NOTE

Effect of Somatostatin (Growth Hormone Inhibiting Factor: GIF) on TRH-induced TSH Release in Rats

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Synopsis

Intravenous preadministration of somatostatin (Growth Hormone Inhibiting Factor: GIF) inhibited TRH-induced TSH release in rats anesthetized by pentobarbiturate. There was dose dependent negative interaction between the inhibitory effect of GIF and releasing effect of TRH. TSH releasing effect of small dose of TRH was inhibited completely by preadministration of GIF, while large dose of TRH overcame the inhibitory effect of GIF. The mechanism responsible for inhibitory effect of GIF on TRH-induced TSH release was discussed.

It has been well known that somatostatin (growth hormone inhibiting factor: GIF or somatotropin-release inhibiting factor: SRIF), isolated and synthesized by Paul Brazeau and his coworkers (1973), lowers circulating level of immunoreactive growth hormone and inhibits the elevation of plasma growth hormone induced by acute administration of pentobarbiturate. Furthermore, it had been reported that synthetic somatostatin inhibited the elevation of plasma TSH induced by acute administration of synthetic TRH in vitro and in vivo (Abstract 1973, Hall et al., 1973). An attempt was made to study the influence of somatostatin on TRH induced TSH release in rats with special reference to quantitative relation between dose of GIF and TRH in vivo.

Material and Method

1) Animals
Male Sprague-Dawley rats, weighing 140-160 g, were used in this experiments. They were housed at temperature 20 ± 2°C and humidity 50 ± 5%, and fed Oriental Lab Chow and tap water ad libitum.

2) Chemicals
Synthetic somatostatin used in this experiments was provided kindly by Dr. Yanaihara and solutions for the studies were made in 0.9% saline. Synthetic TRH was the commercial preparation(Pyro-Glu-His-Pro-NH2-tartarate). Anesthesia of rats was performed by pentobarbiturate (4.5 mg/100 g. B.W.).

3) Radioimmunoassay for rat-TSH
The measurement of rat plasma TSH was performed by a double antibody method, using NIAMD-Rat TSH-I-1 for iodination, NIAMD-Anti Rat TSH-S-1, NIAMD-Rat TSH-RP-1 as standard, and anti-rabbit-γ-globulin-goat serum as precipitating antibody. Plasma samples were assayed in volumes of 0.2 ml or less. Assay sensitivity was 10 ng of NIAMD-Rat TSH-RP-1 and results were expressed in µg/ml of this standard. (Bassiri et al., 1974)

4) Method
100 µg, 50 µg and 10 µg of somatostatin were pretreated into the juglar vein of 4 rats, respectively, under pentobarbital anesthesia, 0.9% saline was injected as control. Ten minutes after administration of somatostatin of 100 µg, 50 µg and 10 µg, TRH was administered intravenously in doses of 0.5 ng, 1 ng and 5 ng (This result was showed in Table 1). Ten minutes after 10 µg somatostatin, 1 ng, 10 ng and 100 ng of TRH was administered respectively (The result was showed in Table 2).

Blood sample of 1 ml/ for each rat was withdrawn
Table 1. Effect of somatostatin on TRH-induced TSH release

<table>
<thead>
<tr>
<th></th>
<th>TRH (0.5 ng)</th>
<th>TRH (1 ng)</th>
<th>TRH (5 ng)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Saline</td>
<td>0.30</td>
<td>0.64</td>
<td>0.48</td>
</tr>
<tr>
<td>GIF (100 µg)</td>
<td>0.18</td>
<td>0.15</td>
<td>0.18</td>
</tr>
<tr>
<td>GIF (50 µg)</td>
<td></td>
<td>0.10</td>
<td>0.12</td>
</tr>
<tr>
<td>GIF (10 µg)</td>
<td>0.10</td>
<td>0.32</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* All TSH values were obtained from pooled blood samples of 4 rats by duplicated assay and expressed as mean.

Table 2. Effect of somatostatin on plasma TSH levels to various TRH doses

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>30 (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH (1 ng)</td>
<td>Saline</td>
<td>0.19 ± 0.01</td>
<td>0.84 ± 0.19</td>
<td>1.03 ± 0.09</td>
</tr>
<tr>
<td>GIF (10 µg)</td>
<td>0.15 ± 0.05</td>
<td>0.38 ± 0.06</td>
<td>0.55 ± 0.17</td>
<td>0.28 ± 0.04</td>
</tr>
<tr>
<td>TRH (10 ng)</td>
<td>Saline</td>
<td>0.20 ± 0.06</td>
<td>1.56 ± 0.24</td>
<td>1.38 ± 0.38</td>
</tr>
<tr>
<td>GIF (10 µg)</td>
<td>0.13 ± 0.04</td>
<td>1.26 ± 0.41</td>
<td>1.16 ± 0.14</td>
<td>0.43 ± 0.06</td>
</tr>
<tr>
<td>TRH (100 ng)</td>
<td>Saline</td>
<td>0.20 ± 0.02</td>
<td>2.48 ± 0.28</td>
<td>3.28 ± 0.33</td>
</tr>
<tr>
<td>GIF (10 µg)</td>
<td>0.18 ± 0.02</td>
<td>1.85 ± 0.15</td>
<td>1.85 ± 0.15</td>
<td>1.24 ± 0.08</td>
</tr>
</tbody>
</table>

* p < 0.05 in comparison to control group.
** Plasma TSH values were expressed as mean ± SE (of 4 rats).

The results showed that somatostatin was effective in suppressing TSH release when administered before TRH. However, larger doses of TRH (10 ng and 100 ng) were able to overcome the inhibitory effect of somatostatin.

Discussion

It has been well documented that TRH...
activity might be inhibited or modified by preadministration of several hormones i.e., thyroxine (T₄) (Martin et al., 1972), triiodothyronine (T₃) (Vale et al., 1967), corticosteroid (Otsuki et al., 1973) and estrogen (Carlson et al., 1973).

It seems very interesting to declare whether a new synthesized hypothalamic hormone, somatostatin, might have modifying effect on TRH activity or not. Intravenous injection of synthetic somatostatin has inhibitory effect of GH release in man and rats during various GH releasing stimuli, such as insulin induced hypoglycemia (Hall et al., 1973), acute administration of pentobarbital-Na (Brazeau et al., 1974), electrical stimulation (Martin et al., 1974), chlorpromazine (Sawano et al., 1974), and prostaglandin E₁, (Ooshima et al., 1974). Partial or complete inhibitory effect of somatostatin on TRH induced TSH release were observed in our experiment described before. Since plasma TSH level of rats pretreated with somatostatin was almost the same to that of saline treated rats, resting plasma TSH level was thought to be unaffected by pretreatment of somatostatin. However, plasma TSH response to TRH was less in rats pretreated with somatostatin than in rats treated by saline. On our observation, TRH-induced TSH response was inhibited by the administration of somatostatin in dose of 10 μg, which was thought to be effective in man (Hall et al., 1973).

These results indicate that the inhibitory action of somatostatin on TRH-induced TSH response was dose dependent and comparable to observations in man. The inhibitory mechanism of somatostatin on TRH induced TSH release is not yet clear, but somatostatin may act on receptor of pituitary thyrotroph concerned with TSH release (TRH receptor) to compete with TRH. There are previous reports that administration of TRH induces TSH and prolactin release in man and animals. Hall (1973) had reported that somatostatin inhibited TRH induced TSH release, but not altered TRH induced prolactin release. Somatostatin presumably competes with TRH for the receptors of pituitary cells related to TSH release but not receptors concerned with prolactin release. It has been already reported that there are negative interaction for TSH release between the dose of T₄ and that of TRH: the definite dose of T₄ inhibit the activity of definite dose of TRH, and large dose of TRH overcome the inhibitory action of T₄ (Vale et al., 1967). Since actinomycin D, puromycin and cycloheximide, a kind of protein synthesis inhibitor, prevent the inhibitory effect of T₄ (Bower et al., 1968), it was postulated that newly synthesized protein might be necessary for inhibitory action of T₄ (Schally et al., 1968). It seems necessary to investigate possible metabolic changes occurring in pituitary cells by administration of somatostatin.

Acknowledgements

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Reference

Hall, R., Besser, G. M., Schally, A. V., Coy, D. H., Evered, D., Goldie, D. J., Kastin,


