MECHANISM OF ACTION OF GROWTH HORMONE IN ALTERING ITS OWN SECRETION RATE: COMPARISON WITH THE ACTION OF DEXAMETHASONE

By
Eugenio E. Muller*, Shinji Sawano, Akira Arimura and Andrew V. Schally

ABSTRACT
Administration of large doses of growth hormone (GH) (2 mg/100 g/day for 5 days) failed to modify growth hormone-releasing factor (GRF) activity in either 1) plasma and the hypothalamus of long-term hypophysectomized rats, 2) the hypothalamus of normal rats. An elevation of pituitary content of GH was observed in normal rats as a consequence of growth hormone treatment. In contrast to growth hormone, dexamethasone (50 μg/100 g/day for 5 days) induced considerable decrease of GRF activity in both plasma and the hypothalamus of long-term hypophysectomized rats, as well as in the hypothalamus of normal rats. No alteration of pituitary GH content was observed in normal rats as a consequence of chronic dexamethasone treatment. GH (1 mg/100 g) given 30 minutes before administration of a hypothalamic extract blocked the GH-depleting activity of the latter, while dexamethasone (50 μg/100 g) given one hour before apparently was ineffective. It is suggested that growth hormone suppresses its own secretion rate acting directly on the pituitary gland, while the action of dexamethasone on GH secretion, takes place mainly at the level of the hypothalamus.

The existence for growth hormone (GH) secretion of an »autofeedback« mechanism in which the plasma concentration of the hormone directly influences

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its own secretion from the pituitary gland, has been recently postulated. Muller & Pecile (1966) observed that exogenous growth hormone inhibited the release of growth hormone which follows insulin-induced hypoglycaemia, while Krulich & McCann (1966) noticed that daily, subcutaneous injections of large doses of growth hormone for 6 days resulted in an increase of the hormone in the pituitary gland.

These studies, however, did not elucidate the mechanism of action of GH in modifying its own secretion rate. In particular it was not clear whether the suppressive action of growth hormone on its secretion took place at the level of the hypothalamus through impairment of the synthesis and/or release of its hypothalamic neurohumour growth hormone-releasing factor (GRF), or directly at pituitary level.

We have recently shown that GRF activity can be demonstrated in plasma of rats hypophysectomized about 3 months previously, but is undetectable in plasma of normal animals, or animals hypophysectomized one week before (Muller et al. 1967 a).

In order to throw light on the mechanism by which GH alters its own secretion rate, we have investigated the effect of daily administration of high doses of growth hormone on 1) plasma and hypothalamic GRF activity of long-term hypophysectomized rats, and 2) hypothalamic GRF activity of normal rats. Recently it has been observed that cortisol treatment impairs GH release (Hartog et al. 1964; Frantz & Rabkin 1964) through an action involving the hypothalamic control of GH secretion (Pecile & Muller 1966).

It therefore seemed pertinent to compare the effect of growth hormone with that of a highly potent synthetic steroid such as dexamethasone.

MATERIALS AND METHODS

Hypophysectomized animals – Test for plasma GRF activity

Sprague-Dawley female rats, hypophysectomized when 26 days old were obtained from Hormone Assay Laboratories (Chicago, Ill.). These hypophysectomized animals were used about 3 months postoperatively as donors of plasma. They were divided in 4 groups of 5 animals each. The first group was taken as a control and injected only with saline, the second group was treated with growth hormone (2 mg/100 g b. w. given s. c. for 5 days), the third and the fourth groups were treated with dexamethasone (50 µg/rat given i. p. for 5 days) and follicle stimulating hormone (2 mg/rat given s. c. for 5 days) respectively. Blood was collected about 12 hours after the last injection. The animals were anaesthetized with ether and bled from the abdominal aorta into a heparinized syringe. Four to five ml of blood were collected from each rat; the blood from animals of each group was pooled and the plasma separated by centrifugation. The pooled plasma samples were kept frozen until immediately before injection. One ml of the pooled plasma sample from each group of donors was injected into a carotid artery of 30 day-old Sprague-Dawley female rats. Fifteen min after the injection they were decapitated. Their pituitary glands were removed and weighed to the nearest
0.01 mg on a microtorsion balance; hypophysial tissue was then pooled by groups and homogenized in 0.9% saline.

The depletion of pituitary GH in recipient animals was used as an index of GRF activity present in plasma of donor animals. GH activity of the samples was measured by the «tibia test» method of Greenspan et al. (1949).

For the assay of GH were used female Sprague-Dawley rats, hypophysectomized at 26–28 days of age, which were obtained from Hormone Assay Laboratories (Chicago, Ill.). Six to eight rats were used to assay each sample of pituitary homogenates. The results are expressed directly in terms of the width of the epiphyseal cartilage, the values obtained with pituitary glands from each experimental group being compared with those obtained with pituitary glands from saline injected animals. Significance of differences in epiphyseal cartilage width was determined by Student’s t test.

**Test of hypothalamic GRF activity**

The GH-releasing activity of stalk median eminence (SME) extracts of experimental rats was evaluated as follows: acid extracts of the stalk median eminence region of these rats were prepared as reported previously (Pecile et al. 1965). As recipient animals, 30 day-old Sprague-Dawley female rats were used. They were given the equivalent of 2.5 SME in 1.0 ml of saline by intracarotid injection under ether anaesthesia. Fifteen minutes after the injection, the recipient rats were decapitated. GH activity of their anterior pituitary glands was measured as described above.

**Normal animals**

Sprague-Dawley female rats of about 120 g b. w. were obtained from Cheek Jones, Houston, Texas. They were divided into 3 groups of 16 animals each and treated with saline, growth hormone or dexamethasone at the doses and for the time period used for the hypophysectomized animals. Twelve hours after the last injection the animals were killed by decapitation. At autopsy body and pituitary weights were recorded, pituitary GH activity was determined according to the method of Greenspan et al. (1949) (See Table 3). Hypothalamic GRF activity of these animals was determined as described above. Stalk-medium eminence extracts of animals treated with saline and growth hormone were assayed for GRF activity at two dose levels (2.5 and 1.0 SME), while SME extracts of dexamethasone treated animals were assayed at one dose level (2.5 SME) (See Table 4). In these experiments ovine growth hormone (NIH-GH-S7) was used as a reference standard. GH potencies of the pituitary homogenates were calculated by a 4-point assay, according to Finney (1952).

In the series of experiments in which the GH-releasing activity of stalk-medium eminence extracts of normal rats was evaluated in normal rats or in growth hormone or dexamethasone-treated rats the following procedure was used: The extracts of the stalk median eminence region of 40 Sprague-Dawley female rats (110–120 g b. w.) were prepared as reported previously (Pecile et al. 1965). As recipient animals 30 day-old Sprague-Dawley female rats were used. They were divided into three groups of 4 animals each. The first group received as pretreatment saline (0.5 ml/100 g b. w.), the second and the third groups growth hormone (1 mg/100 g b. w.) and dexamethasone (50 μg/100 g b. w.) respectively. At different time intervals after these treatments (See Table 5) and under ether anaesthesia, all recipient animals were given the equivalent of 3 SME in 0.5 ml saline by intracarotid injection. GH activity of their anterior pituitary glands was then measured as described above, and compared to that of pituitary glands of control animals, not receiving hypothalamic extracts. Two series
of experiments were performed. Since similar results were obtained in both experiments, we have reported here only the results of the first experiment.

Blood glucose was measured at the time of sacrifice with a Technicon Auto Analyzer using a modification of the method of Hoffman (1937).

RESULTS

Hypophysectomized animals

From the results reported in Table 1, it appears that GRF activity is present in plasma of rats hypophysectomized for three months since pituitary homogenates of animals treated with 1 ml of this plasma (group B), induced a widening of the epiphyseal width much smaller than that obtained with pituitary glands of saline-treated control animals (group A), indicating a marked decrease of pituitary growth hormone content. This confirms our previous results (Muller et al. 1967 a). The administration of growth hormone does not influence plasma GRF activity of hypophysectomized animals (groups C vs. B and A), while dexamethasone lowers plasma GRF activity considerably (group D vs. A and B). Like growth hormone, follicle-stimulating hormone

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment of plasma donor animals</th>
<th>Material administered to pituitary donor animals</th>
<th>Width of tibia cartilage, ( \mu ) (mean ± S. E.)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>—</td>
<td>Saline (1.0 ml/rat i. c.)</td>
<td>273 ± 5.3</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>Saline (0.5 ml/rat/day for 5 days)</td>
<td>Plasma Hypox (1.0 ml/rat i. c.)</td>
<td>213 ± 7.9</td>
<td>B vs A; 0.001</td>
</tr>
<tr>
<td>C</td>
<td>Growth Hormone (2 mg/100 g b. w./day for 5 days)</td>
<td>Plasma Hypox (1.0 ml/rat i. c.)</td>
<td>229 ± 5.0</td>
<td>C vs A; 0.001 C vs B; N.S.</td>
</tr>
<tr>
<td>D</td>
<td>Dexamethasone (50 ( \mu )g/rat/day for 5 days)</td>
<td>Plasma Hypox (1.0 ml/rat i. c.)</td>
<td>247 ± 7.9</td>
<td>D vs A; 0.01 D vs B; 0.01</td>
</tr>
<tr>
<td>E</td>
<td>Follicle-Stimulating Hormone (2 mg/rat/day for 5 days)</td>
<td>Plasma Hypox (1.0 ml/rat i. c.)</td>
<td>218 ± 12.6</td>
<td>E vs A; 0.01 E vs B; N.S.</td>
</tr>
</tbody>
</table>

* 6–8 hypox assay rats per group were used.
The mean value of tibia cartilage of hypox assay rats was 149 ± 5.6.

502
leaves plasma GRF activity unaffected (group E vs. A and B). In Table 2 are reported the results dealing with hypothalamic GRF activity of the same animals. It can be seen that the intracarotid injection of 2.5 SME obtained from hypophysectomized animals treated with saline, induces a significant reduction of pituitary GH content in recipient animals (group B vs. A), indicating presence of hypothalamic GRF activity. The administration of GH does not influence hypothalamic GRF activity (group C vs. A and B), while no GRF activity is detectable in the hypothalami of hypophysectomized animals treated with dexamethasone (group D vs. A and B). Since no effect on plasma GRF activity was noticed after administration of FSH (see Table 1) the influence of this hormone on hypothalamic GRF activity was not investigated.

An increase of blood glucose values is noticed in the hypophysectomized animals (blood sugar 78 ± 8.3 mg/100 ml), after treatment with growth hormone (blood sugar 106 ± 9.4 mg/100 ml) and dexamethasone (blood sugar 116 ± 8.4 mg/100 ml).

### Table 2.
Growth Hormone-Releasing Activity of Stalk Median Eminence (SME) Extracts of Rats Hypophysectomized (Hypox) for Three Months Treated with Growth Hormone or Dexamethasone.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment of SME donor animals</th>
<th>Material administered to pituitary donor animals</th>
<th>Width of tibia cartilage, µ (mean ± S.E.)***</th>
<th>Hypox blood glucose concentration (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>—</td>
<td>Saline (1.0 ml/rat i. c.)</td>
<td>239 ± 4.1</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>Saline (0.5 ml/rat/day for 5 days)</td>
<td>SME Hypox (2.5 SME/rat i. c.)</td>
<td>218 ± 3.3*</td>
<td>48 ± 8.3</td>
</tr>
<tr>
<td>C</td>
<td>Growth Hormone (2 mg/100 g b. w./day for 5 days)</td>
<td>SME Hypox (2.5 SME/rat i. c.)</td>
<td>214 ± 2.8*</td>
<td>106 ± 9.4**</td>
</tr>
<tr>
<td>D</td>
<td>Dexamethasone (50 µg/rat/day for 5 days)</td>
<td>SME Hypox (2.5 SME/rat i. c.)</td>
<td>243 ± 5.1</td>
<td>116 ± 8.4**</td>
</tr>
</tbody>
</table>

* P < 0.01 vs. group A
** P < 0.001 vs. group B
*** 6-8 hypox assay rats per group were used.
The mean values of tibia cartilage of hypox assay rats was 143 ± 4.2.
**Normal animals**

Recorded in Table 3 are the weights of the bodies, the adrenals and the pituitary gland as well as the pituitary GH activity of animals treated with growth hormone or dexamethasone. Gain in body weight was greater in rats which received growth hormone, than in the controls (30 g and 22 g respectively). This indicates that an effective dose of GH was used. After two days of dexamethasone administration, growth ceased and there was loss of body weight at the end of treatment.

The absolute and relative weights of the pituitary glands are smaller in GH-treated animals, although the difference is not statistically significant, whereas in dexamethasone-treated animals only the absolute value of pituitary weight is significantly smaller. As a result of GH administration, a significant increase of pituitary GH activity is observed ($P < 0.05$), while no change results from the administration of dexamethasone. In Table 4 are reported the results, dealing with hypothalamic GRF activity of normal animals after the treatments. Pituitary glands of rats injected with SME from saline-treated or GH-treated animals, were assayed for GH activity at two dose levels. It is also seen that the administration of GH to normal animals, at the dose previously used, does not influence hypothalamic GRF activity (groups D and E vs. A, B and C), while no GRF activity is present in the hypothalami of animals treated with dexamethasone (group F vs. A, B and C). Blood glucose values after growth hormone (blood sugar 94 ± 4.0 mg/100 ml) and dexamethasone (blood sugar 88.1 ± 5.9 mg/100 ml) treatment are not significantly different from controls (blood sugar 98 ± 8.0 mg/100 ml).

**Site of action of growth hormone and dexamethasone**

In order to explore the possible site of the blocking action of GH on its secretion we have investigated in the last series of experiments the sensitivity of anterior pituitary gland to the GH-depleting effect of extracts of rat SME. As shown in Table 5 the administration of GH, 30 minutes before sacrifice, did not modify pituitary GH content (group B vs. A). Dexamethasone, given one hour before sacrifice decreased, even if not significantly, GH in the pituitary gland (group C vs. A).

Pituitary response to 3 rat SME, fifteen minutes after the intracarotid injection was completely blocked in GH-treated animals (groups F vs. D and E), but was almost identical in saline-treated or dexamethasone-treated animals (groups E and G vs. D). However, as mentioned above, dexamethasone, if given alone, decreases GH in the pituitary gland. Therefore the GH-depleting effect of the hypothalamic extract is not quite apparent (group G vs. C).
### Table 3.
Effect of Growth Hormone (GH) and Dexamethasone on Body Weight, Pituitary Weight and Pituitary GH Activity.

| Groups                      | No. of rats | Body weight g | Pituitary weight | Width of tibia cartilage, μ (mean ± S.E.)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>mg</td>
</tr>
<tr>
<td>Control</td>
<td>16</td>
<td>123.21 ± 1.84</td>
<td>145.5 ± 1.85</td>
<td>5.42 ± 0.14</td>
</tr>
<tr>
<td>Growth Hormone (2 mg/100 g b. w./day for 5 days)</td>
<td>16</td>
<td>119.71 ± 1.08</td>
<td>149.28 ± 1.12</td>
<td>4.97 ± 0.31</td>
</tr>
<tr>
<td>Dexamethasone (50 μg/rat/day for 5 days)</td>
<td>16</td>
<td>120.78 ± 1.60</td>
<td>114.42 ± 1.32</td>
<td>4.71 ± 0.06**</td>
</tr>
</tbody>
</table>

* P 0.05 vs. control
** P 0.02 vs. control
† P 0.001 vs. control
†† P 0.01 vs. growth hormone
††† 6–8 hypox assay rats per group were used
Table 4.
Growth Hormone-Releasing Activity of Stalk Median Eminence (SME) Extracts of Rats Treated with Growth Hormone (GH) or Dexamethasone.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment of SME donor animals (No. and dose in parentheses)</th>
<th>Material administered to pituitary donor animals (doses in parentheses)</th>
<th>A. P. equivalents</th>
<th>GH evaluation</th>
<th>95% Fiducial Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Saline</td>
<td>0.80 mg</td>
<td>Width of tibia cartilage, μg (mean ± S.E.)*</td>
<td>Potency μg GH/mg pituitary</td>
</tr>
<tr>
<td>A</td>
<td>--</td>
<td>Saline (1.0 ml/rat i. c.)</td>
<td>0.80 mg</td>
<td>270 ± 5.2</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>(16) Saline (0.5 ml/rat/day for 5 days)</td>
<td>2.5 SME 0.80 mg</td>
<td>270 ± 8.9**</td>
<td>72.1</td>
<td>56.2-97.9</td>
</tr>
<tr>
<td>B'</td>
<td>(16) Saline (0.5 ml/rat/day for 5 days)</td>
<td>2.5 SME 0.20 mg</td>
<td>207 ± 11.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C</td>
<td>(16) Saline (0.5 ml/rat/day for 5 days)</td>
<td>1.0 SME 0.80 mg</td>
<td>259 ± 7.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>D</td>
<td>(16) GH (2 mg/100 g b. w./day for 5 days)</td>
<td>2.5 SME 0.80 mg</td>
<td>247 ± 6.4**</td>
<td>63.2</td>
<td>44.6-87.4</td>
</tr>
<tr>
<td>D'</td>
<td>(16) GH (2 mg/100 g b. w./day for 5 days)</td>
<td>2.5 SME 0.20 mg</td>
<td>204 ± 10.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E</td>
<td>(16) GH (2 mg/100 g b. w./day for 5 days)</td>
<td>1.0 SME 0.80 mg</td>
<td>257 ± 6.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>(16) Dexamethasone (50 μg/rat/day for 5 days)</td>
<td>2.5 SME 0.80 mg</td>
<td>270 ± 3.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G</td>
<td>Standard GH</td>
<td>15 μg</td>
<td>218 ± 9.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>H</td>
<td>Standard GH</td>
<td>60 μg</td>
<td>255 ± 6.7</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* 7–8 hypophysectomized assay rats per group were used.
** P < 0.02 vs. group A.
Table 5.
Effect of Treatment of Pituitary Donor Rats with GH or Dexamethasone on Depletion of Pituitary GH Content after Injection of Rat SME.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment of pituitary donor animals*</th>
<th>Width of tibia cartilage of assay rats**, μ (mean ± S. E.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Saline***</td>
<td>226 ± 4.3</td>
<td>B vs A; N.S.</td>
</tr>
<tr>
<td>B</td>
<td>GH†</td>
<td>227 ± 9.1</td>
<td>C vs A; N.S.</td>
</tr>
<tr>
<td>C</td>
<td>Dexamethasone††</td>
<td>217 ± 5.1</td>
<td>D vs A; N.S.</td>
</tr>
<tr>
<td>D</td>
<td>Saline*** + Saline i. c.</td>
<td>224 ± 2.2</td>
<td>E vs D; 0.001</td>
</tr>
<tr>
<td>E</td>
<td>Saline*** + SME†††</td>
<td>205 ± 2.7</td>
<td>F vs B; N.S.</td>
</tr>
<tr>
<td>F</td>
<td>GH† + SME†††</td>
<td>224 ± 4.8</td>
<td>F vs D; N.S.</td>
</tr>
<tr>
<td>G</td>
<td>Dexamethasone††† + SME†††</td>
<td>209 ± 3.7</td>
<td>G vs E; 0.001</td>
</tr>
</tbody>
</table>

* 4 recipient rats were used per group.
** 6–8 hypophysectomized rats were used per group.
*** Saline (0.5 ml/100 g i. p.) was given 30 minutes before sacrifice.
† GH (1 mg/100 g i. p.) was given 30 minutes before sacrifice.
†† Dexamethasone (50 μg/100 g i. p.) was given 1 hour before sacrifice.
††† 3 fragments of SME/rat were given i. c.

DISCUSSION

Our results show that high doses of growth hormone given to long-term hypophysectomized animals are unable to induce any change in plasma or hypothalamic GRF activity. These findings do not support the hypothesis that there exists a feedback mechanism for control secretion which operates between the pituitary gland and the hypothalamus. The failure of GH administration to alter plasma and hypothalamic GRF activity in the hypophysectomized animals, might reflect the inability of the hormone to counteract the enhanced secretion of GRF from the hypothalamus present in the long-term hypophysectomized animals (Muller et al. 1967 a).

However, the finding that growth hormone does not impair synthesis and/or release of hypothalamic GRF activity in normal animals, clearly rules out this possibility. Administration of growth hormone for 5 days resulted in elevation in pituitary GH level, in agreement with previous findings (Kruilich & McCann 1966). We do not think that our negative results can be ascribed to the use of insufficient doses of growth hormone, since the amount of hormone we used in the present studies (2 mg) is about 10 times larger than the estimated daily endogenous secretion of growth hormone in the rat. Evidence for the existence
of a feedback mechanism operating between the pituitary gland and the hypothalamus has already been presented for gonadotrophins (Szontagh & Uhlarik 1964; David et al. 1966) and ACTH (Motta et al. 1965). These are hormones which are present in considerable amounts at hypothalamic levels (Schally et al. 1965). Absence of growth hormone in the hypothalamus (Schally et al. 1965) leads one to question the existence of a feedback mechanism for the control of GH secretion which entails an action of GH on the hypothalamus.

By contrast with growth hormone, the administration of high doses of dexamethasone to long-term hypophysectomized animals and to normal animals resulted in marked decrease of plasma and hypothalamic GRF activity, indicative of reduced synthesis of the neurohumour in the hypothalamus. The suppressive action of dexamethasone on GRF synthesis supplements the observations of Pecile & Muller (1966) which showed that cortisol treatment in the rat blocks insulin-induced GH release, by creating a deficiency of hypothalamic GRF. Thus, from present and previous observations a pattern of control is beginning to emerge, in which adreno-cortical hormones may impair growth, and appear to do so through a central mechanism. When one considers that cortisol and dexamethasone induced not only suppression of GRF activity in the hypothalamus, but also block CRF synthesis (Brodish & Long 1962; Vernikos-Danellis 1965), further analogies between GH and ACTH regulatory mechanism(s) are apparent (Knobil 1966; Muller et al. 1967b).

In order to explain the suppressive effect of GH on its own rate of secretion, one could alternatively hypothesize the existence of an action exerted directly on the pituitary gland. The observation that GH, given 30 minutes before administration of a hypothalamic extract, blocks GRF activity of the latter, is in keeping with this hypothesis. Assuming for ovine growth hormone a biological half life similar to that of bovine growth hormone in the rat (about 30 minutes, Van Dyke et al. 1950), it seemed appropriate to administer the hormone, shortly before the hypothalamic extract. It was hoped thereby to increase the probability that any suppressive action was due to the hormone itself, rather than to some of its metabolic effects. Such a mode of action could not be excluded in earlier studies (Muller & Pecile 1966; Krulich & McCann 1966).

That GH may control its own secretion rate, acting directly on the pituitary gland and not on the hypothalamus is also suggested by recent studies. In normal rats, bearing a GH-secreting tumour, MacLeod et al. (1966) observed a decrease in pituitary gland growth hormone content, but no change in hypothalamic GRF activity (MacLeod, personal communication). Also Krulich & McCann (1966) noticed that prolonged treatment with GH resulted in depression of GH content of the pituitary gland.

The GH-depleting effect of a hypothalamic extract is not quite apparent in the animals treated with dexamethasone, since administration of this steroid leads within a short time to a decrease of GH content in the pituitary gland.
However, the bulk of our data, which show that dexamethasone acts on the hypothalamic regulatory mechanism of GH secretion, suggests that the pituitary gland is not the primary site of its suppressive action on GH secretion. Dexamethasone, when given 1 hour before (present study) or 4 hours before sacrificing the animal, causes a decrease of pituitary GH content (Muller et al. 1967 b). By contrast no change of pituitary GH content is found after 5 days of dexamethasone administration. The different effects of acute versus prolonged dexamethasone treatment on GH pituitary content are difficult to interpret, especially on considering our method of evaluation. It might be assumed that dexamethasone, if given for only a short time, acts on the hypothalamic GRF to impair GH synthesis and/or release. By contrast, following prolonged administration of dexamethasone a new equilibrium might be reached which would allow a normal content of GH in the pituitary gland in the presence of a reduced content of hypothalamic GRF.

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