Normal sympathetic nervous system response in reflex sympathetic dystrophy

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Summary

We evaluated sympathetic nervous system activity by sympathetic skin response (SSR) recording and we further investigated sympathetic and opioid outflow indirectly in patients with features of reflex sympathetic dystrophy by measuring concentrations of plasma catecholamines (CAs) and their metabolites and plasma met-enkephalin (ME). Six patients were studied. Basal SSR latencies, morphologies and amplitudes were normal in five patients. In one woman, latency and amplitude were also normal but the morphology was disturbed. Basal plasma ME, CA and metabolite levels were similar in the affected and non-affected limbs and a significant increase in plasma ME concentrations was observed in both affected and non-affected limbs after two weeks of steroid treatment. Altogether these results point to an adaptive supersensitivity rather than a sympathetic hyperactivity in this syndrome; also, they indicate that the therapeutic effect of steroids adds, to their known anti-inflammatory action, a stimulatory action on the endogenous opioid system.

KEY WORDS: Catecholamines, complex regional pain syndrome, met-enkephalin, reflex sympathetic dystrophy, sympathetic skin response.

Introduction

Reflex sympathetic dystrophy (RSD) is a complication occurring even after minor injury to, or operation on, a limb. RSD is a descriptive diagnostic term that implicates the sympathetic nervous system in a reflex response to injury, with consequent dystrophic changes.

The pathophysiology of RSD remains unknown. In a revised taxonomic system of RSD, disorders previously considered to be RSD or causalgia were classified under the term complex regional pain syndrome (CRPS), which is based entirely on clinical criteria. The criteria for inclusion under this general term CRPS are the presence of regional pain – spontaneous and/or evoked – and other sensory changes following a noxious event. There are two types of CRPS, I and II, corresponding to RDS and causalgia respectively (1). It has been hypothesized that if injury to a limb normally provokes a rise in opioid-based modulation of activity in the regional sympathetic ganglia, it is possible that failure of this process occurs in some susceptible individuals, leading to localized signs of opioid withdrawal (2). The pain is associated with changes in skin color and temperature, abnormal sweating, edema and sometimes motor abnormalities. Hence, the sympathetic skin response (SSR) has been postulated as a diagnostic test (3).

We evaluated sympathetic nervous system activity by SSR recording and we further investigated sympathetic and opioid outflow indirectly in patients with type I CRPS features, by measuring concentrations of plasma catecholamines (CAs) and their metabolites, and plasma met-enkephalin (ME). Venous blood was taken from the painful and normal limbs before and after steroid treatment.
fortable and skin surface temperature was 32°C. Latencies from the palm ranging from 1.3 to 1.5 msec and amplitudes > 200 µV were considered normal.

Blood samples for simultaneous plasma ME and CA measurement were taken from both upper limbs with subjects resting in supine position. We used an indwelling intravenous needle inserted 30 minutes before sampling. All subjects were tested between 9 and 10 a.m., before and after two weeks of treatment with 1mg/kg/day prednisone.

Blood for ME measurements was put into polypropylene tubes kept on ice containing 10 mg/ml of a protease inhibitor cocktail (10,000 IUC/ml aprotinin, 0.23 mM citric acid, and 0.024 mM EDTA). Blood was centrifuged at 4°C and plasma was immediately stored at -20°C. ME was extracted from plasma by adsorption chromatography in Amberlite XAD-2 columns. ME was measured by radioimmunoassay using specific antisera (5). Under these experimental conditions, ME immunoreactivity corresponded to the free ME molecule as evidenced by reverse-phase high pressure liquid chromatography (RP-HPLC) (5). Iodinated ME was used as a tracer. Antiserum for ME showed a 100% cross-reactivity with met-(O)-enkephalin, 0.3% with leucine-enkephalin and less than 0.01% with leu-enkephalin-arginine, dynorphin and endorphins (6).

Blood for free plasma CA (adrenaline (A), noradrenaline (NA), dopamine (DA)) and dihydroxyphenylglycol (DHPG), dihydroxyphenylalanine (DOPA) and dihydroxyphenylacetic acid (DOPAC) measurements was poured into plastic tubes kept on ice containing 5 µl heparin/ml whole blood. Plasma was immediately separated by centrifugation at 2000 g for 20 min at 4°C and kept at -70°C until processed. Catechols in 1000 µl aliquots of plasma were partially purified by batch alumina extraction, and separated by RP-HPLC using a 4.6 x 250 mm Zorbax R X-C18 column (New England Nuclear, Du Pont, Boston, MA, USA). Quantifications were made by current produced upon exposure of the column effluent to oxidizing and then reducing potentials in series using a triple-electrode system (Coulochem II, ESA, Bedford, MA, USA) (7). Recovery through the alumina extraction step averaged 70-80% for CAs and 45-55% for DHPG. Catechol concentrations in each sample were corrected for recovery of a dihydroxybenzylamine internal standard. Levels of DHPG, DOPA and DOPAC were further corrected for differences in recovery of the internal standard and this catechol in a mixture of external standard. Written consent was obtained from all patients.

The significance of the differences found in patient plasma levels from both sides before and after prednisone treatment was analyzed by T test for paired samples. Data were expressed as mean ± SEM.

Results

Table II shows data from the SSR studies. Basal SSR latencies, morphologies and amplitudes were normal in five patients. In one woman (patient no. 6), amplitude was lower but still within the normal range. Latency was also normal but the morphology was disturbed. Figure 1 shows the recording from a representative patient with normal SSR parameters and from patient 6. Plasma ME concentrations in basal conditions in both limbs are shown in Figure 2. Basal plasma ME levels were similar for the affected and non-affected limbs: 0.21±0.01 and 0.24±0.01 pmol/ml respectively. In spite of a tendency to lower plasma A and DOPAC concentrations in the basal samples from the affected limb, no significant differences could be observed in plasma levels of DOPA, CA, DHPG (the intraneuronal metabolite of NA), and DOPAC (the metabolite of DA) between the two limbs explored (Table III).

After 2 weeks of prednisone treatment all patients im-

Table I - Clinical characteristics of CRPS type I patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Initial Injury</th>
<th>Duration (mths)</th>
<th>Pain</th>
<th>Temperature</th>
<th>Hyperhydrosis</th>
<th>Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>26</td>
<td>upper limb distortion</td>
<td>0.5</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>35</td>
<td>elbow fracture</td>
<td>1.6</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>52</td>
<td>shoulder fracture</td>
<td>4</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>48</td>
<td>upper limb distortion</td>
<td>3</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>76</td>
<td>skin injury</td>
<td>3.4</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41</td>
<td>upper limb distortion</td>
<td>4</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Table II - Individual SSR responses obtained after median nerve stimulation on the affected side.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Latency msec</th>
<th>Amplitude µV</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.45</td>
<td>1540</td>
<td>normal</td>
</tr>
<tr>
<td>2</td>
<td>1.38</td>
<td>2500</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>1.48</td>
<td>750</td>
<td>normal</td>
</tr>
<tr>
<td>4</td>
<td>1.33</td>
<td>1700</td>
<td>normal</td>
</tr>
<tr>
<td>5</td>
<td>1.40</td>
<td>3410</td>
<td>normal</td>
</tr>
<tr>
<td>6</td>
<td>1.33</td>
<td>520</td>
<td>abnormal</td>
</tr>
</tbody>
</table>

M. Figuerola et al.
proved clinically. Clinical improvement was established by a subjective improvement of spontaneous pain and lack of painful response to mechanical stimuli. No differences were found in plasma CA levels after prednisone treatment (Table III). Five of the six patients had normal values of plasma DA (normal range: 0-200 pg/ml) and one patient presented increased levels of plasma DA in the unaffected limb, before and after prednisone treatment.

A significant increase in plasma ME concentrations was observed in both affected and non-affected limbs after two weeks of prednisone treatment: 0.33±0.02 and 0.34±0.02 pmol/ml respectively (p<0.003 vs basal values) (Fig. 2).

Discussion
This study evaluates SSR, opioid and sympathetic activity simultaneously in CRPS I. The pathogenesis of CRPS I is not yet understood, and diagnosing and treating patients is difficult. SSR has been advocated as a simple means of assessing sympathetic sudomotor outflow in central and peripheral nervous system disorders. SSR is a change in skin potential following arousal stimulation, first described by Tarchanoff (8). It is a polysynaptic reflex that is activated by a variety of afferent inputs (9). The final efferent pathway involves pre- and post-ganglionic sympathetic sudomotor fibers and ultimately activation of sweat glands by the sympathetic outflow. The reflex is coordinated in the posterior hypothalamus, upper brain stem reticular formation and spinal cord. The responses are generated in deep layers of the skin by reflex activation of sweat glands via cholinergic sudomotor sympathetic efferent fibers. Because the reflex is multisynaptic, latency, amplitude, wave form and tendency to habituation are variable. The potentials may be mono, bi or triphasic (4, 9).

It has been reported that in RSD, the mean amplitude of SSR in the involved limb is greater than in the uninvolved limb, and onset latency of SSR in the involved limb is shorter than that of the uninvolved limb (9). Conversely, we found normal responses in 5/6 evaluated patients. The only patient (number 6) who presented the abnormal SSR response exhibited no other peculiarity. However, as in other generalized abnormalities of sympathetic sudomotor dysfunction, autonomic dysfunction or small fiber neuropathy, the correlation of the abnormal SSR is often poor. There is no close correlation between the presence or the absence of SSR and the severity of the autonomic dysfunction. So the results are not conclusive.

Early features of CRPS I in a limb (inappropriate pain, altered cutaneous sensation, excessive sweating, periph-

![Fig. 1 - SSR response. Upper panel: normal bilateral SSR obtained after median nerve stimulation in a representative patient. Lower panel: upper line represents the SSR obtained from the affected limb (normal latency and amplitude; abnormal configuration). Lower line represents the normal SSR obtained from the unaffected limb (patient no. 6).](image)

![Fig. 2 - Plasma ME levels in basal conditions and after prednisone treatment in both limbs.](image)
eral vascular instability and tremor) resemble the general effects of autonomic arousal associated with opioid withdrawal. Injury to a limb normally provokes a rise in opioid-based modulation of activity in regional sympathetic ganglia. It is possible that failure of this process occurs in some susceptible individuals, leading to localized signs of opioid withdrawal (2). The site of action of the opioids within the ganglion would most probably be on the presynaptic terminals of preganglionic nerve fibers (10). Increased blood concentrations of opioids are known to occur during strenuous muscular exercise (11). This effect might be mirrored by decreased opioid activity within the stellate and lumbar sympathetic ganglia when the adjacent limb is immobilized.

Considering a failure of the opioid-based modulation of activity in regional sympathetic ganglia as responsible, at least in part, for the syndrome, it is possible that the common practice of immobilization of minor limb injuries could contribute to the abolition of regional opioid modulation, by reducing neural traffic between limb and spinal cord (2). However, basal plasma ME levels in our patients were within our control range and we did not find any differences when comparing painful and non-painful sides.

The importance of the sympathetic nervous system in the generation of pain has been the focus of a long, if controversial, debate (12). Sympatholytic therapy can abolish pain and hyperalgesia, and in CRPS patients an intracutaneous injection of adrenoceptor agonists rekindled pain and hyperalgesia. An explanation consistent with these findings is that primary afferents acquire a sensitivity to CAs, which in some conditions extends to the receptive terminals innervating a symptomatic skin region. On the other hand it has been assumed that an increase in sympathetic outflow causes sweating and changes in peripheral blood flow in CRPS I (13). However, multiunit-microelectrode recordings of sympathetic outflow to affected skin failed to confirm that the sympathetic outflow is increased. Furthermore, the vasoconstrictor tone was found to be reduced rather than increased in the affected limb. Since CAs and ME are released from the periphery (i.e., sympathetic ganglia), levels should be similar on both sides of the body if both limbs are kept in similar environments. Different plasma concentrations in the painful and normal limbs would indicate that the local clearance rate differed on the two sides.

Our results show a tendency of adrenaline and DOPAC to be lower in the painful limb, so this entity appears to be associated with reduced rather than increased sympathetic outflow. We have no explanation for the higher plasma DA levels found in one patient in the unaffected limb. No differences in plasma A concentrations between affected and unaffected limbs have been reported. Besides, plasma NA and DHPG levels have been found to be lower on the painful side. These findings, like ours, do not support the view that autonomic disturbances in CRPS are due to sympathetic overactivity, but are more consistent with an adaptive supersensitivity of the SNS (13).

Sudeck in 1902 first attributed an inflammatory pathogenesis to CRPS I. The idea of an inflammatory pathogenesis is based on the observation that in the acute phase all classical signs and symptoms of inflammation are present. Moreover, the therapeutic effect of corticosteroids in some patients supports this idea (14). In addition, scintigraphic investigations with marked immunoglobulins have shown an intraosseous plasma extravasation in patients with CRPS I, which supports an inflammatory component of the disorder (15).

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It is difficult to explain the whole syndrome as exclusively peripheral. Lesioned afferent axons may generate spontaneous and evoked ectopic impulses, so the decoding of both nociceptive and non-nociceptive afferent information exerted by supraspinal systems is changed, resulting in distorted information processing in CNS.

All our patients were treated with 1mg/kg/day prednisone and their symptoms improved. After two weeks they were free from pain. At that moment an increase in plasma ME concentration in both limbs was observed, pointing to a general effect of steroid action. Previously, we had found an increase in plasma ME levels after

### Table III - Plasma levels of CA, DOPA, DOPAC and DHPG in the two limbs explored

<table>
<thead>
<tr>
<th></th>
<th>Affected Limb</th>
<th>Non Affected Limb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Treatment</td>
<td>Post Treatment</td>
</tr>
<tr>
<td>A pg/ml</td>
<td>37±9</td>
<td>41±10</td>
</tr>
<tr>
<td>NA pg/ml</td>
<td>246±67</td>
<td>221±60</td>
</tr>
<tr>
<td>DA pg/ml</td>
<td>168±54</td>
<td>86±20</td>
</tr>
<tr>
<td>DOPA pg/ml</td>
<td>936±223</td>
<td>1072±283</td>
</tr>
<tr>
<td>DOPAC pg/ml</td>
<td>1907±311</td>
<td>2108±191</td>
</tr>
<tr>
<td>DHPG pg/ml</td>
<td>992±119</td>
<td>1100±157</td>
</tr>
</tbody>
</table>

Abbreviations: A = adrenaline; NA = noradrenaline; DA = dopamine; DOPA = dihydroxyphenylalanine; DOPAC = dihydroxyphenylacetic acid; DHPG = dihydroxyphenylglycol.
prednisone treatment in patients with cluster headache (16).

Altogether, the results from this study seem to indicate an adaptive supersensitivity rather than a sympathetic hyperactivity in this syndrome. The therapeutic effect of steroids adds to their known anti-inflammatory action a stimulatory action on the endogenous opioid system.

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