 4.3. Clinical implications

Our data suggest that systemic administration of glucocorticoids can prevent hyperalgesia without blocking acute pain and may thus be beneficial in clinical situations of enhanced pain sensitivity. Administration of high-dose dexamethasone after lumbar disk surgery suppressed movement-evoked pain; this sign can be considered as an indicator of central sensitization to mechanical stimuli and it was reduced by approximately 25%—that is, similar to the reduction of secondary hyperalgesia in our data [29]. Other studies on hypoalgesia by perioperative glucocorticoid administration during minor surgical procedures are inconclusive with regard to the proposed antihyperalgesic specificity, as hyperalgesia was not specified as a therapeutic endpoint [6,41,49]. In these conditions, clinical pain-reductive glucocorticoid efficacy is commonly associated with antiedematous effects [24].

Transient partial pain relief by systemic glucocorticoids has been observed for complex regional pain syndromes as an example of dysfunctional pain syndromes [33]. As an example of neuropathic pain syndromes, Kotani et al. found an effect of intrathecal glucocorticoid injections on intensity and area of dynamic mechanical allodynia in postherpetic neuralgia [37]. The same low dose of hydrocortisone as used in our experiments significantly improved sensory leg discomfort in patients with restless legs syndrome, a neurological disease characterized by substantial hyperalgesia to the same pinprick stimuli used in our experimental model of hyperalgesia [25,67].

### 4.4. Conclusions

In the studies presented here, we demonstrate a causal influence of systemic application of hydrocortisone (synthetic cortisol) in a surrogate model of neurogenic hyperalgesia, indicating a potential implication of adrenocortical activity in specific modulation of hyperalgesic states, which is conceivable as a nonopioid form of stress-induced hypoalgesia [21,36]. Hypercortisolism thus would constitute a protective factor against neurogenic pain, which speaks in favor of perisurgical hydrocortisone supplementation as prophylaxis of pain chronicity, whereas hypocortisolism may be considered a risk factor for chronic pain [30,60].

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