Abnormal Growth Hormone Responses to CB-154 and Thyrotropin-Releasing Hormone (TRH) in Patients with Acromegaly

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CB-154 (2-Br-α-ergocriptine) stimulates growth hormone (GH) release in normal subjects. In acromegaly, however, this agent often decreases plasma GH level paradoxically. In order to examine the mechanism of the so-called "paradoxical decrease" in plasma GH with CB-154, GH responses to CB-154 were compared with GH responses to thyrotropin-releasing hormone (TRH), arginine, and luteinizing hormone-releasing hormone (LH-RH) in 20 cases of acromegaly. CB-154, as well as L-dopa, elicited decrease in GH in those patients whose GH secretion was more responsive to TRH and less responsive to arginine. These results suggest that, like L-dopa, CB-154 has similar dual actions of TRH antagonistic GH decrease and GH-RF (GH-releasing factor) facilitative GH increase. Moreover, it was speculated from this study that CB-154 has no significant effect on LH-RH release. The value of (increase ratio of GH on TRH)/increase ratio of GH on arginine) can be used as an index for the indication of chronic CB-154 therapy in patients with acromegaly. —— acromegaly; paradoxical GH decrease; CB-154; TRH; arginine; LH-RH

Like L-dopa and apomorphine, CB-154 (2-Br-α-ergocriptine) is one of the dopaminergic agonists which activate dopamine-receptor (Corrodi et al. 1973). It elevates the plasma concentrations of GH in normal subjects (Camanni et al. 1975), but it paradoxically decreases secretion of GH in patients with acromegaly (Liuzzi et al. 1974a; Camanni et al. 1975). Based on this phenomenon, CB-154 has recently been used widely for the therapy of acromegaly (Liuzzi et al. 1974a; Sachdev et al. 1975; Thorner et al. 1975; Belforte et al. 1977; Waas et al. 1977). But, at present, the mechanism of the so-called "paradoxical GH decrease" with CB-154 in acromegaly is still unknown.

Dopamine possesses broad actions on the release of several hypothalamic hormones such as GH-RF (GH-releasing factor) (Müller et al. 1968; Boyd et al. 1970; Martin 1973; Merimee and Rabin 1973), TRH (thyrotropin-releasing hormone) (Brown et al. 1972; Onaja et al. 1974), LH-RH (luteinizing hormone-releasing hormone) (Fuxe et al. 1969; Schneider and McCann 1969) and PIF (prolactin release-inhibiting factor) (Donoso et al. 1971; Buckman et al. 1973).

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On the other hand, TRH (Irie and Tsushima 1972), LH-RH (Rubin et al. 1973), and arginine (which is thought to release GH-RF) (Lawrence et al. 1970; Pecile et al. 1972; Martin 1973; Merimee and Rabin 1973) often stimulate GH release in acromegalic patients. On an assumption that TRH, LH-RH and GH-RF might participate in the dopaminergic stimulants induced GH decrease in acromegals, we previously examined the relationships between paradoxical GH decrease with L-dopa and several combinations of GH increase with TRH, arginine, and LH-RH in these patients. According to statistical analyses, a significant correlation was observed on GH decrease with L-dopa when acromegalic patients were more responsive to TRH and less responsive to arginine ($r=-0.881$, $p<0.001$) (Hanew et al. 1977a).

In order to know if this correlation is generally acceptable for other dopaminergic stimulants, we examined the relationships between paradoxical GH decrease with CB-154 and several combinations of GH increase with TRH, arginine, and LH-RH in patients with acromegaly.

**Patients and Methods**

**Patients**

Twenty patients with acromegaly, 6 males and 14 females, aged between 18 and 61 years were subjected to the study. Nine of them had been previously treated with linear irradiation and/or transfrontal hypophysectomy. The other 11 cases were untreated patients.

**Procedures**

*Control study.* Physiological fluctuations in plasma GH levels were determined according to the method previously reported (Hanew et al. 1976).

*Tests.* CB-154 (2-Br-a-ergocriptine, Sandoz, Basel) 2.5 mg was administered orally and blood samples were taken via the indwelling needle catheter placed in an antecubital vein at 1 hr, 0 hr before and 1 hr interval for 5 hr after the administration. TRH (500 µg i.v.), arginine (0.5 gm/kg of BW i.v. for 30 min), and LH-RH (100 µg i.v.) tests were done according to the methods previously reported (Hanew et al. 1977a).

All tests were started between 07:00 and 09:00 a.m. after an overnight fast. Plasma GH levels were measured by a double antibody radioimmunoassay method (Schalch and Parker 1964). Purified human GH used for standards was provided by Dr. A.E. Wilhelmi, NIH. Intra- and between-assay coefficients of variation in GH radioimmunoassay were 3.9 and 7.4%, respectively.

Statistical significance was determined by Student’s $t$ test.

**Results**

*Fluctuations of plasma GH*

Physiological fluctuations of plasma GH within 2.5 hr were quite small as reported elsewhere (Hanew et al. 1976), and the mean ($\pm$ s.e.m.) range of variation in this series was $-9.6$ ($\pm2.4$) and $+18.6$ ($\pm4.3$) from the initial GH levels (Fig. 1). Therefore, in the evaluation of responses to exogenous stimuli, we regarded tentatively the increment of GH above 50% as an increase and the decrement of GH exceeding 50% from the basal value as a decrease.
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Fig. 1. Spontaneous fluctuations of plasma GH within 2.5 hr.

Table 1. Plasma GH (ng/ml) responses to 4 agents in 20 patients with acromegaly

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>TRH</th>
<th>Arginine</th>
<th>LH-RH</th>
<th>CB-154</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Basel</td>
<td>LR.*</td>
<td>Basel</td>
<td>I.R.*</td>
</tr>
<tr>
<td>1 T.K.</td>
<td>59 F</td>
<td></td>
<td>15.5</td>
<td>46.61</td>
<td>13.8</td>
<td>2.14</td>
</tr>
<tr>
<td>2 M.I.</td>
<td>56 F</td>
<td></td>
<td>9.1</td>
<td>40.16</td>
<td>11.6</td>
<td>3.05</td>
</tr>
<tr>
<td>3 Y.On.</td>
<td>61 F</td>
<td></td>
<td>6.9</td>
<td>28.26</td>
<td>5.4</td>
<td>3.48</td>
</tr>
<tr>
<td>4 K.Y.</td>
<td>63 F</td>
<td></td>
<td>8.1</td>
<td>18.70</td>
<td>11.8</td>
<td>1.22</td>
</tr>
<tr>
<td>5 E.S.</td>
<td>26 F</td>
<td></td>
<td>5.4</td>
<td>16.94</td>
<td>14.0</td>
<td>2.24</td>
</tr>
<tr>
<td>6 K.K.</td>
<td>43 F</td>
<td></td>
<td>49.0</td>
<td>13.98</td>
<td>36.6</td>
<td>3.50</td>
</tr>
<tr>
<td>7 K.S.</td>
<td>37 M</td>
<td></td>
<td>110.0</td>
<td>10.63</td>
<td>27.5</td>
<td>1.29</td>
</tr>
<tr>
<td>8 S.S.</td>
<td>37 F</td>
<td></td>
<td>6.5</td>
<td>10.63</td>
<td>6.8</td>
<td>2.94</td>
</tr>
<tr>
<td>9 Sh.O.</td>
<td>34 M</td>
<td></td>
<td>17.8</td>
<td>4.49</td>
<td>34.8</td>
<td>1.36</td>
</tr>
<tr>
<td>10 M.A.</td>
<td>48 F</td>
<td></td>
<td>41.3</td>
<td>3.91</td>
<td>41.3</td>
<td>1.89</td>
</tr>
<tr>
<td>11 M.S.</td>
<td>35 F</td>
<td></td>
<td>15.8</td>
<td>3.41</td>
<td>8.8</td>
<td>1.76</td>
</tr>
<tr>
<td>12 K.Ku.</td>
<td>45 F</td>
<td></td>
<td>33.3</td>
<td>2.41</td>
<td>32.5</td>
<td>3.05</td>
</tr>
<tr>
<td>13 I.W.</td>
<td>43 M</td>
<td></td>
<td>20.0</td>
<td>1.68</td>
<td>8.5</td>
<td>2.94</td>
</tr>
<tr>
<td>14 K.Kw.</td>
<td>53 F</td>
<td></td>
<td>29.6</td>
<td>1.38</td>
<td>28.3</td>
<td>5.25</td>
</tr>
<tr>
<td>15 S.Sa.</td>
<td>44 F</td>
<td></td>
<td>22.5</td>
<td>1.22</td>
<td>19.3</td>
<td>1.19</td>
</tr>
<tr>
<td>16 M.K.</td>
<td>46 M</td>
<td></td>
<td>26.0</td>
<td>1.12</td>
<td>25.5</td>
<td>1.05</td>
</tr>
<tr>
<td>17 J.S.</td>
<td>26 F</td>
<td></td>
<td>92.0</td>
<td>1.10</td>
<td>78.5</td>
<td>2.25</td>
</tr>
<tr>
<td>18 Y.O.</td>
<td>42 M</td>
<td></td>
<td>41.3</td>
<td>1.09</td>
<td>85.0</td>
<td>1.06</td>
</tr>
<tr>
<td>19 S.O.</td>
<td>51 F</td>
<td></td>
<td>17.6</td>
<td>1.07</td>
<td>11.0</td>
<td>1.18</td>
</tr>
<tr>
<td>20 M.E.</td>
<td>37 M</td>
<td></td>
<td>32.7</td>
<td>1.00</td>
<td>24.8</td>
<td>1.05</td>
</tr>
</tbody>
</table>

* I.R. (increase ratio): Peak GH value/basal GH value.
† % change: Maximum percent change of GH from basal value.
Comparison of GH responses to CB-154 and to TRH

Plasma GH responses to TRH, arginine, LH-RH and CB-154, and interrelationships between GH response to CB-154 and several combinations of GH responses to the other 3 agents were shown in Table 1 and Table 2, respectively.

Eleven of 20 patients with acromegaly showed a paradoxical decrease with CB-154 (paradoxic responders), and percent decrease from basal value varied from -51.5 to -92.8% (Mean -74.6%; Table 1). Two cases (K. Kw. and I.W.), however, showed an increase in GH as normal subjects (normal responders).

After administration of TRH, 13 out of 20 patients showed an increase in GH above 50% from the basal value (Table 1). Among them, 10 cases were paradoxical responders to CB-154 and one case (I.W.) was normal responder to CB-154.

There proved a significant negative correlation between the percent change of GH induced by CB-154 and log value of increase ratio (I.R. = peak GH value/
basal GH value) of GH released by TRH (represented as I.R. on TRH) ($r=-0.555$, $p<0.02$; Table 2 and Fig. 2). But, there was no correlation between GH responses to CB-154 and I.R. on TRH when simply compared.

Comparison of GH responses to CB-154 and to arginine

Both CB-154 and arginine stimulate GH release in normal subjects (Eddy et al. 1974; Camanni et al. 1975). After administration of arginine, 11 out of 20 cases showed an increase in GH above 50% from the basal value (Table 1). Of these 11 cases, 7 were paradoxical responders and other 2 (K.Kw. and I.W.) were normal responders to CB-154. There were no correlations between the GH response to CB-154 and the GH response to arginine (represented as I.R. on arginine) or the log value of I.R. on arginine (Table 2).

Comparison of GH responses to CB-154 and to LH-RH

After administration of LH-RH, 7 out of 20 cases showed an increase in GH above 50% from the basal value (Table 1). Of these 7 cases, 5 were paradoxical responders, and the other one (I.W.) was normal responder to CB-154. There were no correlations between the GH response to CB-154 and the GH response to LH-RH (represented as I.R. on LH-RH) or the log value of I.R. on LH-RH (Table 2).

Interrelationships between GH response (percent change) to CB-154 and several combinations of GH responses (increase ratios) to TRH, arginine and LH-RH

When changes in GH on CB-154 were compared with the combinations of GH responses to TRH, arginine and LH-RH, comparatively large correlation was
Fig. 3. Interrelationship between the percent change of GH on CB-154 and log (T/A×L) (logarithm of I.R. on TRH/I.R. on arginine×I.R. on LH-RH).

Fig. 4. Interrelationship between the percent change of GH on CB-154 and log T/A (logarithm of I.R. on TRH/I.R. on arginine).
observed between the changes on CB–154 and I.R. on TRH/(I.R. on arginine × I.R. on LH-RH) \((r=-0.489, p<0.05; \text{Table 2})\). In addition, more significant correlation was observed between the changes on CB–154 and log value of that index \((r=-0.686, p<0.001; \text{Table 2 and Fig. 3})\). Especially, the highest correlation was proved between the changes on CB–154 and log value of I.R. on TRH/I.R. on arginine \((r=-0.689, p<0.001; \text{Table 2 and Fig. 4})\). This result is concordant with the previous study between GH responses to L-dopa and several combinations of GH responses to TRH, arginine, and LH-RH (Hanew et al. 1977a). However, this relationship between percent changes on CB–154 and log (I.R. on TRH/I.R. on arginine) was weaker compared with the study on L-dopa (Hanew et al. 1977a).

**DISCUSSION**

It is well known that dopaminergic stimulants such as L-dopa, apomorphine and CB–154 decrease the GH level paradoxically in patients with acromegaly (Liuzzi et al. 1972, 1974a; Choidini et al. 1974). In addition, these patients often show abnormal GH increase after administration of TRH and LH-RH (Irie and Tsushima 1972; Rubin et al. 1973), which probably stimulate TRH- and LH-RH-receptors on their somatotrophs. Concerning these phenomena, Liuzzi et al. (1974b) found some correlation between paradoxical GH decrease with L-dopa and abnormal GH increase with TRH, although it was statistically not significant.

In a previous report, we (Hanew et al. 1977a) found marked correlations between paradoxical GH decrease with L-dopa and log (I.R. on TRH/I.R. on arginine), and suggested the possibility that L-dopa has the following opposing dual actions; 1) TRH antagonistic GH-lowering action, 2) arginine-like facilitation of GH release via the stimulation of GH-RF. Therefore, we thought that paradoxical GH decrease might be caused when GH-lowering effect of L-dopa was dominant over its GH-elevating effect.

This study showed a close relationship between paradoxical GH decrease with CB–154 and log (I.R. on TRH/I.R. on arginine). These findings would suggest that CB–154 has the similar dual actions as seen in L-dopa just mentioned above.

Recently, Camanni et al. (1977) found paradoxical GH decrease in acromegaly after intravenous infusion of dopamine. Since dopamine does not cross blood brain barriers, they thought that dopamine exerts a direct suppressive effect on pituitary gland. It is reported also that dopamine and TRH are antagonistic in their effect in GH secretion in man (Burrow et al. 1977). In addition, the evidence of direct suppressive effect of CB–154 on GH secretion from cultured adenoma of acromegalic patients was presented by Mashiter et al. (1977). Therefore, the paradoxical GH decrease with CB–154 might be caused by the stimulation of dopamine-receptors of somatotrophs antagonizing the GH-releasing activity of TRH. But, indirect suppressive effect of CB–154 via the release of hypothalamic TRH antagonistic factors cannot be ruled out completely.

In this study, eleven out of 20 cases showed clear GH increase on the administration of arginine. As arginine-induced GH increase in normal men is thought
to take place via the release of hypothalamic GH-RF (Martin 1973; Merimee and Rabin 1973), the following 3 possibilities might be considered, 1) hypothalamic GH-RF reserve is not diminished by the elevated GH levels, 2) this factor is released by arginine in the arginine responsive patients (Martin 1973), and 3) these patients have GH-RF receptors, whereas unresponsive patients might have no receptors on their somatotrophs.

On the other hand, as dopamine is thought to release the hypothalamic GH-RF (Müller et al. 1968), dopaminergic stimulants (such as L-dopa and CB-154) induced GH increase in normal subjects is also thought to be via the release of the factor (Boyd et al. 1970; Martin 1973; Merimee and Rabin 1973). In connection with these findings, the fact that the cases which were more responsive to arginine than to TRH (e.g., I.W., K.Kw. and K.Ku.) showed clear increases or a slight decrease in GH on the administration of CB-154 give a support to our hypothesis that even if in patients with acromegaly those dopaminergic stimulants would possess the similar GH-RF releasing activity like arginine.

A significant correlation was also observed between paradoxical GH decrease with CB-154 and \( \log \frac{\text{I.R. on TRH}}{\text{I.R. on arginine} \times \text{I.R. on LH-RH}} \). However, this was not predominant compared with the former index for the CB-154 induced GH decrease. Therefore, it is speculated that CB-154 has not a significant effect on LH-RH release in these patients.

When the relationships between GH responses to CB-154 and several combinations of GH responses to TRH, arginine, and LH-RH in this study were compared with the relationships between GH responses to L-dopa and those combinations of GH responses to the above three agents in previous study (Hanew et al. 1977a), closer relationships were found on L-dopa than on CB-154. This findings might be explained by the fact that GH-lowering effect of CB-154 is longer than that of L-dopa in patients with acromegaly (Chiodini et al. 1975; Sachdev et al. 1975; Belforte et al. 1977). Furthermore, when CB-154 was compared with L-dopa in their effect on GH secretion in 20 cases in this study, one (I.W.) showed an increase in GH on CB-154 but no response on L-dopa. One case (Y.O.) showed an increase on L-dopa but no response on CB-154, and another 2 (K. Ku. and M.K.) paradoxical decreases on CB-154 but no response on L-dopa. The remaining 16 cases, however, showed similar responses in GH both to CB-154 and L-dopa. Thus there exist fine differences in affecting GH secretion between them, although major actions of these two dopaminergic stimulants are similar.

As mentioned already, CB-154 has been used widely for the therapy of active acromegaly. However, long-term CB-154 therapy sometimes decreases the effectiveness, even if the patients initially show paradoxical GH decreases after a rapid test of CB-154 (Sachdev et al. 1975; Belforte et al. 1977). Relating to this problem, we have interesting data that among 7 cases on chronic CB-154 therapy 5 showed good responses to the therapy and the index \( \frac{\text{I.R. on TRH}}{\text{I.R. on arginine}} \) was consistently exceeding 2 (range: 2.1 to 22.2). On the other hand, the index in the remaining
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In two cases was below 1 and they showed no response to the therapy (Hanew et al. 1977b). Therefore, we propose the index to be used as an indication of chronic CB-154 therapy in patients with acromegaly.

In conclusion, the paradoxical GH decrease with CB-154, as well as L-dopa, in patients with acromegaly was more remarkable when their GH secretion was more responsive to TRH and less responsive to arginine, although fine differences in actions between CB-154 and L-dopa were supposed.

References

16) Hanew, K., Aida, M., Sasaki, A. & Yoshinaga, K. (1977b) CB-154 therapy of


