Inhibitory Effect of Cerebellin on Rat Thyroid Gland

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ABSTRACT
Cerebellin (CER) is a 16-amino acid peptide originally isolated from rat cerebellum, which has been recently reported to stimulate adrenal-gland secretion. We have investigated the effects of the prolonged administration of CER and its analogue [Des-Ser]-CER (CERA) (15 nmol/kg day for 6 days) on the growth and function of rat thyroid gland. CER and CERA markedly increased the weight of thyroid gland. Thyroid follicles contained large amounts of colloid and their epithelial cells were shorter than those of control rats. Accordingly, morphometry showed that epithelium/colloid ratio was strikingly lowered. These changes strongly suggest that CER and CERA exert an inhibitory effect on rat thyroid-gland secretion, downstream to colloid synthesis. However, serum concentrations of thyroid-stimulating hormone and thyroid hormones were not significantly altered by CER and CERA treatment, thereby making it likely that the inhibitory effect is only partial.

Cerebellin (CER) is a 16-amino acid peptide originally isolated from rat cerebellum (9), that exerts a neuromodulatory function in the central nervous system (2, 10). CER expression, as protein and mRNA, has been subsequently detected in several extracerebellar tissues and organs, including heart, kidney, stomach and normal and tumorous adrenal medulla (2, 8). Earlier in vivo and in vitro studies showed that CER exerts a sizeable secretagogue action on catecholamines and corticosteroid hormones (1, 6, 7).

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In the course of our recent in vivo studies on the adrenal cortex (6), we observed a marked enlargement of the thyroid gland in CER administered rats. Hence, it appeared of interest to investigate whether CER and its analog (Des-Ser)-CER (CERA) affect the function of the pituitary-thyroid axis in rats.

MATERIALS AND METHODS
Adult female Wistar rats (180–190 g body weight) were kept under a 14:10 h light-dark cycle (illumination onset at 8:00 a.m.) at 23°C, and maintained on a standard diet and tap water ad libitum. The animals were divided into three experimental groups (n=8), two of which were given daily subcutaneous injections of 15 nmol/kg CER or CERA (Bachem, Bubendorf, Switzerland) dissolved in 0.2 mL 0.9% NaCl for 6 days. The control group received only the saline vehicle. Rats were decapitated between 10:00 and 11:00 a.
RESULTS AND DISCUSSION

The prolonged administration of CER and CERA caused a marked increase in the weight of thyroid gland (Fig. 1). Thyroid follicles contained large amounts of colloid and their epithelial cells were notably shorter than those of control rats (Fig. 2). Morphometry confirmed these qualitative findings, showing that, although the volumes of both epithelium and colloid were increased, the epithelium/colloid ratio was strikingly reduced (Fig. 1). CER and CERA treatment did not provoke significant changes either in the serum concentrations of TSH, tT4, iFT4, tT3 and fT3 or in the tT3/tT4 ratio (Table 1).

Taken together, these findings suggest that CER and CERA exert an inhibitory effect on thyroid-gland function. In fact, epithelium/colloid ratio, which increases in the case of TSH hypersecretion, is a very sensitive parameter to evaluate thyroid-gland function (3, 4, 11). Since

Fig. 1 Effects of CER and CERA-A on thyroid-gland weight (A), volume of follicular epithelium (B), volume of colloid (C) and epithelium/colloid ratio (D). Bars are means ± SEM (n = 8). *P < 0.05 and **P < 0.01 from control (C) group.

<table>
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<tr>
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<th>Controls</th>
<th>CER</th>
<th>CERA</th>
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<tbody>
<tr>
<td>TSH (pmM)</td>
<td>98.9 ± 9.9</td>
<td>122.1 ± 9.5</td>
<td>121.2 ± 29.6</td>
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<tr>
<td>tT3 (nM)</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.2 ± 0.1</td>
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<tr>
<td>tT3 (pM)</td>
<td>7.4 ± 0.4</td>
<td>7.0 ± 0.3</td>
<td>7.1 ± 0.3</td>
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<tr>
<td>iFT4 (pM)</td>
<td>49.6 ± 6.4</td>
<td>48.0 ± 3.8</td>
<td>48.1 ± 4.3</td>
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<tr>
<td>tT3/tT4 (×1000)</td>
<td>37.8 ± 2.7</td>
<td>33.2 ± 2.6</td>
<td>34.9 ± 2.2</td>
</tr>
<tr>
<td>tT3/tT4 (×1000)</td>
<td>29.4 ± 2.9</td>
<td>28.9 ± 2.4</td>
<td>25.6 ± 1.9</td>
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Data are means ± SEM (n = 8).

CER and CERA markedly lower it, it appears reasonable to conceive that these peptides impair post-synthetic steps of thyroid-hormone secretion: i.e. endocytosis and proteolysis of thyroglobulin or secretion per se. Iodine uptake or availability is not affected because tT3/tT4 ratio is unchanged in CER and CERA administered rats.

However, these changes are not coupled with
significant variations in the blood levels of both TSH and thyroid hormones, thereby suggesting that CER- or CERA-induced inhibition of thyroid gland secretion is only partial. The discrepancy between morphological and functional findings could be tentatively explained by considering that structural changes reflect the sum of the CER- and CERA-induced partial impairment of colloid utilization during the 6 days of treatment, which however is too small to evoke significant changes in the blood hormonal levels. The exact mechanism by which CER and CERA inhibit pituitary-thyroid axis remains to be elucidated.

REFERENCES