Cyclosporine A Inhibits the Secretion of Certain Anterior Pituitary Hormones in Patients with Nephrotic Syndrome

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Abstract. To clarify the effects of cyclosporine A (CsA) on the secretion of serum thyrotropin (TSH), prolactin (PRL), luteinizing hormone (LH) and follicular stimulating hormone (FSH), we performed TRH and LH-RH testing in 4 patients with the nephrotic syndrome before and after the administration of CsA, 6 mg/Kg/day for 4 to 12 weeks. Prior to CsA all patients responded normally to TRH with respect to TSH and PRL secretion. Two patients showed normal response of LH and FSH to LH-RH stimulation while the response in 2 other patients, who were both menopausal, was exaggerated. By the third or fourth week of CsA administration the basal and peak TSH and PRL values declined significantly in all patients in response to TRH stimulation while those of LH and FSH showed only a modest decrease in response to LH-RH stimulation. Two to 4 weeks after the cessation of CsA the response of TSH, PRL and FSH returned to the pretreatment level. These observations suggest that 1) CsA exerts an inhibitory effect on the secretion of at least TSH and PRL in humans, and 2) the effect of CsA on the pituitary may be partially reversible after the cessation of the therapy.

Keywords: Cyclosporine A, TSH, PRL, Gonadotropin, Nephrotic syndrome.

CYCLOSPORINE A (CsA), a cyclic undecapeptide of fungal origin, is used widely as an immuno-suppressive agent in treating patients undergoing organ transplantation [1, 2] and those with certain autoimmune diseases [3-5]. It was recently reported that this agent exerts such effects on the rat endocrine system as suppression of androgen synthesis [6-9], inhibition of adrenocortical function [10], suppression of the secretion of adrenocorticotropic (ACTH) and corticosterone [11], stimulation of prolactin (PRL) secretion [12] and inhibition of insulin secretion [13]. However, there are no reports on its effects on pituitary function in humans. In this study, we evaluated the effects of CsA on the secretion of thyrotropin (TSH), PRL, luteinizing hormone (LH) and follicular stimulating hormone (FSH) in patients with the nephrotic syndrome.

Methods

From April 1990 to March 1991, four steroid-resistant patients with the nephrotic syndrome, 2 males and 2 menopausal females, were admitted to our hospital for the purpose of receiving CsA, which has been shown to be effective in treating some cases of this disorder [14]. Their mean age was 51 years, range 40–64 years. The histological diagnosis (made by renal biopsy) was focal glomerulosclerosis in 2 patients and membranous nephropathy in the 2 others. All patients received CsA orally, 6 mg/Kg/day for 4 to 12 weeks. The
Table 1. Clinical data on 4 patients with nephrotic syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<td>age</td>
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<td>40</td>
<td>64</td>
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<tr>
<td>sex</td>
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<td>M</td>
<td>F</td>
<td>F</td>
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<td>body weight (kg)</td>
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<td>65.5</td>
<td>64.6</td>
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<td>FGS</td>
<td>MN(^b)</td>
<td>MN</td>
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<tr>
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<td>0.8</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>serum total protein (g/dl)</td>
<td>4.3</td>
<td>5.0</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>proteinuria (g/day)</td>
<td>7.3</td>
<td>2.1</td>
<td>2.6</td>
<td>3.5</td>
</tr>
<tr>
<td>serum CsA concentration (ng/ml)</td>
<td>150</td>
<td>109</td>
<td>193</td>
<td>180</td>
</tr>
<tr>
<td>complications</td>
<td>IGT(^c)</td>
<td>IGT</td>
<td>HT(^d)</td>
<td>IGT</td>
</tr>
</tbody>
</table>

\(^a\) focal glomerulosclerosis; \(^b\) membranous nephropathy; \(^c\) impaired glucose tolerance; \(^d\) hypertension; CsA, Cyclosporine A.

medication was administered each day at 1000 h; the serum trough level of CsA was determined at 0700 h (range 109–193 ng/ml, which was in the optimal range). The mean serum creatinine level in the patients was 1.4 mg/dl (range 0.7–2.9 mg/dl), and the mean daily urinary protein excretion was 3.9 g/day (range 2.1–7.3 g/day). Of the 4 patients, 2 had hypertension, and 3 had impaired glucose tolerance (Table 1).

All patients gave their informed consent to participate in this study and received TRH and LH-RH loading tests 3 times during this study: before the initiation of CsA treatment, during its administration (in the 3rd or 4th week of treatment) and 2 to 4 weeks after the cessation of therapy. After an overnight fast, TRH (500 \(\mu\)g) and LH-RH (100 \(\mu\)g) were administered simultaneously as a load dose, and blood samples were collected at 0, 15, 30, 60, 90, 120 min to measure the serum levels of TSH, PRL, LH and FSH. Monitored data during this study were renal function (including serum creatinine and the 24 h creatinine clearance), proteinuria, serum protein, thyroid function (Free T\(_3\), Free T\(_4\) and TSH) and serum estradiol.

PRL, LH and FSH were measured by an immunoradiometric assay (Daichi-Radioisotope Laboratory, Tokyo, Japan), Free T\(_3\) and Free T\(_4\) by a radioimmunoassay (Amersham Japan, Tokyo, Japan), TSH by a two-site immunoenzymometric assay (Tosoh, Yamaguchi, Japan), and serum estradiol by a radioimmunoassay (CIS-Diagnostic, Chiba, Japan).

Data are given as the mean ± SEM. Statistical analysis was performed by means of paired Student’s t-test. Significance was defined as a P value less than 0.05.

Results

During the study, there was no significant change in renal function, the extent of daily proteinuria, thyroid function or the serum estradiol level (data not shown).

Before CsA treatment, basal and peak TSH, PRL, FSH and LH in response to TRH and LH-RH stimulation were as follows: TSH, 2.3±0.1 to 10.5±2.5 \(\mu\)U/ml; PRL, 5.6±1.7 to 35.3±15.7 ng/ml; FSH, 50.1±41.2 to 62.5±45.3 mIU/ml, and LH, 29.5±23.4 to 77.1±36.0 mIU/ml.

During CsA treatment, basal and peak TSH and PRL in response to TRH stimulation were significantly decreased (TSH, 1.4±0.3 to 4.8±1.5 \(\mu\)U/ml and PRL, 3.8±1.7 to 19.9±9.2 ng/ml, Fig. 1).
Cyclosporine A inhibits pituitary secretion

Fig. 2. Changes in basal and peak FSH and LH values in response to LH-RH stimulation before, during, and after Cyclosporine A (CsA) treatment. Values are given as the mean ± SEM.

After cessation of CsA treatment, basal and peak TSH and PRL in response to TRH stimulation returned to the pretherapy level (TSH, 2.0±0.4 to 12.1±4.7 µU/ml and PRL, 4.4±1.0 to 25.2±12.3 ng/ml, Fig. 1). Basal and peak FSH and LH in response to LH-RH stimulation were both decreased during CsA treatment in all patients, especially in menopausal women, but not to a significant extent (FSH, 37.3±33.8 to 50.1±38.0 mIU/ml and LH, 19.2±15.7 to 71.4±35.2 mIU/ml, Fig. 2). Following the cessation of CsA administration, basal and peak FSH in response to LH-RH stimulation returned to the pretreatment level. Basal LH also returned to the pretreatment level but the peak value in response to LH-RH stimulation decreased further (FSH, 53.1±25.6 to 69.1±30.7 mIU/ml and LH, 24.2±10.9 to 67.9±20.2 mIU/ml, Fig. 2).

Discussion

While CsA has been shown to exert a variety of effects on the endocrine system both in vivo and in vitro [6–13], there are no reports on its effects on anterior pituitary function in humans. Our data clearly show that CsA inhibits the secretion of TSH and PRL significantly in patients with the nephrotic syndrome. Concerning FSH and LH, the extent of the decrease in both hormones during CsA treatment did not reach statistical significance. This may be due to the fact that we had only a small number of subjects with different basal levels of gonadotropins. We believe that increasing the number of subjects can clarify the inhibitory effect of CsA on the secretion of gonadotropins, and the study is now going on. On the other hand, it is not clear whether CsA directly affects their secretion by the pituitary or instead suppresses the release of TRH and LH-RH from the hypothalamus. Although Sikka et al. [8] showed that the hypogonadotropic hypogonadism induced by CsA in intact male rats was mediated through the hypothalamic-pituitary axis, primarily at the hypothalamic end, we recently found that CsA decreased the basal secretion of PRL and PRL mRNA levels in GH3 cells (unpublished observations). It is therefore possible that CsA acts directly on the pituitary.

It has been shown in rats that the CsA-induced inhibition of the hypothalamic-pituitary-testicular axis is completely reversible within 4 weeks of the cessation of CsA administration [7]. Our data demonstrate that the inhibitory effects of CsA on the secretion of TSH, PRL and FSH are reversible also in humans within 2 to 4 weeks after its discontinuance, except for LH secretion. Since the patients’ thyroid and gonadal status were unaffected during this study, it seems that a negative feedback mechanism is probably not responsible for the reversibility. The reason why the secretion of LH failed to revert to normal after CsA treatment is not clear. We recently described a patient with Klinefelter’s syndrome who developed a decrease in serum gonadotropin, particularly of LH, after the administration of CsA for complicated focal glomerulosclerosis [15]. In this case, the decrease in LH persisted for at least 6 weeks posttherapy. Thus a longer period of time may be required to restore LH secretion.

Concerning the effect of CsA on PRL secretion, Cardon et al. demonstrated that this agent stimulates PRL secretion one hour after its administration to normal rats [12]. Our results in humans were contrary to theirs. Although the reason for the discrepancy is not clear, there are several
possible explanations: 1) a differing duration of CsA treatment; 2) a difference in the CsA level when the PRL concentration was measured, e.g. under the peak or the trough; 3) species difference; and 4) the presence of renal dysfunction in our patients.

In conclusion, CsA inhibits the secretion of TSH and PRL, and possibly inhibits that of FSH and LH. These effects on the pituitary appear to be partly reversible after the cessation of CsA. Further investigation of the sites of action of CsA is required.

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References