EFFECT OF CYPROHEPTADINE ON THYROTROPHIN AND PROLACTIN SECRETION IN NORMAL MAN

By

J. Golstein\(^1\), L. Vanhaelst\(^2\),
O. D. Bruno\(^3\) and M. L'Hermite\(^4\)

ABSTRACT

In order to investigate the effect of cyproheptadine, a compound with antiserotonergic activity, on the secretion of thyrotrophin (TSH) and prolactin (PRL), the nocturnal secretory patterns of these hormones have been studied in 4 normal men in the basal state and after an oral treatment with the drug. In addition, the TSH and PRL responses to TRH of 6 women were compared in the basal conditions and after cyproheptadine treatment. The TSH nocturnal secretion was slightly modified by drug treatment. The response to TRH as well as the basal levels were comparable in the treated and non-treated subjects. In contrast, the PRL secretion measured through the nocturnal investigation was significantly inhibited by cyproheptadine administration as were the PRL basal levels in the TRH test. The PRL response to TRH was comparable in both situations.

There are increasing numbers of studies dealing with the importance of the serotonergic mechanisms in the regulation of pituitary hormones secretion. Such studies, based on the comparative effects of serotonin agonists and antagonists, lead to rather controversial conclusions. As far as the regulation of TSH secretion is concerned, studies on euthyroid subjects are scarce. Administration of cyproheptadine, a drug with antiserotonin properties, was shown to blunt the TRH-induced TSH release (Egge et al. 1977; Ferrari et al. 1976),
suggesting a direct action of this drug at the pituitary level; yet, in these studies cyproheptadine effect on PRL response to TRH appeared variable. Methysergide, a clinically used blocker of serotonin receptors, was found to strongly suppress the sleep-related PRL secretion (Mendelson et al. 1975). In addition infusion of cyproheptadine blunted the PRL increase in response to the administration of 5-hydroxytryptophan (Kato et al. 1974).

On the other hand, it is well established that TSH and PRL secretions present circadian variations with a maximal increase occurring during the night (Vanhaelst et al. 1972; Weitzman 1976). This occurrence of circadian maxima across the sleep-period was taken into account to further evaluate the effects of cyproheptadine on the secretion of TSH and PRL. The drug was administered in normal volunteers and the nocturnal patterns of the different hormones were compared with the profiles recorded in the same subjects in the basal state.

In addition, the effect of the drug on the TRH-induced TSH and PRL responses was examined to try to clarify its possible action on the pituitary cells.

SUBJECTS AND METHODS

Four normal male volunteers, aged 25–26 years, with no history of mental illness, were investigated after an oral treatment with cyproheptadine (Periactin®), 4 mg at 08.00, 14.00, 20.00 and 24.00 h, during 3 consecutive days. Blood sampling was performed, through an iv catheter inserted at 21.00 h, every 15 min from 21.30 h until 10.00 h the next morning; the last dose of cyproheptadine was administered just before the subjects went to bed. They were sleeping as usual and great care was taken to avoid sleep disturbance. These 4 subjects had been submitted to a similar investigation on endocrine rhythms without any previous medication 12 months before.

In addition, 6 normally menstruating women were submitted to TRH stimulation tests with iv injection of 200 μg TRH while they were in the luteal phase of their cycle. Two such stimulation tests were performed in a fasting state at 4 weeks interval, one under basal condition and one under cyproheptadine treatment with 4 x 4 mg per day during 3 days. The last dose of cyproheptadine was given 1 h before the beginning of the TRH test. Three women were submitted first to the control test and one menstrual cycle later to the test under cyproheptadine, while for the other 3 subjects this sequence was reversed. Blood samples were collected at frequent time intervals from −30 min to 120 min.

Plasma levels of TSH and PRL were measured using specific radioimmunoassays (Golstein & Vanhaelst 1975; L’Hermite & Midgley 1971; Badawi et al. 1974). In the TSH assay, the limit of sensitivity is 0.6 μU/ml, intra-assay and inter-assay coefficients of variation are 5% and 10%, respectively. PRL was expressed in μU/ml of the Research Standard 71/222 (MRC)1). In the PRL assay the limit of sensitivity is 20

1) One ng of the VLS n°2 preparation of the human pituitary PRL = 22 μU of the standard 71/222.


Table 1.
Characteristics of the TSH nocturnal patterns.

<table>
<thead>
<tr>
<th>Subjects no</th>
<th>Basal state</th>
<th>After cyproheptadine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amplitude of the nocturnal rise (% of the mean)</td>
<td>Time of occurrence of the rise (h)</td>
</tr>
<tr>
<td>1</td>
<td>152</td>
<td>05.30</td>
</tr>
<tr>
<td>2</td>
<td>132</td>
<td>06.30</td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td>04.00</td>
</tr>
<tr>
<td>4</td>
<td>149</td>
<td>05.45</td>
</tr>
</tbody>
</table>

\[ t = 0.651 \quad 6.299 \quad 8.878 \]
\[ P = \text{N.S.} \quad <0.01 \quad <0.005 \]

µU/ml; intra-assay and inter-assay coefficients of variation are 5% and 8%, respectively. The patterns recorded during the nocturnal investigation span were compared without – and after drug treatment using a covariance analysis with 2 factors (subjects and treatment) and 1 cofactor (time); analysis of PRL data was performed after logarithmic transformation of the values. In order to eliminate artefactual data which could result from stress, the results of the first 4 samples of each experiment (values from 21.30 h to 22.15 h) were not taken into account. The patterns were divided into 3 phases: pre-sleep period from 22.30 h to 24.00 h, sleep period from 24.15 h to 08.00 h and awakening time from 08.15 h to 10.00 h; they were also analyzed as a whole. The following characteristics of each profile were determined: amplitude of the nocturnal rise (expressed in per cent of the mean level), time of occurrence of this rise (expressed in hours), and number of episodic variations (an episodic variation is taken into account when its value exceeds the preceding and the following value for at least twice the coefficient of variation). These characteristics were analyzed using the \( t \)-test for paired data. Finally one-way variance analysis was used to compare either the basal levels of the TRH-induced hormonal responses measured without and after cyproheptadine administration.

RESULTS

The mean TSH nocturnal patterns are shown in Fig. 1. Covariance analysis did not allow to detect any significant effect of cyproheptadine upon the levels measured during the nocturnal investigation span. However, the listed characteristics of the profiles presented in Table 1 reveal some significant
Mean values (± SEM) of serum TSH during the nocturnal investigation span.

Mean values (± SEM) of serum PRL during the nocturnal investigation span.


Fig. 2.
Table 2.
Characteristics of the PRL nocturnal patterns.

| Subjects no | After cyproheptadine | | Basal state | | | |
|---|---|---|---|---|---|
| | Amplitude | Time of | Number of | Amplitude | Time of | Number of |
| | of the | occurrence | episodic | of the | occurrence | episodic |
| | nocturnal | of the rise | variations | nocturnal | of the rise | variations |
| | rise | (h) | | rise | (h) | |
| 1 | 185 | 06.45 | 11 | 188 | 08.30 | 14 |
| 2 | 261 | 04.45 | 8 | 193 | 01.30 | 16 |
| 3 | 206 | 05.15 | 14 | 169 | 05.00 | 9 |
| 4 | 245 | 01.45 | 13 | 170 | 06.15 | 13 |

\[ t \] 2.489 \[ P \] N.S. \[ t \] 0.172 \[ P \] N.S. \[ t \] 0.551

Fig. 3.
Mean values (± sem) of serum TSH before and after TRH administration (arrow).


210
Mean values ($\pm$ SEM) of serum PRL before and after TRH administration (arrow).


alterations after drug treatment: delayed nocturnal rise ($P < 0.001$) and increased number of episodic variations ($P < 0.005$). In contrast, covariance analysis evidenced for PRL a significant inhibition of the nocturnal secretory pattern ($F = 23.74; P < 0.001$) as shown in Fig. 2. When this pattern was dissociated into 3 phases, only during the sleep period this inhibitory effect was significant (pre-sleep period $F = 0.537$, N.S.; sleep period $F = 50.913$, $P < 0.001$; awakening time $F = 0.004$, N.S.). The characteristics of the profiles, i.e. amplitude, of the nocturnal rise, time of its occurrence, or number of episodic variations, were not significantly altered (Table 2). Figs. 3 and 4 illustrate the TSH and PRL responses to TRH. Variance analysis failed to detect any significant variations between both experiments for both hormonal responses. In contrast PRL, but not TSH, basal levels were significantly lowered after cyproheptadine administration ($F = 30.89$, $P < 0.001$).

DISCUSSION

Depending on the respectively investigated hormones, cyproheptadine induced either qualitative or quantitative variations in the nocturnal profiles.

As far as TSH secretion is concerned, cyproheptadine treatment did not modify the basal levels in the nocturnal experiment as well as in the TRH experiment. Nevertheless, in all subjects a delay in the occurrence of the nocturnal rise together with an increased number of episodic variations was
observed under drug treatment; it accounts for significant qualitative alterations of the nocturnal TSH profile. It has been shown previously (Vanhaelst et al. 1972), that in basal conditions the TSH circadian rhythm is fairly reproducible for subjects investigated twice at 3 week intervals. Although the fundamental mechanism of the TSH circadian and ultradian variations is still unknown, it was postulated (Vanhaelst et al. 1972) that neuronal interconnections were involved in their genesis. The presently observed alterations under drug treatment are compatible with the hypothesis that serotonergic mechanisms can modulate the regulation of the TSH secretion. The lack of effect of cyproheptadine on TRH-induced TSH release is at variance with the cyproheptadine-blunting effect reported by other investigators (Egge et al. 1977; Ferrari et al. 1976). In the first study (Egge et al. 1977) TRH was administered for 4 consecutive days which might explain a lowering of the TSH response, not related to drug intake, as already observed in control subjects (Haigler et al. 1971; Snyder & Utiger 1973). Ferrari et al. (1976), using a protocol very similar to ours, also reported a depressing effect of cyproheptadine in normal males. In the present study, TRH tests were performed in female volunteers. This sex difference can hardly account for the discrepancy of the results. The present data thus suggest the absence of a direct effect of cyproheptadine on thyrotropes. In contrast with its effect on TSH, cyproheptadine significantly lowered the PRL levels measured during the nocturnal investigation. The results of the statistical analysis reveal that it is mainly during sleep that PRL levels were decreased. This action of cyproheptadine, although less marked, is similar to that of methysergide, another drug with antiserotonin properties, which inhibited sleep-related PRL secretion (Mendelson et al. 1975). Cyproheptadine has been reported to have additional antidopaminergic properties (Stone et al. 1961). In the present study, the decrease of PRL secretion in the presence of the drug allows to rule out an antidopaminergic action since it is clearly demonstrated that agents blocking dopamine receptors stimulate PRL secretion (Shaar & Clemens 1974; McLeod & Lehmeyer 1974; L'Hermite et al. 1978). Similarly, our results cannot be explained by the antihistaminic properties of cyproheptadine; indeed it has been demonstrated that histamine H1 receptor antagonists, such as diphenhydramine, do not affect PRL or TSH levels in adult men (Carlson & Ippoliti 1977). In addition, it has also been shown (Carlson & Ippoliti 1977) that cimetidine, a blocker of histamine H2 receptors, stimulates PRL secretion; this rules out a similar effect of cyproheptadine. The effect of cyproheptadine on episodic variations or on the time of occurrence of the nocturnal rise varied according to the subjects (Table 2). Considerable variability in the circadian pattern of PRL has been described in control subjects and might account for the present finding (Vanhaelst et al. 1973). The lack of effect of cyproheptadine on the PRL response to TRH presently observed is in accordance with the results from Ferrari et al.
(1976), but at variance with those from Egge et al. (1977). Whilst PRL levels during the pre-sleep period and the awakening time were not significantly diminished, the basal levels observed during the TRH test were decreased by drug treatment. This apparent discrepancy could be explained by an increased activity of the receptors involved in the drug action, induced by oestrogen; indeed the TRH tests have been performed in women in the luteal phase of their cycle.

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