The authors thank Hoffman-LaRoche, Inc., for funding this research. Drs. Thomas Milhorat and Fred Scialabba for technical assistance and Ms. Wilma Rivera for manuscript preparation.

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Alpha-1-acid Glycoprotein and Beta-endorphin Alterations in Chronic Pain Patients

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Alpha-1-acid glycoprotein (AG) is an alpha-1 fraction serum protein that binds and reduces bioavailability of various basic drugs.1-5 Unlike other plasma drug binding proteins such as albumin, AG plasma levels are increased in stress responses associated with several clinical situations such as inflammation,6 malignancy,7 rheumatoid arthritis, myocardial infarction, and surgery.8,9 Thus, increased plasma levels of AG may bind and reduce efficacy of basic drugs including analgesics, tricyclic antidepressants, and beta-adrenergic receptor blockers in patients who are stressed.1-4,10,11 Because patients with chronic pain often are stressed and may receive many drugs, we compared AG plasma levels in chronic pain patients to matched control volunteers.

Plasma beta-endorphin (BE) levels decrease in patients with chronic pain,12,13 and the role of opioids in chronic pain and stress remains unclear. We measured BE plasma levels in the same samples and investigated correlations between AG, BE, and other patient variables.
TABLE 1. Characteristics of Chronic Pain and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Chronic Pain Patients</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>49.4 ± 2.8*</td>
<td>36.8 ± 3.3</td>
</tr>
<tr>
<td>Range</td>
<td>31-66</td>
<td>24-60</td>
</tr>
<tr>
<td>BMI (wt (kg)/ht²(m))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>25.1 ± 1.4</td>
<td>22.5 ± 0.6</td>
</tr>
<tr>
<td>Range</td>
<td>14.5-33.4</td>
<td>18.4-28.5</td>
</tr>
<tr>
<td>Number of prescribed drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>3.4 ± 0.7†</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Range</td>
<td>0-11</td>
<td>0-4</td>
</tr>
<tr>
<td>Duration of chronic pain (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>101.7 ± 17.9</td>
<td>0</td>
</tr>
<tr>
<td>Range</td>
<td>7-276</td>
<td></td>
</tr>
<tr>
<td>Pain severity rating (0–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>77.8 ± 4.7</td>
<td>0</td>
</tr>
<tr>
<td>Range</td>
<td>25-100</td>
<td>0</td>
</tr>
</tbody>
</table>

* Significantly different from control group, P < 0.01.
† Significantly different from control group, P < 0.002.

METHODS

With Human Subjects Committee approval and informed written consent, 16 patients from our chronic pain clinic and 15 volunteers with no pain complaints of both genders were studied. The specific diagnoses included postsurgical lumbar epidural scarring, adhesive arachnoiditis, myofascial syndrome, degenerative arthritis, diabetic neuropathy, and ilioinguinal neuritis. Patients and volunteers were determined by history and available laboratory values not to have any renal or hepatic disorders that would affect concentration of plasma proteins. Table 1 contains characteristics of patients and volunteers, including calculated body mass indices

\[ \text{BMI} = \frac{\text{wt (kg)}}{\text{ht}^2 (m)} \]

and subjective pain severity score (0–100) at the time of blood sampling.

Ten milliliters of blood samples were collected by venipuncture (2 p.m. ± 1 h) in prechilled polypropylene tubes containing 100 μl of a solution of bacitracin (2 mg/ml) and EDTA (20 mM). Plasma was isolated by centrifugation and assayed for the concentrations of AG and BE. AG analysis was performed by the single radioimmunoassay method.\(^{14}\) AG antisera were obtained from Dako Corporation (Santa Barbara, California), and human AG standard was obtained from CalBiochem-Behring (San Diego, California). Radioimmunoassay plates were obtained from Miles Scientific (Naperville, Illinois). Beta-endorphin immunoreactivity was measured using a New England Nuclear radioimmunoassay kit.\(^{15}\) To assess the influence of plasma AG on radioimmunoassay determinations of plasma BE, a range of AG concentrations (0, 25, 50, 100, 200 mg/dl) as well as exogenous human BE (50 or 125 pg/ml) were added to control plasma samples and the BE radioimmunoassay performed.

Statistical analyses were performed using Student’s t test, with \( P < 0.05 \) considered significant. Correlation coefficients were determined using standard calculator programs and significance calculated from degrees of freedom and \( r \) value using standard tables.

RESULTS

Demographic characterization found the chronic pain patient group to be slightly older (\( P < 0.01 \)) (table 1). Prescribed medications for the chronic pain patients included analgesics, antidepressants, beta-adrenergic receptor blockers, vasodilators, and others. The mean number of prescribed drugs was significantly more than controls (\( P < 0.002 \)) (table 1).

The plasma AG levels of chronic pain patients were higher than the control volunteer levels (\( P < 0.001 \), table 2). There were no significant differences in plasma AG between males and females in either pain or control groups. No significant correlation was found between age and the level of AG in either group (pain: \( r = -0.17 \), control: \( r = 0.09 \)). Thus, the age difference between the two groups does not account for the difference in plasma AG. Neither duration of pain nor pain severity score had significant correlation with the concentration of AG (\( r = -0.46, -0.41 \), respectively). In the control group there was a significant correlation between BMI and the level of AG (\( r = 0.52, P < 0.05 \)), but there was no such correlation in the pain group (\( r = 0.21 \)).

Plasma BE levels were significantly higher in control group patients than in pain patients (\( P < 0.001 \), table 2). There was no significant correlation between BMI and plasma concentration of BE in either pain (\( r = -0.09 \)) or control groups (\( r = 0.25 \)).

Pain group plasma levels of AG and BE demonstrate a significant negative correlation (\( r = -0.54, P < 0.05 \)). To be sure that elevated AG did not mask the detection of BE, a control plasma was treated with a fixed concentration of BE. AG was added in increasing amounts to this sample and BE levels determined on aliquots. The BE level was unaffected by the increased addition of AG, suggesting the negative correlation between the clinical sample groups is not an artifact.

DISCUSSION

Our findings demonstrate elevated plasma AG levels in chronic pain patients. The elevation may be due to stress of chronic pain, associated depression, drugs and therapy, or other factors and is consistent with previous
Table 2. Plasma Alpha-1-acid Glycoprotein Concentrations and Beta-endorphin Immunoreactivity

<table>
<thead>
<tr>
<th></th>
<th>Plasma Alpha-1-acid Glycoprotein Concentrations</th>
<th></th>
<th>Plasma Beta-endorphin Immunoreactivity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic Pain Patients</td>
<td>Control Group</td>
<td>Chronic Pain Patients</td>
<td>Control Group</td>
</tr>
<tr>
<td></td>
<td>Mean ± SEM (mg/dl)</td>
<td>Number</td>
<td>Mean ± SEM (mg/dl)</td>
<td>Number</td>
</tr>
<tr>
<td>Male</td>
<td>135.4 ± 11.4*</td>
<td>10</td>
<td>87.1 ± 10.9</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>140.0 ± 13.6†</td>
<td>6</td>
<td>75.8 ± 8.5</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>137.1 ± 8.5†</td>
<td>16</td>
<td>81.1 ± 6.7</td>
<td>15</td>
</tr>
</tbody>
</table>

* Significantly different from control group P < 0.01.
† Significantly different from control group P < 0.001.

reports of increased plasma AG in various conditions of chronic stress and disease. Because plasma AG binds and reduces bioavailability of basic drugs including analgesics, tricyclic antidepressants, and beta-adrenergic receptor blockers, elevated plasma AG could account for some aspects of apparent tolerance and reduced efficacy of these drugs.

BE immunoreactivity measurement is cross-sensitive to pituitary beta-lipotropin and perhaps other substances but remains a useful indicator of stress response. Our findings of decreased plasma BE immunoreactivity in chronic pain patients compared with control volunteers are consistent with other studies in which lower levels of plasma or cerebrospinal fluid opioids were reported. Inverse correlation between AG and BE plasma levels among chronic pain patients (and the lack of in vitro BE binding by AG) suggests that AG and BE are alternative modes of stress response in chronic pain patients. Mechanisms controlling hepatic synthesis and release of AG in chronic states are unclear; however, negative feedback by plasma opioids is one possibility.

Plasma AG may be a clinically relevant stress marker. Further studies of plasma AG, its pharmacologic importance, and relations to other stress response variables are indicated.

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