ENDOGENOUS OPIOID TONE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SUMMARY

We have previously shown that there is deficient hypothalamic-pituitary-adrenal (HPA) responsiveness in rheumatoid arthritis (RA) patients. The basis for this deficient response is not known. The purpose of the project was to investigate whether the defective HPA response in RA patients is the result of increased endogenous opioid tone secondary to chronic pain which can suppress corticotrophin-releasing hormone (CRH) production. We conducted a double-blind placebo-controlled cross-over trial to study the effect of the opiate antagonist, naloxone, on psychometric function together with plasma adrenocorticotrophic hormone (ACTH), cortisol and prolactin. Seven RA patients with active and established disease and eight healthy controls were studied. Each received either a bolus i.v. infusion of 20 mg naloxone or normal saline. At least 72 h, they received naloxone if they had previously received normal saline or vice versa. The pain score was statistically significantly higher at baseline in the RA group compared with controls (5.7 ± 3.25 vs 0.35 ± 0.21, P < 0.001). No difference was found in the other psychometric assessments throughout the study. Patients receiving normal saline did not show any significant change in cortisol or ACTH. Cortisol and ACTH showed a sharp and significant rise after naloxone treatment in both RA and normal subjects (P < 0.001 and P < 0.01), but no difference was observed between the two groups. The mean prolactin level showed no significant change in both groups after any treatment. We conclude that endogenous opioid tone does not appear to be a major contributor to the HPA defect in RA. However, the number of patients studied was small and this result will require confirmation from larger trials.

KEY WORDS: Rheumatoid arthritis, Endogenous opioid, Opiate, Hypothalamus-pituitary-adrenal axis, Cortisol, Naloxone, ACTH, Prolactin.

METHODS

Study subjects

We conducted a double-blind placebo-controlled cross-over trial to study the effect of naloxone on ACTH, cortisol, prolactin and psychometric function. Patients with definite RA, as defined by the 1987 ACR criteria [6], were recruited from the rheumatology out-patients clinic. They had active disease, as defined by the presence of at least three out of the four following criteria: (1) ≥6 joints painful to touch or motion; (2) ≥3 swollen joints; (3) ≥45 min early morning stiffness; (4) ≥28 mm erythrocyte sedimentation rate. Control subjects consisted of patients with soft tissue rheumatism or healthy volunteers. We excluded any subject who had thyroid or ovarian disorders, a history of psychiatric illness, oral corticosteroid therapy, cytotoxic therapy (except methotrexate or cyclophosphamide), androgen or oestrogen therapy, major tranquilizers, dopaminergic drugs, disorders of the HPA axis or pregnancy. The study protocol was approved by the Guy's and Lewisham Hospitals Research Ethics Committee. Signed informed consent was obtained from all subjects prior to participation.

Study protocol

Subjects fasted overnight and stopped all long-acting non-steroidal anti-inflammatory drugs (NSAIDs) and painkillers which contain opiates, such as Co-proxamol or Co-dydramol, 24 h before the test was performed.

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TABLE I
Demographic details of rheumatoid arthritis patients and normal controls

<table>
<thead>
<tr>
<th></th>
<th>RA patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>4:3</td>
<td>4:4</td>
</tr>
<tr>
<td>Age, yr (mean)</td>
<td>55 ± 12</td>
<td>52 ± 14</td>
</tr>
<tr>
<td>Disease duration, yr (mean)</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>ESR (mm/h, mean)</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>D-Penicillamine (no.)</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Sulphasalazine (no.)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>NSAIDs (no.)</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

They attended the hospital at 09.00 h and each received either a bolus i.v. injection of 20 mg naloxone or normal saline. After a minimum duration of 72 h, they received naloxone if they had previously received normal saline or vice versa. Pain and psychometric variables, which include relaxation, depression, tension, anger, vigour, confusion, concentration, fatigue, happiness and sadness, were measured using standard visual analogue scales [4,5]. These were administered at times -15, +30 and 60 min post-infusion to assess pain and mood.

Laboratory assessments

Blood samples were taken 15 min prior to naloxone injection and afterwards at 15 min intervals for a total of 120 min. Samples were collected into lithium-heparin tubes, immediately chilled to 4°C and centrifuged at 1500 r.p.m. at 4°C for 15 min. Plasma was aliquoted, quickly frozen in dry ice, and stored at -20°C until assayed for plasma ACTH, cortisol and prolactin. Serum cortisol was measured according to the method of Cunnah et al. [7] and expressed in nmol/l. The interassay coefficient of variation (CV) across the working range of the assay was 8% at 143 nmol/l and 5.5% at 1042 nmol/l with an interassay CV <5% at all values. Plasma ACTH was measured by immunoradiometric assay (Allegro HS-ACTH, Nichols Institute, San Joan Capistrano, CA, USA) and expressed in ng/l. The intra-assay and interassay CV values across the working range of the assay were <5%. Serum prolactin was measured by an immunoradiometric assay and expressed in mU/l. The intra-assay CV across the working range of the assay was <5%; the interassay CV was 6% at 1156 mU/l, rising to 10.6% at 216 mU/l.

Statistical analysis

Results were expressed as the mean ± s.d. The data were statistically analysed in several ways: analysis of variance, paired Student’s t-test for paired parametric variables and the Mann–Whitney U-test for non-paired non-parametric variables. P values of <0.05 were considered significant.

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![Fig. 1.—Plasma cortisol level (nmol/l) at different time points (the arrow indicates the time of naloxone infusion) in the four following groups: ■, RA patients given naloxone infusion; ▲, normal controls given naloxone infusion; ▼, RA patients given placebo infusion; ◆, normal controls given placebo infusion.](https://academic.oup.com/rheumatology/article-abstract/35/5/436/1779813)
RESULTS

Seven patients with active established RA and eight controls were recruited (Table I). There was no change in any of the cardiovascular parameters (blood pressure, pulse rate) after the naloxone infusion, this is in agreement with previous data [2, 8-12].

Pain measurements

The pain score was statistically significantly higher at baseline in the RA group (5.7 ± 3.25 cm) compared with controls (0.35 ± 0.21 cm, \( P < 0.001 \)). No difference was found in other mood assessments between the RA patients and controls both before and after naloxone (data not shown).

Hormonal measurements

Basal. Serum prolactin was higher in RA patients (261 ± 125 mU/l) compared with controls (175 ± 36 mU/l), although this did not reach statistical significance. Neither cortisol (RA 502 ± 181 mU/l vs control 487 ± 125 mU/l) nor ACTH (medians: RA 5.5 ng/l and controls 8.0 ng/l) showed any significant difference before naloxone injection.

After saline infusion. Patients receiving normal saline did not show any significant change in circulating cortisol (Fig. 1), prolactin (Fig. 2) or ACTH (data not shown).

After naloxone infusion. Plasma cortisol showed a sharp and significant rise after naloxone treatment in both RA and normal subjects. In RA patients, cortisol increased statistically significantly from 462 ± 180 to 577 ± 172 nmol/l (\( P < 0.01 \)) 30 min after naloxone infusion. The peak cortisol level in RA patients was 630 ± 152 nmol/l. In normal controls, cortisol increased from 439 ± 129 to 608 ± 172 nmol/l (\( P < 0.01 \)) 30 min after naloxone infusion. The peak cortisol level in normal controls was 620 ± 134 nmol/l. No statistically significant difference was observed between the two groups (Fig. 1).

The mean prolactin level showed no significant change in either group after treatment (Fig. 2). Interestingly, RA patients showed higher prolactin levels than normal controls when receiving either naloxone or saline infusions.

ACTH levels in patients and normal controls were in general very low. In both groups of patients, naloxone induced a marked rise in ACTH (>20 ng/l) in two individuals in each group. However, in most individuals there were small and transient increases in ACTH (data not shown). There were no statistically significant differences between the two groups.
DISCUSSION

The most important finding of this study is that 20 mg of naloxone produced a significant increase in cortisol and ACTH in patients with RA and healthy controls, but no difference was observed between the two groups. We also showed that naloxone had no effect on the prolactin level in both groups. There was no effect on prolactin levels in either group, supporting previous data [13, 14]. There is little evidence that endogenous opioids are important regulators of prolactin release in man [13-15]. Interestingly, we found that the circulating prolactin level was higher in RA patients than controls, although this did not reach statistical significance.

Our results confirmed previous data of Grossman et al. [2] showing that high-dose naloxone (16 mg) in normal subjects produced a peak level in plasma cortisol and ACTH [3, 16]. However, even at high doses, we cannot be absolutely sure that antagonism to opiate receptor occupancy is the only mode of action of naloxone [15]. A previous study showing that there was an additive effect of naloxone with CRH suggested that naloxone works through an ACTH-releasing factor independent of CRH, most probably the other recognized ACTH-releasing factor, vasopressin [17], or possibly both CRH and vasopressin [18]. The above data are also compatible with one previous report on the regulation of prolactin [19] and suggest that naloxone cannot be used as an endogenous surrogate for CRH as a test of the pituitary-adrenal axis [19].

We have shown that despite a significantly higher pain score at the baseline and throughout this study in the RA group compared with controls, we were unable to show any statistically significant difference in plasma cortisol and ACTH levels between RA patients and normal controls. Since RA patients had a higher pain score, they would be expected to have a higher endogenous opioid tone. This suggests that a high endogenous opioid tone does not account for the HPA axis defects in RA patients. However, it can be argued that RA patients with active disease should have a higher level of cortisol, their failure to do so indicating a blunted HPA response. Indeed, this could be explained by our previous finding that RA patients undergoing surgical stress showed a suboptimal cortisol response when compared to patients with osteoarthritis and osteomyelitis [18]. Nonetheless, the results of this study suggest that endogenous opioid tone is unlikely to be a major contributor to the HPA defect in RA, although this may be due to naloxone acting, at least in part, in releasing factors other than CRH. Hence, further studies are needed which investigate the vasopressin pathway in patients with RA.

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REFERENCES

