Stimulation of the Growth Hormone (GH)-Insulin-Like Growth Factor I Axis by Daily Oral Administration of a GH Secretogogue (MK-677) in Healthy Elderly Subjects*

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ABSTRACT

Aging is associated with declining activity of the GH axis, possibly contributing to adverse body composition changes and increased incidence of cardiovascular disease. The stimulatory effects on the GH-insulin-like growth factor I (IGF-I) axis of orally administered MK-677, a GH-releasing peptide mimetic, were investigated. Thirty-two healthy subjects (15 women and 17 men, aged 64–81 yr) were enrolled in a randomized, double blind, placebo-controlled trial. They received placebo or 2, 10, or 25 mg MK-677, orally, once daily for 2 separate study periods of 14 and 28 days. At baseline and on day 14 of each study period, blood was collected every 20 min for 24 h to measure GH, PRL, and cortisol. Attributes of pulsatile GH release were assessed by 3 independent algorithms. MK-677 administration for 2 weeks increased GH concentrations in a dose-dependent manner, with 25 mg/day increasing mean 24-h GH concentration 97 ± 23% (mean ± SE; P < 0.05 vs. baseline). This increase was due to an enhancement of preexisting pulsatile GH secretion. GH pulse height and interpulse interval concentrations increased significantly without significant changes in the number of pulses. With 25 mg/day MK-677 treatment, mean serum IGF-I concentrations increased into the normal range for young adults (141 ± 21 μg/L at baseline, 219 ± 21 μg/L at 2 weeks, and 265 ± 29 μg/L at 4 weeks; P < 0.05). MK-677 produced significant increases in fasting glucose (5.4 ± 0.3 vs. 6.8 ± 0.4 mmol/L at 4 weeks; P < 0.01 vs. baseline) and IGF-binding protein-3. Circulating cortisol concentrations did not change, and PRL concentrations increased 23%, but remained within the normal range. Once daily treatment of older people with oral MK-677 for up to 4 weeks enhanced pulsatile GH release, significantly increased serum GH and IGF-I concentrations, and, at a dose of 25 mg/day, restored serum IGF-I concentrations to those of young adults. (J Clin Endocrinol Metab 81: 4249–4257, 1996)

PULSATILE secretion of GH by the anterior pituitary gland is controlled mainly by two hypothalamic peptides: somatostatin, which is inhibitory, and GH-releasing hormone (GHRH), which is stimulatory (1). In addition to stimulating linear growth before epiphyseal fusion, GH has metabolic effects that persist throughout life. These effects are exerted directly by GH and via its stimulation of insulin-like growth factor I (IGF-I) production (1). In physiological concentrations, GH is anabolic, stimulates muscle development and strength, stimulates loss of fat tissue (particularly from central abdominal sites), and increases bone density (2). GH also exerts cardioprotective effects on blood lipid concentrations, explaining why adult GH deficiency may predispose to premature atherosclerosis and the resultant increased mortality from cardiovascular disease (2, 3).

Normal human aging is associated with declining serum concentrations of GH and IGF-I (4–7). Although normal aging is not typically associated with profound GH deficiency as occurs in patients with pituitary disease (8, 9), mean GH concentrations in people over 60 yr of age are, on the average, about one third to one half those in young adults (4, 9, 11). This reduction may contribute to the decreases in muscle and bone mass and the increases in adipose tissue that accompany normal aging (12). These changes have been partially reversed by GH administration for 6 months to otherwise healthy older men and women (13, 14). The disadvantages of GH therapy are the high cost, the need for parenteral administration, and side-effects, including fluid retention, carpal tunnel syndrome, and glucose intolerance (2, 12–14). We speculate that such side-effects may result from prolonged nonphysiological elevations of circulating GH concentrations after daily sc GH injections (15). If this is the case, enhancement of endogenous pulsatile GH secretion by an
orally administered secretagogue may be a more desirable therapeutic strategy than parenteral GH.

GH-releasing peptide (GHRP) is a synthetic hexapeptide that was developed specifically to stimulate growth. It stimulates pulsatile GH secretion in humans, probably by actions on both the hypothalamus and pituitary, through a novel receptor (16-18). The natural ligand, whose effect it mimics, has yet to be discovered. Compounds have been developed that mimic the stimulatory actions of GHRP on GH release and do not interact with muscarinic or nicotinic cholinergic receptors (19, 20). These compounds are more potent secretagogues than GHRH in older adults (21). We report the effects of oral administration for 2-4 weeks of the sợi dopipheridine MK-677 (20) to healthy older adults. This compound was selected because of its high oral bioavailability and its long duration of action.

Experimental Subjects

The study was approved by the human investigational review boards of the participating centers (University of Virginia, University of Chicago, and Clinical Studies, Florida). Each subject gave written informed consent before enrollment in the study.

Thirty-two subjects, 15 women and 17 men aged 64-81 yr (mean ± SD, 70.2 ± 3.8), were studied in 2 panels. All were healthy nonsmokers with a body mass index (BMI) between 19.9-30.2 kg/m² (mean ± SD, 24.6 ± 2.3). The mean age and BMI did not differ between panels or treatment groups. This age group was chosen because it constitutes a significant portion of elderly subjects who would be candidates for such therapy. Because spontaneous GH secretion is inversely related to BMI (6), it was important to include the wide range of BMIs found in this population. The only medications allowed were stable doses of thyroid hormone replacement, less than 1000 mg acetylcarnitine/day, and up to 1 aspirin tablet/day. Exclusion criteria included a history of diabetes mellitus; significant cardiac, vascular, or other disease; other hormone treatments (estrogen, testosterone, etc.); unusual or extreme dietary habits; or consumption of more than 6 cups of caffeinated beverages/day. All subjects had unremarkable clinical histories and physical examinations; normal urinalyses, electrocardiograms, and chest x-rays; and normal biochemical indexes of renal, hepatic, hematological, and thyroid function. Glycated hemoglobin and serum concentrations of PRL, FSH, and LH (women) and testosterone (men) were in the age-adjusted normal ranges.

Materials and Methods

Study design (Fig. 1)

Subjects were entered into a randomized, double blind, placebo-controlled trial, in which they received once daily the oral study drug (MK-677 or placebo) for each of two 14-day study periods (periods I and II) separated by a 14- to 21-day washout period. At the end of period II, subjects received the study drug for an additional 2-week extension period for collection of IGF-I and safety data. Subjects were studied in one of two panels. In panel A, the study drug was given once a day in the evening (between 2200-2300 h). In panel B, subjects received the study drug in both the morning (between 0700-0900 h) and evening (between 2200-2300 h) to blind treatment time of active drug, at least one of these two treatments per day was placebo.

Period I. Subjects were admitted to the Clinical Research Center (CRC) the day before the study, to acclimate to the unit. Regular CRC diets were consumed during all admissions. Alcohol consumption was not permitted. An iv cannula for blood sampling was inserted into an arm vein by 0700 h on study day 1. Subjects were instructed to consume no more than six cups of caffeinated beverages and 2 alcoholic drinks per day during this period, but had no other dietary limitations. They were instructed to avoid strenuous exercise, but encouraged to continue modest exercise as part of their daily routine.

Subjects were readmitted to the CRC in the evening of study day 14 and underwent repeat 24-h blood and urine collections beginning at 0800 h on study day 15, as on study day 2. The last dose of treatment drug was taken in the evening of study day 15.

Period II. After a washout period of 14-21 days, subjects returned to the CRC, took the first dose of the study drug at 0900 h, were observed for 4 h, and then were discharged. The remainder of the period was the same as period I, with repeat admission and sampling after 2 weeks. Subjects in panels A and B continued to take study drug for an additional 2-week extension period (i.e., total of 28 continuous days of drug administration) and were then seen for assessment of possible side-effects and collection of fasting urine and blood samples.

Analytical methods

Assays. Serum GH concentrations were measured in duplicate by chemiluminescence assay (Nichols Institute Diagnostics, San Juan Capistrano, CA), modified as previously described (22). The sensitivity of the assay was 0.002 μg/L, and the measured GH concentrations in all samples were above this detection limit. The intraassay coefficients of variation were 5.4% at 0.04 μg/L, 4.8% at 0.4 μg/L, 5.7% at 3.4 μg/L, and 9.9% at 8.4 μg/L. The interassay coefficients of variation were 5.6% at 0.04 μg/L, 5.6% at 0.4 μg/L, 7.9% at 3.4 μg/L, and 8.4% μg/L. All 24-h GH profiles from each subject were run in one assay. Cortisol was measured by fluorescence polarization immunoassay (Abbott TDx, Abbott Laboratories, Abbott Park, IL). Values below the lowest standard were reported as less than 83 nmol/L (<3 μg/dl). PRL was measured in a chemiluminescence immunoassay (ACS 180, Ciba Corning Diagnostics Corp., Medfield, MA) with a sensitivity of 0.3 μg/L. Cortisol, GH, and PRL assays were performed at the University of Virginia Medicine Clinical and CRC Core Laboratories. All other assays, including routine serum chemistry, hematology, screening hormone levels, and urinary free cortisol, were performed by Endocrine Sciences (Calabasas Hills, CA). Serum IGF-I was measured by RIA after acid-ethanol extraction, with an assay sensitivity of 10 ng/L (<0.3 μg/L). The expected values are 202-453 μg/L (mean, 330) for 21-25 yr, 327-522 μg/L (mean, 461) for 60-69 yr, and 63-223 μg/L (mean, 153) for 70-79 yr.
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Results

Compliance

Compliance data were available for all subjects; in subjects randomized to active drug, overall compliance was more than 99%. Five of 22 subjects receiving active drug missed 1 dose, and 1 subject missed 2 doses.

Side-effects

Treatment with MK-677 was generally well tolerated. There were no serious clinical or laboratory adverse experiences. There were three reports in panel A of mild abdominal pain and five reports of mild appetite increase in panels A and B (all in drug-treated subjects). Body weight did not change significantly with MK-677 treatment.

Effect of evening MK-677 treatment

GH. Oral administration of MK-677 produced dose-dependent increases in mean 24-h GH concentrations (Fig. 2), which were statistically significant for treatment with 10 and 25 mg, but not 2 mg MK-677 (Table 1). After 2 weeks of placebo administration, there was no significant change in mean 24-h GH concentrations (8 ± 16% greater than at baseline; P = NS), whereas the increases were 57 ± 13% and 97 ± 23% (range, 30-330%) with 10 and 25 mg MK-677, respectively (P < 0.05 vs. baseline for both doses; Fig. 3, upper panel).

Examination of individual 24-h GH concentration profiles (Fig. 4) suggested that MK-677 treatment enhanced pulsatile GH release rather than a sustained increase in serum GH concentrations. This interpretation was supported by the results of Cluster analysis (Table 1), which revealed that treatment with 10 and 25 mg MK-677 resulted in statistically significant increases in the height of GH pulses and interpulse nadir GH concentrations, without any change in the number of GH pulses. Similar results were obtained with the Ultra peak detection algorithm (data not shown). Multiple parameter deconvolution analysis (6, 24) indicated that the increases in serum GH concentrations resulted from increased GHI secretion without changes in GH clearance rates. Treatment with 25 mg MK-677 for 14 days resulted in a 1.7-fold increase in the amount of GH secreted per 24 h compared to baseline (277 ± 32 to 164 ± 27 μg; P = 0.017) without a significant change in GH disappearance half-life (21.0 ± 1.7 vs. 20.2 ± 0.8 min). The increase in GH secretion was accounted for by a 1.6-fold increase in the mass of GH secreted per pulse (3.5 ± 0.4 vs. 2.1 ± 0.3 μg/L distribution volume; P = 0.045) without a significant change in the number of GH secretory pulses per 24 h (13.1 ± 0.5 vs. 11.9 ± 0.8) or the contribution of basal secretion to total 24-h production (20 ± 3.7% vs. 17.6 ± 4%). The second, independent deconvolution technique (5) estimated the increase in 24-h GH production rates with 25 mg MK-677 to be slightly larger (364 ± 20 vs. 178 ± 8 μg/24 h; P = 0.011) due to shorter estimates of the GH half-life (16.7 ± 0.8 min).

IGF-I. Administration of MK-677 also resulted in dose-dependent increases in serum IGF-I concentrations (Table 1 and
PM Dosing

Fig. 3. Percent changes from baseline (geometric mean ± geometric SE) of 24-h mean GH concentrations (micrograms per L) after 2 weeks of treatment (upper panel) and of serum IGF-I concentrations (micrograms per L) after 2 and 4 weeks of treatment (lower panel) with placebo (n = 10) and once daily oral evening (PM) MK-677 doses of 2 mg (n = 10), 10 mg (n = 12), and 25 mg (n = 10). * Significant change from baseline (P < 0.05).

FIG. 3. Percent changes from baseline (geometric mean ± geometric SE) of 24-h mean GH concentrations (micrograms per L) after 2 weeks of treatment (upper panel) and of serum IGF-I concentrations (micrograms per L) after 2 and 4 weeks of treatment (lower panel) with placebo (n = 10) and once daily oral evening (PM) MK-677 doses of 2 mg (n = 10), 10 mg (n = 12), and 25 mg (n = 10). * Significant change from baseline (P < 0.05).

Comparison of evening vs. morning treatment with 10 mg/day MK-677

GH. The 24-h mean GH profiles after evening and morning administration of placebo or 10 mg/day MK-677 are shown in Fig. 6. The 24-h mean GH percent increase from baseline was significant after both morning and evening oral admin-
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Fig. 4. Twenty-four-hour GH concentration profiles of six older subjects at baseline (○) and on day 14 of treatment with oral MK-677, administered once daily in the evening between 2200-2300 h. Blood samples were collected every 20 min. Two upper panels, 10 mg/day MK-677 (○); four lower panels, 25 mg/day MK-677 (△).

Fig. 5. Serum IGF-I concentrations (micrograms per L) of individual subjects at baseline and after 2 and 4 weeks of treatment with daily evening oral placebo (○; n = 10; left panel) or 25 mg MK-677 (△; n = 10; right panel). The shaded zone represents the assay normal range for adults 21-25 yr old (202-453 pg/L).

Although there was a trend toward a greater response to the drug in older subjects, the response to MK-677 in individual subjects could not be predicted from any baseline measurement. For example, in the 10 subjects treated with 25 mg/day MK-677, no significant correlations (P > 0.1) were detected between the percent changes in either the mean 24-h mean GH concentration or the serum IGF-I concentration after 2 weeks of treatment and any of the following baseline measurements: mean 24-h GH concentration, IGF-I concentration, age, BMI, or age-BMI product.

Other hormone and glucose results

Results of treatment with 2 mg MK-677 are not shown, as there were no associated significant changes in any parameter. Serum cortisol concentrations were determined every 20 min for 24 h in all panel A subjects. Mean serum cortisol was not significantly different from baseline after 25 mg MK-677 for 14 days (mean ± se, 226.2 ± 5.5 vs. 231.8 ± 5.5 nmol/L; P = 0.31), and the ultradian pattern of serum cortisol concentrations was preserved (Fig. 8). Similarly, 24-h urinary free cortisol measurements were not significantly different (data not shown).

The mean serum PRL concentration increased 24% after the administration of 25 mg MK-677 (mean ± se, 7 ± 0.5 to 8.6 ± 0.7 μg/L; P ≤ 0.01 vs. baseline). No gender-associated differences in this response were detected. Serum T₃ and TSH were not significantly affected by MK-677 treatment. T₄ concentrations were significantly lower than baseline after 2 weeks of treatment with both placebo and 25 mg MK-677; the changes in the MK-677 treated group were not significantly different from those in the control group.

The effects of evening treatment with 10 and 25 mg MK-677 on IGF-II; IGF-binding protein-1 (IGFBP-1), -2, and -3; fasting glucose; and fasting insulin concentrations are shown in Table 2. MK-677 treatment was associated with statistically significant increases in fasting concentrations of IGF-II, IGFBP-3, glucose, and insulin and decreases in IGFBP-1 and -2.

Pretreatment fasting blood glucose concentrations were below 8 mmol/L (144 mg/dL) in all subjects MK-677 treat-
ment was associated with statistically significant dose-dependent increases in fasting blood glucose concentrations. After the administration of 25 mg MK-677, glucose concentrations had increased 25.3 ± 6.6% and 26.9 ± 6.8% above baseline by 2 and 4 weeks, respectively. Three of the 10 subjects who received 25 mg/day and 1 of the 12 who received 10 mg/day had increases in fasting glucose concentrations to above 8 mmol/L at either 2 or 4 weeks compared to none of the placebo-treated subjects. The highest fasting blood glucose level measured was 9.7 mmol/L in a subject who had received 10 mg MK 677 for 2 weeks in the evening. The change in glucose after administration of 25 mg MK-677 correlated with BMI ($r = 0.77; \ P < 0.01$).

**Discussion**

Once daily oral administration of MK-677 to older adults increased serum GH concentrations in a dose-dependent manner by enhancing pulsatile GH secretion. Serum IGF-I concentrations increased into the normal range for young adults in 8 of 10 subjects after 4 weeks of treatment with 25 mg/day MK-677, with a mean increase of 88%. Administration of MK-677 in the morning resulted in greater increases in serum IGF-I compared to the effects of evening treatment. This is the first study to demonstrate that serum GH and IGF-I concentrations can be increased in older adults by chronic administration of an oral GH secretagogue.

MK-677 is a spiropiperidine that mimics the actions of GHRP-6 (19, 20). Both MK-677 and GHRP-6 bind to the same unique non-GHRH, nonsomatostatin receptors in the pituitary to stimulate GH secretion via protein kinase C- and calcium-dependent mechanisms (17–20, 26–29). In addition to direct effects on the pituitary, MK-677 and GHRP-6 probably act on the hypothalamus (17). GHRP-6 has greatly reduced GH-releasing efficacy when administered to subjects with hypothalamic-pituitary disconnection (30, 31) and has a synergistic stimulatory effect on GH secretion when coadministered with GHRH (32). This suggests that it acts as a functional somatostatin antagonist and/or releases another, as yet unidentified, hypothalamic releasing factor (17). Both GHRP-6 and the GHRP-mimetic secretagogues stimulate the hypothalamic arcuate nucleus neurons in which GHRH is synthesized (33, 34). In sheep, hexarelin, a GHRP-6 analog, stimulates hypothalamic secretion of GHRH (35). In older adults, the GH response to GHRP-6 and GHRP-mimetic secretagogues is greater than that to GHRH (21, 36).

The net effect of these actions is that both GHRP-6 (16) and MK-677 enhance the preexisting pulsatile pattern of GH secretion. The primary effect of aging on GH secretion is to decrease the amplitude of GH pulses ($\beta$, 6). Oral administration of MK-677 partially reversed these effects of aging by increasing both the height of the GH pulses and the nadir GH concentrations between pulses. These higher serum GH concentrations resulted from an increased mass of GH secreted per pulse, with no significant change in the number of GH secretory pulses or the half-life of GH clearance. Similar
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TABLE 2. Effect of oral evening treatment with placebo (PBO; n = 10), 10 mg/day MK-677 (n = 12), and 25 mg/day MK-677 (n = 10) for 2 and 4 weeks on physiological indicators of GH activity in older adults

<table>
<thead>
<tr>
<th>Dose/day Baseline Conc. 2 weeks 4 weeks</th>
<th>Concentration</th>
<th>p*</th>
<th>p#</th>
<th>Concentration</th>
<th>p*</th>
<th>p#</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-II (mg/L)*</td>
<td>PBO</td>
<td>425 ± 50</td>
<td>382 ± 39</td>
<td>405 ± 39</td>
<td>10 mg</td>
<td>406 ± 28</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>411 ± 26</td>
<td>452 ± 35</td>
<td>492 ± 31</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IGFBP-1 (mg/L)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO</td>
<td>15.4 ± 2.0</td>
<td>14.7 ± 3.0</td>
<td>21.3 ± 3.6</td>
<td>&lt;0.05</td>
<td>637 ± 105</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10 mg</td>
<td>19.3 ± 3.7</td>
<td>15.2 ± 3.8</td>
<td>10.3 ± 2.6</td>
<td>&lt;0.05</td>
<td>10.05</td>
<td></td>
</tr>
<tr>
<td>25 mg</td>
<td>16.2 ± 4.2</td>
<td>16.5 ± 4.0</td>
<td>10.3 ± 2.6</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>IGFBP-2 (mg/L)*</td>
<td>PBO</td>
<td>655 ± 121</td>
<td>543 ± 108</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td></td>
<td>10 mg</td>
<td>488 ± 67</td>
<td>392 ± 69</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>25 mg</td>
<td>593 ± 97</td>
<td>413 ± 66</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGFBP-3 (mg/L)*</td>
<td>PBO</td>
<td>2.98 ± 0.3</td>
<td>2.58 ± 0.2</td>
<td>2.8 ± 0.3</td>
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<tr>
<td></td>
<td>10 mg</td>
<td>2.55 ± 0.3</td>
<td>2.76 ± 0.4</td>
<td>3.8 ± 0.2</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>2.86 ± 0.2</td>
<td>3.26 ± 0.2</td>
<td>3.6 ± 0.2</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)*</td>
<td>PBO</td>
<td>5.2 ± 0.3</td>
<td>5.3 ± 0.3</td>
<td>5.3 ± 0.2</td>
<td></td>
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<tr>
<td></td>
<td>10 mg</td>
<td>5.4 ± 0.2</td>
<td>6.3 ± 0.4</td>
<td>6.8 ± 0.4</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>5.4 ± 0.3</td>
<td>6.7 ± 0.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)*</td>
<td></td>
<td>8.3 ± 1.1</td>
<td>7.7 ± 1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO</td>
<td>6.1 ± 1.8</td>
<td>8.7 ± 2.1</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>10.6 ± 0.9</td>
<td>12.9 ± 1.5</td>
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</tbody>
</table>

* P values to assess the significance of changes from baseline.
* P values to assess the significance of the comparison with PBO.
* Values expressed as the mean ± se.
* n = 8, n = 11 for PBO and 10 mg, respectively, due to insufficient blood sample for assay.
* Multiply by 18.018 to convert to mg/dL.
* n = 9 due to insufficient blood sample for assay.
* Values expressed as the geometric mean ± geometric se.

Effects in older adults were observed with a continuous iv infusion of a related compound, L-692,429 (37). The increased interpeak GH concentrations may be the result of increased basal (nonpulsatile) secretion or the larger GH secretory pulses (i.e. with larger pulses, the GH concentrations do not decline to baseline before the onset of the next pulse). Nevertheless, it is clear that the majority of GH secretion remained pulsatile during MK-677 treatment. Whereas basal secretion accounts for 38-69% of 24-h GH production in acromegaly (38), less than 20% of GH secretion was attributable to basal secretion during MK-677 treatment. As the metabolic actions of GH are modulated by the pattern of GH exposure to tissues (39), we speculate that enhancement of pulsatile GH release may produce fewer side-effects and greater benefits than the sustained increase in GH concentrations produced by daily sc GH administration (15), but this remains to be determined.

The greater stimulation of GH release by morning than evening MK-677 administration was an unexpected finding, although a similar conclusion had been suggested by two earlier studies. However, both of those studies unfortunately were limited by the use of less sensitive GH assays (16, 40). Somatostatin release is thought to be stimulated by food ingestion and decreased during sleep, resulting in greater GH secretion rates at night than during the day in fed subjects (1). Thus, our results support the hypothesis that MK-677 functionally antagonizes somatostatin action.

The effects of MK-677 are relatively specific to the GH-IGF-I axis. Blood concentrations of cortisol and thyroid hormones were not significantly affected by the drug. Mean serum PRL levels increased approximately 24% after daily treatment with 25 mg MK-677; this increase is statistically, although probably not clinically, significant. Consistent with the known effects of GH (2, 15, 41), circulating concentrations of IGF-II and IGFBP-3 increased, IGFBP-1 and -2 levels decreased, and fasting blood glucose and insulin concentrations increased. The changes in glucose were correlated with BMI, suggesting that the GH stimulatory effects of MK-677 may result in impaired glucose tolerance in individuals with predisposing risk factors. It is not known whether these effects on carbohydrate metabolism will persist with longer term administration of MK-677. If so, the usefulness of this drug could be limited. In GH-deficient subjects, GH replacement therapy results in insulin resistance at 6 weeks, but this effect is diminished at 26 weeks, by which time significant decreases in body fat had occurred (42). Thus, if enhanced GH secretion produced by chronic MK-677 treatment results in loss of body fat, then it is possible that insulin sensitivity will improve over time.

If prolonged treatment with oral GH secretagogues results in favorable effects on body composition, functional capacity, and serum lipids, then such secretagogues may have a therapeutic role in a variety of conditions where the pituitary is intact but GH secretion is reduced. Candidates for treatment could include older adults with musculoskeletal impairment and patients with catabolic conditions for which...
short term GH therapy has been shown to have beneficial
effects, including human immunodeficiency virus/acquired
immunodeficiency syndrome wasting (43), burns (44),
chronic obstructive pulmonary disease (45), and those re-
quiring parenteral nutrition after major surgery (46). The
majority of children with GH deficiency and short stature
have normal or near-normal GH release in response to
GIRH (47), indicating a dominant hypothalamic rather than
pituitary cause of their GH deficiency. As chronic treatment
with parenteral GHRH significantly increases growth velocity
in these children (48), oral GH secretagogues may be
efficacious in this setting as well. Consistent with this pos-
sibility, we recently found that oral administration of MK-
677 increases circulating IGF-I concentrations and enhances
pulsatile GH release in selected GH-deficient adults who
were treated with GH during childhood (49).

In summary, once daily oral treatment of healthy older
adults with the GH secretagogue MK-677 for up to 4 weeks
enhanced pulsatile GH release and produced dose-respon-
sive increases in circulating concentrations of GH and IGF-I.
At a dose of 25 mg/day, MK-677 restored serum IGF-I con-
centrations in most older subjects to levels seen in young
adults. Administration of 10 mg/day MK-677 in the morning
increased IGF-I to a greater extent than treatment in the
evening. Further studies are needed to establish the long
term safety of this drug, particularly its effect on glucose and
insulin levels, and to determine the effect of long term ad-
ministration of such compounds in a variety of conditions
associated with GH deficiency. Our findings suggest that
oral GH secretagogues may provide significant therapeutic
advantages over administration of GH in these conditions.

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test assistance. We also thank the General Clinical Research Center Core
Laboratory for performing the cortisol and PRL

References

   In: Wilson JD, Foster DW, eds. Williams' textbook of endocrinology, 7th ed.
   Philadelphia: Saunders; 221-310.
   the 24-hour profile of growth hormone secretion in man: importance of endoge-
6. Veldhuis JD, Liem AY, South S, et al. 1995. Differential impact of age, sex-
   steroid hormones, and obesity on basal IGF-I pulsatile growth hormone se-
   cretion in men as assessed in an ultrasensitive chemiluminescence assay. J Clin
   Endocrinol Metab. 80:3900-3908.
   influence of age on the 24-hour integrated concentration of growth hormone
   secretion in normal individuals. J Clin Endocrinol Metab. 60:313-316.
   hormone deficiency (GHD) in adults [letter]. J Clin Endocrinol Metab.
   80:3900-3908.
    are specific determinants of the frequency and amplitude of GH secretory
    bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol
    Metab. 73:1081-1088.
   of recombinant human growth hormone on metabolic indices, body compo-
   sition, and bone turnover in healthy elderly women. J Clin Endocrinol Metab.
   79:470-479.
15. Jorgensen J0L. 1991. Human growth hormone replacement therapy: pharma-
   (GH)-releasing peptide (GHRP) infusion enhances pulsatile GH secretion
   and specifically attenuates the response to a subsequent GHRP bolus. J Clin
   Endocrinol Metab. 76:1202-1208.
   growth hormone-releasing hexapeptide, GHRP. Endocrinology. 128:2027-2035.
   Identification of a new G-protein linked receptor for growth hormone secre-
   of L-163,191 (MK-677), a potent orally active growth hormone secretagogue.
   Proc Natl Acad Sci USA. 92:7001-7005.
   novel growth hormone secretagogue, L-692,429, in healthy older subjects.
   J Clin Endocrinol Metab. 79:483-494.
22. Veldhuis JD, Johnson ML. 1986. Cluster analysis: a simple, versatile, and
23. Veldhuis JD, Carlson ML, Johnson ML. 1987. The pituitary gland secretates in
   bursts: appraising the nature of glandular secretory impulses by simultaneous
   multiple-parameter deconvolution of plasma hormone concentrations. Proc
   Natl Acad Sci USA. 84:7686-7690.
   gistic effects of Hist-o-Trp-Ala-Trp-d-Phe-Lys-NH2 on growth hormone (GH)
   releasing factor-stimulated GH release and intracellularosmosis 3'-5'-mono-
   phosphate accumulation in rat primary pituitary cell culture. Endocrinology.
   124:2791-2798.
   growth hormone releasing peptide (GHRP-1) on growth hormone secretion from
   role of protein kinase-C in Hist-o-Trp-Ala-Trp-d-Phe-Lys-NH2-induced growth
   hormone release from rat primary pituitary cells. Endocrinology. 129:3337-3342.
   hormone secretagogue, L-692,429, induces phosphatidylinositol hydrolysis and
   hormone secretion by pituitary tumors. Biochem Biophys Res Commun.
   218:290-296.
   Blocked growth hormone-releasing peptide (GHRP-6) induced GH secre-
   tion and absence of the synergistic action of GHRP-6 plus GH-releasing
   hormone in patients with hypothalamic-pituitary disconnection: evidence that
   GHRP-6 main action is exerted at the hypothalamic level. J Clin Endocrinol
   Metab. 80:942-947.
   Absence of growth hormone (GH) secretion following administration of either
   GH-releasing hormone (GHRH), GH-releasing peptide (GHRP6), or GHRP6
   plus GHRP6 in children with neonatal pituitary stalk transection. J Clin
   Endocrinol Metab. 80:381-384.
31. Rousset CV, Reynolds GA, Orci D, Brarera CM, Pezzoli SS, Thorner MO.
   1990. Growth hormone (GH)-releasing peptide stimulates GH release in normal
   men and acts synergistically with GH-releasing hormone. J Clin Endocrinol
   Metab. 70:975-982.
   hormone-releasing peptide activates hypothalamic arcuate neurons. Neurosci
   Lett. 53:303-306.
   and non-peptide growth hormone secretagogues in the rat. Neuroendocrinol
   ogy. 61:56-43.
MK 677 ENHANCES PULSATILE GH RELEASE IN OLDER ADULTS


