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MK-677, an Orally Active Growth Hormone Secretagogue, Reverses Diet-Induced Catabolism*

M. G. MURPHY, L. M. PLUNKETT, B. J. GERTZ, W. HE, J. WITTREICH, W. M. POLVINO†, AND D. R. CLEMMONS

Merck Research Laboratories (M.G.M., B.J.G., W.H., J.W., W.M.P.), Rahway, New Jersey 07065; and Department of Medicine, University of North Carolina at Chapel Hill (L.M.P., D.R.C.), Chapel Hill, North Carolina 27514

ABSTRACT

The reversal of diet-induced negative nitrogen balance by GH suggests a possible therapeutic role for GH treatment in catabolic patients. A double-blind, randomized, placebo-controlled, two-period, cross-over study was designed to investigate whether MK-677, an orally active nonpeptide mimic of GH-releasing peptide, can reverse diet-induced protein catabolism. Eight healthy volunteers (ages 24–39 yr) were calorically restricted (18 kcal/kg·day) for two 14-day periods. During the last 7 days of each diet period, subjects received either oral MK-677 25 mg or placebo once daily. There was a 14- to 21-day washout interval between periods. During the first week of caloric restriction (*i.e.* diet alone), daily nitrogen losses were similar for both treatment groups (mean ± SE; MK-677 group −2.67 ± 0.40 g/day *vs*. placebo group −2.83 ± 0.26 g/day). During the second week (diet and study drug), mean daily nitrogen balance was 0.31 ± 0.21 g/day in the MK-677 treatment group compared with −1.48 ± 0.21 g/day in the placebo group ($P < 0.01$). MK-677 improved nitrogen balance integrated over the 7 days of treatment; area under the curve day 8–14 nitrogen balance response was +2.69 ± 5.0 (SE) for MK-677 and −8.97 ± 5.26 g·day for placebo ($P < 0.001$). MK-677 produced a peak GH response of 55.9 ± 31.7 μg/L after single dose (day 1 of treatment) and 22.6 ± 9.3 μg/L after a week of dosing compared with placebo treatment peak GH values of approximately 9 (treatment day 1) and approximately 7 μg/L (treatment day 7). Following the initial 7-day caloric restriction, insulin-like growth factor-I (IGF-I) declined from 232 ± 25 to 186 ± 19 ng/mL in the MK-677 group and from 236 ± 19 to 174 ± 23 ng/mL in the placebo group. Mean IGF-I concentration increased significantly during MK-677 to 264 ± 31 ng/mL (mean for the last 5 days of treatment) compared with 188 ± 19 ng/mL with placebo ($P < 0.01$). No significant difference in IGF binding protein-2 was found between the MK-677 and placebo treatments. However, the mean in IGF binding protein-3 for the last 5 days of MK-677 treatment was also significantly increased to 3273 ± 330 ng/mL (mean ± SE) compared with placebo 2604 ± 253 ng/mL ($P < 0.01$). Neither the serum cortisol nor the PRL response was significantly greater after 7 days of MK-677 dosing compared with 7 days of placebo. MK-677 (25 mg) was generally well tolerated and without clinically significant adverse experiences. In conclusion, MK-677 reverses diet-induced nitrogen wasting, suggesting that if these short-term anabolic effects are maintained in patients who are catabolic because of certain acute or chronic disease states, it may be useful in treating catabolic conditions. (*J Clin Endocrinol Metab* **83:** 320–325, 1998)

GH is a potent anabolic hormone capable of promoting linear growth, weight gain, and whole-body nitrogen retention (1). GH treatment has been shown to increase muscle mass in older men (2) and promote protein accretion in hypopituitary subjects (3). These anabolic properties suggest that it may be useful in the treatment of catabolic patients, particularly catabolism induced or worsened in severity by inadequate caloric intake. The anabolic actions of GH have been exploited to partially reverse the catabolic effects of dietary energy restriction (4, 5), excessive energy utilization through exercise (6), surgery (7), glucocorticoid excess (8), and aging (2). Unfortunately, despite the availability of recombinant human GH, treatment with GH is costly and requires parenteral administration. Therefore, GH secretagogues that stimulate the secretion of endogenous GH, some of which are active when administered orally, are reasonable alternatives.

GH-releasing peptide (GHRP-6), a synthetic hexapeptide, has been demonstrated to be a potent, relatively selective, GH secretagogue in all species tested, including humans (9–11). Compounds have been developed that mimic the stimulatory actions of GHRP on GH release in animals and man (12, 13). Continuous 24-h iv infusion of one of these compounds, the substituted benzolactam L-692,429, was shown to stimulate pulsatile GH release and increase mean circulating GH concentrations in healthy older adults (14, 15).

MK-677 is a nonpeptide spiropiperidine previously demonstrated to be functionally indistinguishable *in vitro* and *in vivo* from the potent peptide GH secretagogue GHRP-6 (16). MK-677 is active after oral administration in animals (16, 17). In healthy young men, MK-677 was substantially more efficacious than GHRH, producing a mean peak GH concentration of 22.1 μg/L after an oral dose of 25 mg (M. G. Murphy, data on file, Merck Research Laboratories).

Dietary energy restriction induces a predictable catabolic response in normal subjects (4, 5). This loss of nitrogen is associated with a decrease in insulin-like growth factor-I (IGF-I) and an increase in GH (19, 20), suggesting GH resistance. However, the resistance is not absolute, because ad-

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Address all correspondence and requests for reprints to: M. Gail Murphy, Merck Research Laboratories, Building 10, Sentry Parkway, Bluebell, Pennsylvania 19422.

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† Participated while at Merck Research Laboratories

ministration of exogenous GH will effect an increase in IGF-I and increase nitrogen retention (4, 5). Because MK-677 is a potent GH secretagogue, the present study was undertaken to determine whether MK-677 could reverse the catabolic response to dietary energy restriction in healthy volunteers.

Subjects and Methods

Subjects

Eight healthy male volunteers were recruited. They were 24–39 yr old (mean age, 32.3 yr), within 20% of ideal body weight (Metropolitan Life Insurance tables), and ranged from 64–83.5 kg (mean, 73.2 kg). All subjects were in general good health on the basis of medical history, physical exam, electrocardiogram, and routine laboratory safety studies. All subjects were nonsmokers. Total testosterone and thyroid function tests (T_4 and T_3 by RIA, and sensitive TSH by immunoradiometric assay) were normal at screening for all subjects. The study was approved by the University of North Carolina Institutional Committee for the Protection of the Rights of Human Subjects and written informed consent was obtained from each subject.

Study design

This was a double-blind, placebo-controlled, randomized, two-period, cross-over study. Moderate catabolism was produced in eight healthy young adult volunteers by restricting their dietary intake. During the first 7 days of each 14-day treatment period, subjects received a hypocaloric diet and were administered a single-blind placebo tablet each night at bedtime. During the last 7 days of each 14-day study period, subjects continued the same caloric-restricted diet and received either 25 mg MK-677 or placebo orally once daily at bedtime. The sequence of MK-677 and placebo treatments during the last 7 days of caloric restriction was randomized among the subjects according to a computer-generated allocation schedule. There was a 14- to 21-day washout interval between periods, during which time the subjects consumed their normal diet. Previously, this period of time has been shown to restore nitrogen balance and IGF-I to values that are comparable with those that were present before dietary restriction (21).

Subjects were permitted to continue most of their daily activities outside the hospital but refrained from vigorous exercise. During each of the two 14-day diet study periods, subjects consumed breakfast and dinner at the General Clinical Research Center of the University of North Carolina. Lunch was provided by the research unit, and subjects were allowed to consume it outside the unit. During each 14-day study period, subjects were fed a diet containing 18 kcal/kg ideal body weight including 1 g protein/kg ideal body weight. Nonprotein calories were provided as 50% carbohydrate and 50% fat. The nutrient content of the diet was determined using United States Department of Agriculture food tables (22). Dietary compliance was monitored by weighing the food left after each meal and by observations of the constancy of weight loss and urinary nitrogen excretion. Daily 24-h urines were collected for urea and ammonia nitrogen, free cortisol, and creatinine.

Routine hematology, serum chemistries, and urinalyses were obtained in the prestudy period on days 1, 7, 8, 11, 14, and 24 h after dosing, and between 3–5 days after the last dose was administered. Blood was sampled as described below at designated intervals during each treatment period for hormone assay.

Measurements

Body weight was recorded daily during each treatment period. Urinary creatinine excretions and 24-h urinary urea and ammonia nitrogen were measured in the chemistry laboratory of the University of North Carolina (U.N.C. Hospitals) by autoanalyzer (23). Urine collections for which the creatinine varied by more than 15% from the mean for an individual were omitted from the analysis. This included 2 samples from a total of 240. Daily nitrogen balance was calculated by subtracting the urinary nitrogen (urinary urea and ammonia) and 245 mmol (estimate of stool and integument losses) from the daily nitrogen intake as determined by food tables (22). Fasting blood samples were collected for serum IGF-I, IGF binding protein-2 (IGFBP-2), and IGFBP-3 levels on days 1, 7, and 8 (predose and 0.5 h postdose); days 9–13 (8 h postdose; ~0800–0900 h); and day 14 (predose, 8 and 24 h postdose). IGF-I concentrations were measured by RIA after separating IGF-I from IGF-I binding proteins using octdecasil/silica cartridges (C-18 Sep-Pak: Waters Associates, Milford, MA) (24, 25). The results are expressed as micrograms per liter after correcting for losses during extraction. The interassay coefficient of variation for this assay is 6.1%. IGFBP-2 and IGFBP-3 were assayed at the University of North Carolina according to previously published methods (26, 27). The interassay coefficients of variation are 11% and 7%, respectively. All other serum and urine hormones were assayed at Endocrine Sciences (Callabasas Hills, CA). GH concentrations were determined using a double antibody RIA with a reported sensitivity of 0.3 μg/L and an interassay variability [coefficient of variation (CV)] of 7–11% over the 3–20 μg/L range. PRL was measured by immunochemiluminometric assay, with a reported sensitivity of 0.2 μg/L and an interassay CV of 5.8% at 3 μg/L. Serum cortisol was assayed by an RIA technique with a reported sensitivity of 1 ng/dL and an interassay CV of 7–8% over an approximate 8–26 μg/dL range. Urinary cortisol was measured using an RIA technique after chromotography according to standard procedures at Endocrine Sciences (28).

Routine hematology, chemistry, and urinalysis were performed with standard methodology at the laboratory of the University of North Carolina hospital. Prestudy and posttreatment total serum testosterone and thyroid function tests were performed at Endocrine Sciences according to their standard procedures.

Statistical methods

The effect of MK-677 on protein catabolism was evaluated via an analysis of nitrogen balance. The trapezoidal area under the nitrogen balance curve during the second 7 days of each period ($AUC_{days\ 8-14}$) was computed based on the curve for daily nitrogen balance for each subject in each period. This analysis was selected to provide an overall cumulative measurement of total nitrogen balance over time.

The effect of MK-677 on GH was assessed by analyses of the trapezoidal area under the GH concentration curve from 0–8 h postdose and the peak GH concentration on days 8 and 14. The effect of MK-677 on IGF-I was assessed by an analysis of the serum IGF-I concentration posttreatment to baseline ratio and area under the IGF-I response curve from days 8–14. The specificity of MK-677 was assessed through the analysis of serum cortisol and PRL ($AUC_{0-8\ h}$ and peak concentration on days 8 and 14), and 24-h urinary free cortisol excretion (days 8 and 14). Posttreatment-to-baseline ratios (day 14/day 8) were also assessed for serum TSH, T_3, T_4, and testosterone.

In all cases, baseline was defined as the mean of pretreatment values obtained on day 8 for each period. Parameters (*e.g.* AUC, peak, ratios of day 14 to day 8 response, and postdose/baseline ratio as appropriate) were analyzed using ANOVA models appropriate for a two-period cross-over design. There was no significant carryover. When necessary, response variables were transformed to ensure that data adhered to the model assumptions.

One sample *t* test comparing the day 14/day 8 ratios with zero was used to assess the significance of the response. All values except for nitrogen balance and GH response data are presented as mean ± SD.

To assess the significance of changes in IGF-I, IGFBP-2, and IGFBP-3, the values for single-day comparisons between treatment groups were analyzed using a two tailed *t* test. Similarly, *t* testing was used to analyze significance when data from multiple test days were pooled for comparison.

Results

Nitrogen balance

Nitrogen balance calculated daily for MK-677 and placebo treatments is shown in Fig. 1. During the first week of caloric restriction (*i.e.* diet alone), daily nitrogen losses were similar for both treatment groups (mean ± SE values were −2.67 ± 0.40 g/day and −2.83 ± 0.26 g/day for the MK-677 and placebo groups, respectively). During the second week (diet and study drug), MK-677 improved average daily nitrogen balance to 0.31 ± 0.21 g/day compared with −1.48 ± 0.21 g/day in the placebo group. Nitrogen losses clearly reversed

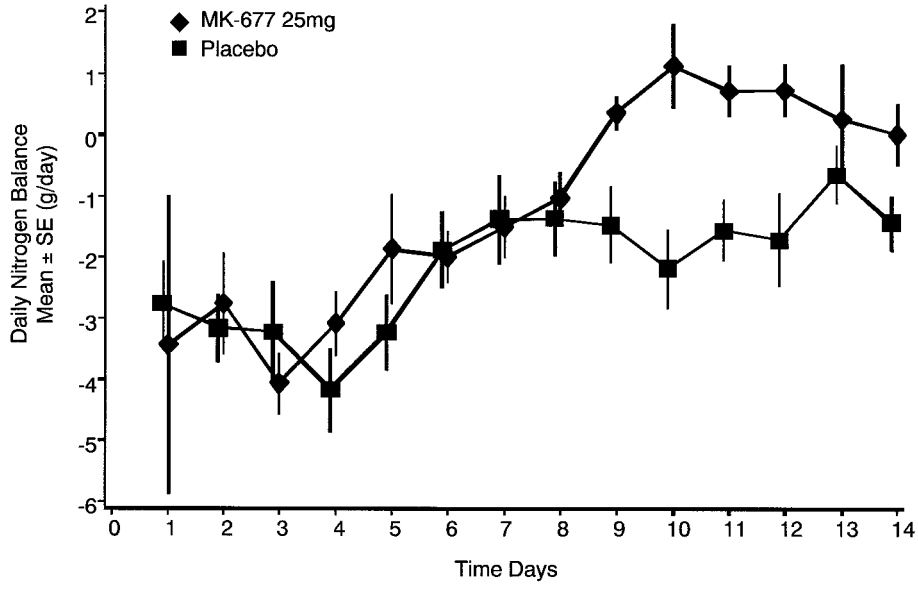

FIG. 1. Changes in nitrogen balance in response to MK-677 and placebo. Results are expressed as means ± SE and were derived from measurements of urea and ammonia nitrogen in 24-h collections as described in *Subjects and Methods*. Compared with control period, improvements in nitrogen balance obtained during MK-677 treatment were significant ($P < 0.001$). MK-677 (◆) *vs.* placebo (■).

TABLE 1. GH response to MK-677

Treatment	n	Day 8[a]		n	Day 14[a]	
		Peak GH (ng/mL)	GH $AUC_{0\text{-}8\ h}$ (ng · h/mL)		Peak GH (ng/mL)	GH $AUC_{0\text{-}8\ h}$ (ng · h/mL)
MK-677 (25 mg)	8	55.9 ± 9.7[b]	207 ± 33.7[b]	8	22.6 ± 3.0[c]	58.2 ± 4.4[c]
Placebo	8	9.0 ± 0.6	29.4 ± 3.3	8	7.4 ± 2.5	27.3 ± 8.0

[a] Geometric mean ± SE.
[b] $P < 0.001$ *vs.* placebo.
[c] $P < 0.05$ *vs.* placebo.

after the first dose in the MK-677 treatment group (day 8). In the MK-677 treatment group, daily nitrogen balance increased to approximately +1 and approximately +0.3 g/day after 2 and 7 days treatment, respectively [*vs.* ~ −2 and ~ −1 g/day on the same days for placebo (Fig. 1)]. MK-677 improved overall nitrogen balance integrated over the subsequent 7 days of treatment; $AUC_{days\ 8\text{–}14}$ nitrogen balance was +2.69 ± 5 (SE) *vs.* −8.97 ± 5.26 g/day for MK-677 and placebo treatments, respectively ($P = 0.001$). Further, when the mean $AUC_{days\ 8\text{–}14}$ was compared with 0, the 25-mg MK-677 treatment was associated with a nearly significant increase ($P = 0.09$), whereas placebo treatment was associated with a significant decrease ($P = 0.001$). Analysis of $AUC_{days\ 8\text{–}14}$ based on nitrogen balance corrected for creatinine excretion yielded similar results. Changes in serum urea nitrogen were consistent with the nitrogen balance results. Serum urea nitrogen decreased from a mean of 14.6 ± 2.4 to 12.9 ± 2.1 mg/dL over the last 4 days of each interval of placebo treatment. In contrast, the subjects remaining on MK-677 had a mean serum urea nitrogen that decreased from 13.8 ± 2.3 to 9.55 ± 1.9 mg/dL. This change was significantly greater than the change that occurred with placebo $P < 0.01$.

Dietary restriction during the first week (days 1–7) caused all subjects to lose an average approximately 2.5 kg. During the study treatment week (days 8–14), there was less weight loss in the MK-677 treatment group compared with the placebo group (day 14/day 8 mean weight ratio = 0.99 for MK-677 compared with 0.98 for placebo; $P < 0.05$).

GH response

The peak and integrated ($AUC_{0-8\ h}$) GH response for days 8 and 14 are shown in Table 1. MK-677 produced a peak GH response of 55.9 ± 31.7 μg/L after the first dose (day 8) and 22.6 ± 9.3 μg/L after a week of dosing (day 14) compared with peak GH responses of approximately 9 μg/L (day 8) and approximately 7 μg/L (day 14) with placebo ($P < 0.05$ for both comparisons).

IGF-I and IGFBPs

The changes in nitrogen balance were accompanied by changes in IGF-I levels (Fig. 2). Following the initial 7 days of caloric restriction, IGF-I declined for each group from a mean of 236 ± 56 ng/mL to 174 ± 64 ng/mL in the placebo group and from 232 ± 69 ng/mL to 185 ± 53 ng/ml in the group that subsequently received MK-677 [P = not significant (NS)]. IGF-I increased progressively to 256 ± 84 ng/mL by day 3 of MK-677 treatment, then remained elevated through the last treatment day. The placebo group showed no change. When the mean value for the last 5 days of MK-677 treatment (264 ± 31 ng/mL) was compared with the mean value for placebo subjects (188 ± 19 ng/mL), the difference was significant ($P < 0.01$). When the individual daily values from days 10–14 were compared, the individual values for days 10–14 on MK-677 treatment were significantly greater than the placebo treatment values ($P < 0.05$). No significant difference in IGFBP-2 was found between the

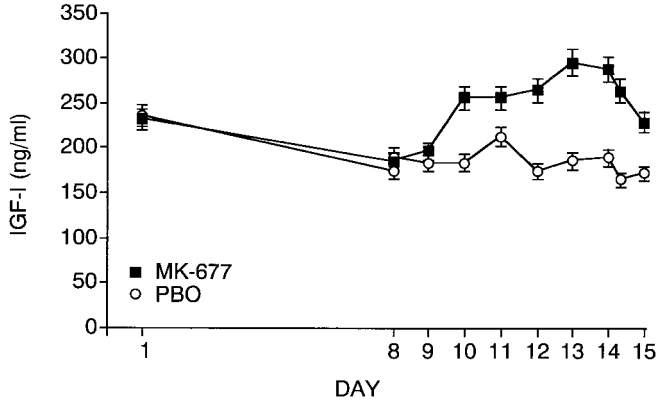

FIG. 2. Changes in serum IGF-I concentrations during treatment. MK-677 (■) and placebo (○) were administered, and blood samples obtained as described in *Subjects and Methods*. Results are mean ± SD for eight subjects. Compared with control period, increases in serum IGF-I concentrations obtained during MK-677 treatment were significant ($P < 0.05$).

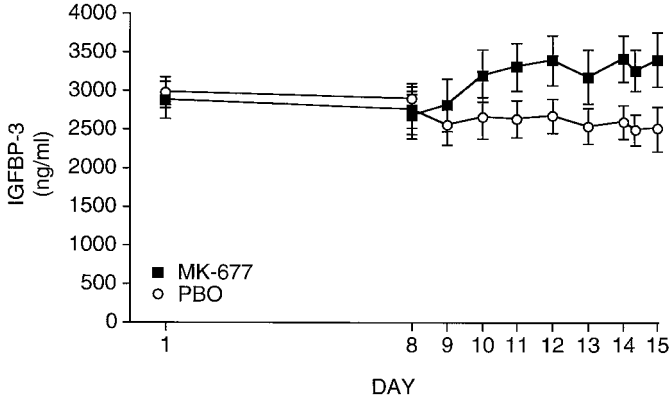

FIG. 3. Changes in serum IGFBP-3. Results show responses of eight subjects to MK-677 (■) and placebo (○), which were administered as described in *Subjects and Methods*. Compared with control period, increases in serum IGFBP-3 concentrations obtained during MK-677 treatment were significant ($P < 0.05$).

MK-677 and placebo treatments (data not shown). IGFBP-3 also increased significantly during treatment (Fig. 3). Dietary restriction resulted in a decline from 2974 ± 578 ng/mL to 2752 ± 514 ng/mL in the placebo group after 7 days of restriction. The decrease in the MK-677 group was similar from 2871 ± 659 ng/mL to 2747 ± 623 ng/mL (P = NS). Following MK-677, IGFBP-3 increased progressively to a mean day-12 (fifth treatment day) value of 3374 ± 917 ng/mL ($P < 0.05$ compared with day 8). In contrast, the placebo group showed no change (day-12 value = 2673 ± 636 ng/mL; P = NS compared with day 8). When the average IGFBP-3 value for the last 5 treatment days on MK-677 (3273 ± 330 ng/mL) was compared with placebo (2604 ± 253 ng/mL), the difference was significant ($P < 0.01$).

Cortisol and PRL

Cortisol and PRL concentrations are known to be increased by single doses of GHRP-6 and its nonpeptide mimetics (13, 14). The changes in these hormones during MK-677 treatment are shown in Table 2. Although there was an effect of MK-677 on serum cortisol $AUC_{0-8\ h}$ on day 8 (120.3 ± 28.0 μg·h/dL *vs.* 54.8 ± 15.1 μg·h/dL for placebo, $P = 0.001$), the comparison of the mean cortisol response on day 14 showed no difference between treatment groups (cortisol $AUC_{0-8\ h}$: MK-677 71.2 ± 18.4 μg·h/dL *vs.* placebo 60.2 ± 14.1 μg·h/dL, $P > 0.2$). MK-677 also increased urinary cortisol on day 8 (first dose) but not on day 14 (seventh dose) as shown in Table 2.

There was also a small effect of MK-677 on serum PRL concentrations on day 8 (first dose) that was substantially attenuated by day 14 (seventh dose) (peak PRL = 26.6 ± 12.8 μg/L *vs.* 17.4 ± 6.3 μg/L for MK-677 and placebo on day 8, respectively, compared with peak PRL = 18.4 ± 8.1 μg/L and 15.2 ± 11.9 μg/L for MK-677 and placebo, respectively, on day 14).

Safety

Four of the eight subjects experienced clinical adverse experiences, all of which were rated as mild and rapidly resolved without sequela. Adverse experiences included short-lived complaints of stomach ache and dizziness (n = 1, MK-677), diarrhea (n = 1, placebo), and headache (n = 2, both placebo). Two subjects discontinued participation in the study during the initial week of dietary restriction because they did not wish to comply with caloric restrictions. There were no changes in the serum chemistries or hematological tests that were considered of clinical significance, although an elevated fasting blood glucose concentration (142 mg/dL) was noted on day 14 in one subject on MK-677.

Discussion

Our results show that 25 mg MK-677 given orally for 7 days in healthy male volunteers improved nitrogen balance during dietary caloric restriction, a model for the treatment of a catabolic state. The effect of MK-677 occurred promptly and persisted for the 7 days of treatment. Nitrogen balance was positive after 2 and 7 days of treatment. The magnitude of this increase relative to response after placebo treatment was clinically meaningful, because the subjects averaged a 1.8 g/day improvement in nitrogen balance. It is not known whether these short-term effects will be maintained beyond 7 days (a slight waning of effect can not be excluded (Fig. 1)). Whether the effect on nitrogen balance would persist beyond 7 days was not evaluated in this study because there was limited clinical experience with longer periods of administration. However, if this response were sustained for several weeks, it would likely diminish the loss of skeletal muscle and visceral protein seen during catabolic states. GH has previously been shown to nearly reverse nitrogen wasting to a mean of −0.2 ± 0.5 g/day after 5 days (29). Using this model and a similar degree of caloric restriction, the magnitude of change in nitrogen balance after MK-677 is similar to that seen after GH treatment. We conclude that MK-677 increases endogenous GH secretion sufficient to reverse this degree of nitrogen loss in normal volunteers who are made catabolic by caloric restriction and is therefore anabolic.

The oral dose of 25 mg MK-677 was chosen for this study because it produced a substantial GH response (peak GH >10 μg/L; mean peak 22.1 μg/L) when administered

TABLE 2. Cortisol and PRL responses to MK-677

Treatment	Study day	n	Peak cortisol (μg/dL)	Cortisol $AUC_{0-8\ h}$ (μg·h/dL)	Urinary cortisol (μg/g creatinine)	Peak PRL (μg/dL)	PRL AUC (μg·h/dL)
MK-677	8	8	19.3 ± 5.4	120.3 ± 28.0[a]	18.3 ± 7.4	26.6 ± 12.8[a]	159.0 ± 58.7[a]
Placebo	8	8	16.8 ± 2.0	54.8 ± 15.0	13.4 ± 4.0	17.4 ± 6.3	101.1 ± 38.0
MK-677	14	8	15.9 ± 3.0	71.2 ± 18.4	11.4 ± 3.1	18.4 ± 8.1	110.5 ± 38.2
Placebo	14	8	17.0 ± 3.4	60.2 ± 14.1	13.6 ± 3.1	15.2 ± 11.9	87.2 ± 65.9

Mean ± SD.
[a] $P < 0.001$ *vs.* placebo.

after an overnight fast to a group of healthy young nonobese males (M. G. Murphy, Merck). The peak GH response to MK-677 was similar in the present study. GH increases were sustained after the last dose of MK-677, documenting persistent secretagogue activity for the duration of the study. This suggests that the catabolic response induced by caloric restriction does not prevent the GH response of the pituitary to this compound.

MK-677-treated subjects had a 36% increase in serum IGF-I levels compared with the placebo-treated subjects, and this was associated with positive changes in nitrogen balance. Because we did not evaluate 24-h GH secretion, it is difficult to determine how this degree of increase in IGF-I would compare with the increase that occurs in response to an equivalent amount of exogenously administered GH. Caloric deprivation can reduce IGF-I response to GH (21) and may have played a role in limiting the IGF-I response to 36%. It is unlikely that a 36% increase in IGF-I at day 14 attenuated the GH response to MK-677, because this is substantially below the serum levels of IGF-I that are required to suppress spontaneous GH release in normal volunteers (30).

Although a 36% increase in IGF-I is substantially below that noted previously in subjects who were undergoing a similar degree of caloric restriction and received exogenous GH (21, 31), it was nonetheless associated with a positive effect on nitrogen balance. Whether an even greater effect on IGF-I and nitrogen balance would be achieved by increasing the dose of MK-677 was not evaluated in the current protocol because there was limited clinical experience with higher doses. However, the GH response in healthy males does not plateau until 100 mg MK-677 is given (mean peak = 71.2 μg/L) (M. G. Murphy, Merck). This suggests that use of a higher dose of MK-677 in this study might have resulted in a greater increase in GH and possibly a greater change in nitrogen balance.

There was a modest increase in cortisol and PRL after the first dose of MK-677, as previously has been shown for this drug and GHRP-6 (13, 14). These increases in cortisol and PRL were within the normal range, transient, and of a magnitude comparable with normal physiological conditions, such as sleep, exercise, or mental stress (32–34). However, even this small effect was substantially attenuated by the seventh dose of MK-677, such that no significant difference between treatments was evident by day 14. This has been previously reported (35).

Injection of recombinant GH improves nitrogen balance in patients undergoing surgery (7), in patients with chronic obstructive pulmonary disease (36), and in normal subjects receiving glucocorticosteroids (8). Use of GH in these types of catabolic patients may be limited, however, if toxicity to GH such as carbohydrate intolerance (37) or fluid retention (4) occurs. In such situations, MK-677 might prove advantageous because it results in a more physiological pattern of GH release, which might be associated with smaller effects on blood glucose and fluid retention. Whether MK-677 will prove less toxic in catabolic patients who may be predisposed to develop hyperglycemia during illness, or who have underlying glucose intolerance, will need to be carefully assessed in future studies.

In summary, we observed in this short-term study that oral administration of MK-677 reverses the protein catabolism caused by dietary caloric restriction. These data suggest that MK-677 may be useful as adjunctive therapy in certain catabolic states. The degree of GH stimulation observed appears to be sufficient to improve nitrogen balance under the stress of caloric restriction. Whether the short-term anabolic effects observed in our volunteers apply also to patients who are catabolic because of certain acute or chronic disease states remains to be established. Future studies should attempt to determine whether the anabolic effects of MK-677 will persist with prolonged treatment, and whether they will be associated with clinical benefits, such as shorter hospital stay and accelerated convalesence.

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