Effect of Thyrotropin Releasing Hormone Injection on Blood Growth Hormone (GH), TSH and Growth Hormone Releasing Hormone (GHRH) Concentrations in Cancer Patients

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Abstract

In order to investigate whether endogenous GHRH and somatostatin were involved in the mechanism of the paradoxical GH rise after TRH injection, changes in serum GH and plasma GHRH were examined before and after TRH injection in 12 cancer patients and changes in serum TSH and GH were similarly studied in 76 cancer patients including 31 GH-responders and 45 GH-nonresponders to TRH. TRH stimulated GH secretions without altering the circulating GHRH concentration in 4 of the 12 cancer patients.

There was neither a significant correlation between the increase from the basal to maximum GH and GHRH after TRH injection in the 12 cancer patients nor a reciprocal relationship between the increase in GH and TSH after TRH injection in the 76 cancer patients.

These findings suggested that the paradoxical GH rise after TRH injection in cancer patients was exerted by its direct action at the pituitary level, and not mediated through the hypothalamus.

Thyrotropin-releasing hormone (TRH) stimulates both TSH and prolactin secretion in normal subjects, but does not significantly affect GH secretion. There have also been many reports demonstrating that an abnormal increase in plasma GH can be induced after TRH injections in patients with various diseases including acromegaly and gigantism due to GH cell adenoma (Irie and Tushima, 1972; Fagilia et al., 1972) and ectopic growth hormone releasing hormone (GHRH) producing tumors (Ch'ng et al., 1976; Collu et al., 1977), renal failure (Czernichow et al., 1976), cirrhosis of the liver (Zanoboni and Zanoboni), depression (Maeda et al., 1970) and anorexia nervosa (Maeda et al., 1970).

We have also demonstrated a significant increase in GH after TRH injection in cancer patients (Kamijo et al., 1980, 1983). The mechanism of TRH-induced paradoxical response of GH still remains to be clarified.

The present research is intended to determine whether endogenous GHRH or somatostatin is involved in this paradoxical response in cancer patients.
Materials and Methods

Eighty-seven cancer patients including 38 gastric cancers (ca), 13 hepatocellular ca, 11 colon ca, 8 esophageal ca, 6 pulmonary ca, 5 pancreatic ca and 6 others were studied.

TRH (500 µg) was given intravenously and venous blood was collected through an indwelling needle before and after TRH injection. All subjects studied gave informed consent to the investigation.

All tests were performed between 8 a.m. and 10 a.m. and samples were stored at −20°C until the assay of serum GH (Kamijo et al., 1983), TSH (Kamijo et al., 1988), and plasma GHRH by radioimmunoassay, as previously reported in detail by Ohyama et al. (1987).

Plasma GHRH was extracted with silicagel (C-20) and eluted with 0.1 N-HCl: acetone (1:4) mixture. The antiserum, obtained from New England White Rabbit immunized with GHRH (1-44)NH₂ was proved to recognize the middle portion of GHRH(1-44)NH₂.

The intraassay result for 1 sample using pooled plasma was 4.3±0.5 pg/ml (M±SD, CV; 11.6%) and 2 arranged samples obtained by addition of GHRH to pooling plasma were 10.3±0.8 (CV; 7.6%) and 18.0±0.9 (CV; 5.2%). Recovery rates in 3 samples ranged from 86.2 to 103%. The interassay data for 3 samples from pooled plasma which were also prepared in a similar way and measured at 5 different times were 8.3±1.5 (CV; 18.4%), 18.0±1.7 (CV; 9.6%) and 33.1±2.8 (CV; 8.5%), respectively.

A definition of GH responder to TRH was made by means of the criteria, as previously described (Kamijo et al., 1983).

Student's t-test was used for the statistical analysis.

Results

The clinical features of cancer patients and their GH responsiveness to TRH are shown in Table 1.

No increase in the plasma GHRH concentration after TRH administration was seen in 4 TRH-responsive cancer patients, as shown in Fig. 1. Fig. 2 reveals that there was no correlation between the increase in plasma GHRH and in serum GH after TRH injection in the 12 cancer patients.

The increase in serum GH after TRH injection was not significantly correlated with the increase in serum TSH after TRH injection.

<table>
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<tr>
<th>Case</th>
<th>Age</th>
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<th>GH Time in minutes</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>15</td>
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<td>(1) GH-Responder Group</td>
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<td></td>
<td></td>
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</tr>
<tr>
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<td>63</td>
<td>M</td>
<td>Gastric ca</td>
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<tr>
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<td>53</td>
<td>F</td>
<td>Colon ca</td>
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<td>72</td>
<td>M</td>
<td>HCC</td>
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<tr>
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<td>75</td>
<td>F</td>
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<td>69</td>
<td>M</td>
<td>Panc. ca</td>
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<td>M</td>
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</table>

(ca: cancer, HCC: hepatocellular carcinoma, Panc: pancreas and Mal. meso.: malignant mesothelioma)
Fig. 1. Effect of TRH injection on plasma GHRH concentrations in cancer patients. (A) indicates GH responder and (B) GH non-responder.

injection in the 76 cancer patients, as shown in Fig. 3.

Discussion

We demonstrate that TRH stimulates GH secretion without a significant change in the plasma GHRH concentration in some cancer patients.

Recently it has been reported concerning patients with GHRH producing tumor that TRH acutely stimulates plasma GH without altering circulating GHRH (Ch'ng et al., 1985; Barkan et al., 1986). Barkan et al. suggest that a paradoxical GH re-

Fig. 2. Correlation between the increase in serum GH and plasma GHRH concentrations after TRH injection in cancer patients. (*Increase from basal to maximum value)

Fig. 3. Correlation between increase in serum GH and TSH values after TRH injection in cancer patients.
response to TRH in an acromegalic patient resulting from a GHRH-producing tumor may be exerted at the pituitary level, consequent to prolonged exposure of the pituitary gland to high concentrations of GHRH.

In the present study, it is also reported that there is no significant correlation between the paradoxical response of serum GH to TRH and the increase in serum TSH after TRH injection.

Somatostatin plays a physiological role in the inhibition of TSH secretion (Vale et al., 1975; Ferland et al., 1976; Urman and Critchlow, 1983), although Williams et al. (1988) showed in man that the overall effects indicated an approximate 10-fold greater potency of somatostatin in inhibiting GH compared to TSH secretion. It must therefore be possible that the serum TSH response to TRH is correlated with the hypothalamic somatostatin content, although no exact method to establish this hypothesis has yet been made available. The hypothesis that the GH response to insulin hypoglycemia is mediated by decreased somatostatin release also has some discrepancies because insulin hypoglycemia has an inhibitory effect on serum TSH response to TRH (Kelijman and Frohman, 1988) and the high degree of correlation between plasma GH response to insulin and GHRH in obesity is also demonstrated (Williams et al., 1984).

The results of the present study indicate that TRH stimulates GH secretion at a locus of the pituitary gland, not through the hypothalamus.

Acknowledgements

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References


