Arginine and Growth Hormone-Releasing Hormone Restore the Blunted Growth Hormone-Releasing Activity of Hexarelin in Elderly Subjects*


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ABSTRACT

Although both spontaneous and stimulated GH secretion undergo an age-related decline, the secretory capacity of somatotrope cells is preserved in human aging. In the present study we compared the GH responses to hexarelin, GHRH, and the combined administration of hexarelin and GHRH or arginine in young and elderly subjects. Thirteen young (24- to 30-yr-old) and 16 elderly (65- to 84-yr-old) normal males were divided into 2 groups. The first group (7 young and 8 elderly subjects) received the following as single iv injections during 3 different treatment sessions: hexarelin (2 μg/kg), GHRH (2 μg/kg), or hexarelin (2 μg/kg) plus GHRH (2 μg/kg). The second group (6 young and 8 elderly subjects) was administered single iv injections of hexarelin (2 μg/kg) or hexarelin (2 μg/kg) plus arginine (0.5 g/kg) during 2 different treatment sessions. In both groups basal IGF-I levels in the elderly were lower than those in young subjects (114.5 ± 18.7 vs. 211.5 ± 19.1 μg/L; P < 0.001). In the first group the GH response to hexarelin was greater in young compared to elderly subjects (area under the curve from 0-120 = 4849 ± 601 vs. 2112 ± 683 μg·min·L⁻¹; P < 0.001). GHRH elicited a lower GH response than that induced by hexarelin in both young (1455 ± 102 μg/min·L⁻¹; P < 0.02) and elderly subjects (563 ± 87 μg/min·L⁻¹; P < 0.02). GHRH potentiated the somatotrope response to hexarelin in both young (7725 ± 503 μg·min·L⁻¹; P < 0.02) and elderly subjects (3885 ± 612 μg·min·L⁻¹; P < 0.02), but to a lesser extent in the latter (P < 0.001). In the second group, the GH response induced by hexarelin was also higher in young subjects than in elderly subjects (4819 ± 668 vs. 1649 ± 459 μg·min·L⁻¹; P < 0.001). The GH response to hexarelin was potentiated by arginine in elderly (4139 ± 1057 μg·min·L⁻¹; P < 0.001), but not in young subjects (4743 ± 774 μg·min·L⁻¹). This study shows that the maximal effective dose of hexarelin releases more GH than the maximal effective dose of GHRH in both normal young and elderly subjects. The effect of hexarelin on GH secretion is age dependent, and the GH response to the combined administration of hexarelin and GHRH was significantly higher in young subjects compared to elderly subjects. Arginine does not potentiate the GH response to hexarelin in young subjects, whereas it significantly enhances it in elderly subjects. These findings suggest that hexarelin acts, at least partially, independently from GHRH and/or somatostatin. These results also support the presence of a somatostatinerergic hyperactivity in aging, which is probably related to a concomitant reduction in the activity of GHRH-secreting neurons. (J Clin Endocrinol Metab 79: 1440-1443, 1994)

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Hexarelin is a new hexapeptide (His-d-2-methyl-Trp-Ala-Trp-d-Phe-Lys-NH₂) (22) that is more stable than GHRP-6, the most widely studied GHRP, under a number of conditions of degradation (23). Although its mechanism of action is similar to that of GHRP-6, in rats hexarelin is more potent than GHRP-6 after both iv (24) and sc administration (25).

In man, hexarelin has a potent dose-dependent and reproducible GH-stimulating effect after iv (26, 27), sc, intranasal, and oral administration (27). The aim of the present study was to compare the GH responses to the maximal effective doses of hexarelin and GHRH (21) and to the combined administration of hexarelin and GHRH or arginine in young and elderly subjects.

**Subjects and Methods**

**Peptides and drugs**

Vials containing 100 μg lyophilized hexarelin were kindly provided by Europeptides (Argenteuil, France). Vials containing 50 μg lyophilized GHRH-(1-29) (Cerel) were purchased from Serono (Milan, Italy). Hexarelin and GHRH were dissolved in 2 mL isotonc saline to be administered as an iv bolus. Vials containing 30 g (in 100 mL solution) arginine hydrochloride (Arginine, Damor, Naples, Italy) were purchased from Damor (Naples, Italy).

**Study design**

Sixteen normal elderly males (aged 65–84 yr) and 13 normal young males (aged 24–30 yr) took part in the present study. All subjects had normal lifestyles and were within 20% of their ideal body weight. All were in good health, and none of the subjects was taking medication before the start of study. Informed consent was obtained from all subjects.

Subjects received various treatments in random order separated by a wash-out period of at least 3 days. Study drugs were administered between 0830–0900 h after an overnight fast and 30 min after venous cannulation, which was kept patent by the slow infusion of isotonc saline.

The first group of young and eight elderly subjects received the following iv treatments during three different sessions: hexarelin (2 μg/kg), GHRH (2 μg/kg), and hexarelin (2 μg/kg) plus GHRH (2 μg/kg).

The second group of six young and eight elderly subjects received the following iv treatments during two different sessions: hexarelin (2 μg/kg) and hexarelin (2 μg/kg) plus arginine (0.5 g/kg infused over 30 min from 0–30 min).

Blood samples were taken at baseline (−15 and 0 min) and then every 15 min up to 120 min after hexarelin and/or GHRH administration.

**Adverse events**

Hexarelin and GHRH induced a transient facial flushing in three and eight subjects, respectively. More prolonged facial flushing was observed in all subjects after the com-
FIG. 2. GH responses to hexarelin (2 μg/kg, iv), administered alone or combined with arginine (0.5 g/kg infused over 30 min from 0–30 min), in six young (left panel) and eight elderly (right panel) males.

TABLE 1. AUC₀–120 of serum GH levels (micrograms per min/L) after GHRH, hexarelin, hexarelin plus GHRH, and hexarelin plus arginine administration.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Young</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Hexarelin</td>
<td>4849 ± 601</td>
<td>2112 ± 683</td>
</tr>
<tr>
<td>GHRH</td>
<td>1455 ± 102</td>
<td>563 ± 87</td>
</tr>
<tr>
<td>Hexarelin + GHRH</td>
<td>7725 ± 503</td>
<td>3885 ± 612</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hexarelin</td>
<td>4819 ± 668</td>
<td>1649 ± 459</td>
</tr>
<tr>
<td>Hexarelin + Arginine</td>
<td>4743 ± 774</td>
<td>4139 ± 1057</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM.

bined administration of the peptides. No adverse events were observed after arginine infusion.

Discussion

This study demonstrates that, like GHRP-6 (28, 29), hexarelin has an age-related GH-releasing activity. However, although the stimulating effect of the maximally effective dose of hexarelin on somatotrope secretion is reduced in human aging, it releases more GH than the supramaximal effective dose of GHRH even in elderly subjects. Our results also indicate that the combined administration of hexarelin and GHRH has a synergistic effect in elderly subjects, as previously reported in young subjects (30).

This study also shows that in human aging, the GH releasable pool is markedly larger than previously thought. This observation is supported by previous animal (6) and human (3, 4) studies. In addition, our results indicate that hexarelin, like other GHRPs, has a different mechanism of action from that of GHRH in stimulating somatotrope secretion. GHRPs and GHRH have different receptor sites on the pituitary (16, 17, 18), and GHRP receptor activation does not increase intracelluar cAMP levels, contrary to GHRH (19). The GH-releasing activity of GHRPs and their synergistic effect with GHRH are greater in vivo than in vitro (17, 20), thus suggesting that GHRPs also act at the hypothalamic level, where specific receptors have been identified (21). Normal GHRH activity is needed before GHRPs can exert their GH-releasing effect (20, 31). Therefore, the reduced activity of hexarelin, either alone or combined with GHRH in human aging, may be explained by a decrease in the activity of GHRH-secreting neurons or by changes in GHRH receptors, as shown by other studies conducted in animals (7, 11, 32) and man (5, 33).

We found that arginine, an amino acid that probably acts by suppressing endogenous somatostatin release (9, 10), counteracts the age-related decrease in the GH-releasing effect of hexarelin in elderly subjects. Both animal (6, 8) and human (3, 4) studies suggest that there is a pronounced somatostatinergic hyperactivity in human aging. This could explain the age-related decline in both spontaneous and stimulated GH secretion and the effectiveness of arginine in restoring the response to hexarelin in the elderly. Arginine’s failure to increase the GH response to hexarelin in young subjects, however, remains to be clarified. It may be that GHRPs act at the pituitary level by antagonizing the effect of somatostatin. In fact, GHRPs counteract the hyperpolarizing effect of somatostatin on rat somatotrope cell membrane (18). In man, the GH-releasing effect of hexarelin is blunted, but not abolished, by a high dose of exogenous somatostatin (30), which abolishes the somatotrope response to all known GH secretagogues, including GHRH (30, 34). Thus, it could be hypothesized that hexarelin’s antagonism of somatostatin at the pituitary level is partially overridden in aging by a pronounced hypothalamic somatostatinergic activity.

In conclusion, this study shows that the maximally effective dose of hexarelin releases more GH than the maximally effective dose of GHRH in both normal young and elderly subjects. The effect of hexarelin on GH secretion is age dependent, and the GH response to the combined administration of the two drugs was significantly higher in young subjects compared to elderly subjects. Arginine does not potentiate the GH response to hexarelin in young subjects, whereas it significantly enhances it in elderly subjects. These findings suggest that hexarelin acts, at least partially, independently from GHRH and/or somatostatin. These results also support the presence of a somatostatinergic hyperactivity in aging, which is probably related to a concomitant reduction in the activity of GHRH-secreting neurons.

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References

GH-RELEASING EFFECT OF HEXARELIN IN HUMAN AGING


