Impaired prolactin response to hyperthermia in heroin addicts

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Abstract. The response of PRL, FSH and LH to sauna-induced hyperthermia was examined in 8 male former heroin addicts (studied after 14-24 days of abstinence) and 8 age- and sex-matched control subjects. The basal levels of PRL tended to be higher in former drug users than in control subjects (p=0.07). After sauna, there were no changes in the addict group, whereas a significant increase was observed in normal subjects (p<0.001). Baseline plasma LH and FSH levels were significantly lower in former drug users (p=0.02), but no change was found after sauna in either group. These findings are consistent with the existence of a deficient adaptation to thermal stress in chronic drug users, even after a relatively short drug-free period.

In previous studies we have shown that sauna-induced hyperthermia stimulated the secretion of beta-endorphin and ACTH in normal men (1), but not in heroin addicts, even after a relatively short (14 days) period of abstinence (2).

Since prolactin secretion is modulated by the endogenous opiate system (3), and its levels increase after thermal stress in normal men and women (4), we have examined the response of plasma PRL to sauna in a group of heroin addicts recently admitted to a therapeutic community.

Subjects and Methods

The subjects included in this study were 8 male former drug users, 18 to 30 years of age, who had joined a therapeutic community 14-24 days before the study, and 8 age- and sex-matched healthy volunteers, without a history of drug abuse. These subjects have been already examined in a previous study (2). The former drug users were involved in a long-term rehabilitation programme and were expected to stay for many months in the community group. All had abused heroin (approximately 0.5-1 g/day) for 12-48 months. Upon admittance to the community, they had stopped drug abuse, and, at the time of the study, they were essentially drug-free. The absence of morphine in plasma was confirmed with a commercial radioimmunoassay (Bio-Rad, Milano, Italy); that of methadone, heroin or morphine in the urine was confirmed with a multiple enzyme-linked immunoassay (Syve, Palo Alto, CA). The research protocol was reviewed and approved by the local ethical committee. All subjects gave their informed consent to participate in the study.

The subjects were studied at 08.00 h, after a 12-h abstinence from food, alcohol and tobacco; their physical activity before the test was minimal. After an indwelling Teflon catheter had been inserted into an antecubital vein, the subjects were allowed to rest for half an hour. Then they sat for 30 min in a sauna room where the temperature was 90°C and the relative humidity 10%. After the sauna, the subjects remained in a resting position for additional 30 min at room temperature.

Pulse rate, sublingual temperature, and blood pressure were recorded just before and immediately after the sauna, and after the 30-min rest period at room temperature. At the same time points, venous blood was drawn into ice-cold Vacutainer tubes, containing a mixture of EDTA and aprotinin, and immediately centrifuged at 0°C. Plasma was frozen within 10 min of collection, and stored at −70°C until assayed for PRL, FSH and LH.

PRL, FSH and LH were measured with commercial enzyme-linked immunosassays (Boehringer, Mannheim). The sensitivity of the PRL assay is 1 μg/l and the within- and between-assay coefficients of variations (CV) are 3 and 7%, respectively. The sensitivity of both the FSH and the LH assay is 0.5 IU/l, and the within- and between-assay CVs are 4 and 7%, respectively.

Comparisons between the basal levels of the parameters examined in the two groups were made by using the Mann-Whitney test. The hormonal variations after sauna were tested by the Wilcoxon matched pair test. The results are expressed as mean ± SEM (N=8) for each point).
Results

The changes in sublingual temperature, pulse rate and blood pressure during the experiment are shown in Table 1. At the end of the sauna, the sublingual temperature, the heart rate, and the systolic blood pressure increased significantly, whereas the diastolic blood pressure fell slightly. All these parameters returned to the basal levels after the 30-min rest period at room temperature. There was no difference in body temperature, heart rate or diastolic blood pressure between the two groups throughout the study. However, the increase in systolic blood pressure was significantly lower in former addicts than in control subjects (p<0.05).

The basal levels of PRL were higher in former heroin addicts than in the control subjects, with the difference approaching the conventional level of statistical significance (p=0.07). After sauna, there were no changes in the addict group, whereas a significant increase was observed in normal subjects (p<0.001). Baseline plasma LH and FSH levels were significantly lower in former drug users (p=0.02 in both cases). No change was observed after sauna in either group (p>0.15 in all cases) (Fig. 1).

Table 1.
Changes in body temperature and cardiovascular parameters; * = p<0.05 vs baseline; ‡ = p<0.05 for the difference between groups.

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>End of sauna</th>
<th>30 min after sauna</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sublingual temperature (°C)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Addicts</td>
<td>36.5±0.4</td>
<td>39.5±0.3a</td>
<td>36.4±0.2</td>
</tr>
<tr>
<td>Controls</td>
<td>36.7±0.2</td>
<td>39.4±0.3a</td>
<td>36.6±0.3</td>
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<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Addicts</td>
<td>77±6</td>
<td>144±7a</td>
<td>79±8</td>
</tr>
<tr>
<td>Controls</td>
<td>74±6</td>
<td>138±7a</td>
<td>77±5</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Addicts</td>
<td>120±7</td>
<td>130±8</td>
<td>113±8</td>
</tr>
<tr>
<td>Controls</td>
<td>121±4</td>
<td>158±7b</td>
<td>115±6</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addicts</td>
<td>84±5</td>
<td>69±4a</td>
<td>78±4</td>
</tr>
<tr>
<td>Controls</td>
<td>78±3</td>
<td>67±4a</td>
<td>77±5</td>
</tr>
</tbody>
</table>

Fig. 1.
Changes in the hormonal levels during the study in control subjects (dotted line) and heroin addicts (solid line). Single star: p<0.05 between groups; double star: p<0.01 vs baseline.

Discussion

Compared with control subjects, the heroin addicts examined in this study showed lower basal levels of FSH and LH and a clear trend to increased basal values of PRL. These results, which agree with our previous findings (5), support the hypothesis that opioid drugs stimulate PRL secretion (3) and inhibit the production of GnRH by the hypothalamus (6).

In normal subjects, sauna induced an increase in plasma PRL, which might be related to a possible role of the hormone in the regulation of water and electrolyte balance (7). Therefore, PRL is likely to be involved in the endocrine response to hyperthermia, whereas FSH and LH do not seem to be influenced by thermal stress, as previously suggested by others (4).

In contrast, PRL levels were not altered by hyperthermia in former drug users. In earlier studies, we have shown that after a sauna, plasma ACTH
and beta-endorphin increase in normal subjects but not in heroin addicts (1), in whom a suppressed synthesis and/or an altered enzymatic cleavage of pro-opiomelanocortin (POMC) from the anterior pituitary may be present (8).

In this context, the lack of a PRL response to thermal exposure suggests that the chronic abuse of opiates impairs the normal pituitary response to this exogenous stimulus. Moreover, this functional abnormality appears to persist for a long time, since it was still present after 14-24 days of complete abstinence. The deficient adaptation to thermal stress is further confirmed by the blunted increase in systolic blood pressure observed in these subjects, a finding we had already described (2).

The precise mechanism(s) whereby prolonged opiate abuse modifies pituitary secretion are at present unclear, but these substances can interfere with the neurotransmitter pathways controlling the hormonal release from the pituitary gland (3). In this regard, it is intriguing to notice that a dysfunction of the serotonergic system in heroin addicts is suggested by the increase in the urinary excretion of 5-hydroxy-indol acetic acid (9) and by the fact that the serotonin precursor, 5-hydroxy-tryptophan, may reduce the effects of heroin withdrawal (10).

The impaired PRL responsiveness to sauna might also result from a chronic stimulation of basal PRL secretion, with the subsequent exhaustion of intracellular stores and refractoriness to exogenous stimuli. However, this mechanism seems less likely, because we have shown in previous studies that in drug addicts the PRL response to TRH, an agent acting directly on pituitary cells, is increased and not decreased (11,12). Therefore, an impairment of the neural control mediating the response to thermal stress appears more probable.

In conclusion, heroin addicts studied after 14-24 days of abstinence showed decreased basal levels of LH and FSH, a tendency to increased plasma PRL in the basal state, and a deficient endocrine and cardiovascular response after thermal stress. These findings are consistent with the induction of long-lasting alterations in the cerebral monoaminergic pathways by morphine-like substances.

References

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