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Two-Month Treatment of Obese Subjects with the Oral Growth Hormone (GH) Secretagogue MK-677 Increases GH Secretion, Fat-Free Mass, and Energy Expenditure*

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ABSTRACT

Obesity is associated with blunted GH secretion, unfavorable body composition, and increased cardiovascular mortality. The objective of this study was to investigate the effects of oral treatment with the GH secretagogue MK-677 on GH secretion and body composition in otherwise healthy obese males. The study was randomized, double blind, parallel, and placebo controlled. Twenty-four obese males, aged 18–50 yr, with body mass indexes greater than 30 kg/m^2 and waist/hip ratios greater than 0.95, were treated with MK-677 25 mg (n = 12) or placebo (n = 12) daily for 8 weeks.

Serum insulin-like growth factor I (IGF-I) increased approximately 40% with MK-677 treatment ($P < 0.001$ *vs.* placebo). Serum IGF-binding protein-3 was also significantly increased ($P \leq 0.001$ *vs.* placebo). GH and PRL (peak and area under the curve values) were significantly increased after the initial dose of MK-677. Significant increases, with the exception of peak PRL, persisted at 2 and 8 weeks of treatment. The increases in GH and PRL after the initial dose were significantly greater than the increase seen after multiple doses. Serum and urinary concentrations of cortisol were not increased at 2 and 8 weeks (P = NS, *vs.* placebo). Fat-free mass increased significantly in the MK-677 treatment group when determined with dual energy x-ray absorptiometry ($P < 0.01$) or using a four-compartment model ($P < 0.05$). Total and visceral fat were not significantly changed with active therapy. The basal metabolic rate was significantly increased at 2 weeks of MK-677 treatment ($P = 0.01$) but not at 8 weeks ($P = 0.1$). Fasting concentrations of glucose and insulin were unchanged, whereas an oral glucose tolerance test showed impairment of glucose homeostasis at 2 and 8 weeks.

We conclude that 2-month treatment with MK-677 in healthy obese males caused a sustained increase in serum levels of GH, IGF-I, and IGF-binding protein-3. The effects on cortisol secretion were transient. Changes in body composition and energy expenditure were of an anabolic nature, with a sustained increase in fat-free mass and a transient increase in basal metabolic rate. Further studies are needed to evaluate whether a higher dose of MK-677 or a more prolonged treatment period can promote a reduction in body fat. (*J Clin Endocrinol Metab* **83:** 362–369, 1998)

GH-RELEASING peptides (GHRPs), including the well known hexapeptide GHRP-6, were first discovered by Bowers *et al.* (1–3). Other GHRPs, such as GHRP-1, GHRP-2, and hexarelin (4, 5), and nonpeptidyl GH secretagogues, such as orally active MK-677 (6–8), have since been developed. Recently, a specific GHRP receptor has been identified (9), although the natural ligand to this receptor has not yet been identified.

In obesity, GH secretion is blunted, with a decrease in the amount of GH secreted per burst without any major impact on GH secretory burst frequency (10). GH release is also blunted after administration of most GH secretagogues (Ref. 11 and references therein). It has been shown, however, that GHRP-6 elicits a larger increase in GH secretion than GHRH after single dose administration, and their combined administration produces a massive GH response in obese subjects (12).

Striking similarities exist between obesity in males and adult GH deficiency, such as an increased amount of body fat, insulin resistance, and increased cardiovascular mortality (13–17). GH treatment has demonstrated favorable effects on most features of GH deficiency in adults (15) and significant improvement of the various perturbations associated with abdominal/visceral obesity (18).

In the present study we investigated whether 2-month treatment with the oral GH secretagogue MK-677 can induce a significant GH response capable of affecting body composition and energy expenditure in healthy obese males.

Subjects and Methods

Subjects

Twenty-four males, 19–49 yr of age with body mass indexes (BMIs) greater than 30 kg/m^2 and waist/hip ratios greater than 0.95, were studied. They were recruited using advertisements in local newspapers. Exclusion criteria included fasting blood glucose above 6.4 mmol/L and blood pressure greater than 165/95 mm Hg. Except for obesity, all subjects were in good general health, and none used concomitant medication.

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Two subjects were discontinued from the study after approximately 1–2 weeks. One subject had a 3-fold increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), both of which decreased spontaneously to prestudy values after discontinuation of treatment with the study drug (MK-677). Of note, this subject had violated the protocol by ingesting alcohol around the time of the elevation of AST and ALT. One subject was discontinued when hypothyroidism was diagnosed based on a prestudy T_4 value, and the subject was given appropriate T_4 replacement therapy. The two discontinued subjects were replaced by two new subjects who received the same treatment as the subjects they replaced.

Study design

This was an 8-week, randomized, double blind, parallel, and placebo-controlled trial of the oral administration of MK-677 in healthy obese subjects. Subjects were randomized to receive oral MK-677 (25 mg) or a matching dose of placebo daily for 8 weeks (n = 12/group). The dose was administered with 150 mL water between 0800–0900 h. Compliance was checked by weekly tablet counts. The study was approved by the ethics committee at the University of Göteborg and by the Swedish Medical Products Agency (Uppsala, Sweden). Informed consent was obtained from each subject before the start of the study.

Study protocol

The subjects were instructed not to change their ordinary daily caloric intake or physical activity during this study. In this study, GH secretion, body composition, energy expenditure, and glucose homeostasis are reported; these are the primary end points of this study. The secondary end points are bone metabolism, thyroid hormones, and lipid profiles; these will be reported elsewhere.

Before the start of the study, subjects underwent a complete physical examination with laboratory safety assessments. Subjects were in the fasted state and voided their bladder before the measurements. Body weight was measured to the nearest 0.1 kg using a 6800 Digital Indicator (Detecto Scale, Webb City, MO). Body height was measured barefoot and to the nearest 0.01 cm. BMI was calculated as body weight divided by the square of body height. Waist circumference was measured in the standing position with a flexible plastic tape placed midway between the lower rib margin and the iliac crest, and hip girth was measured at the widest part of the hip. Systolic and diastolic blood pressures were measured after at least 10 min of supine rest, using the sphygmomanometric cuff method.

The patients were studied as out-patients. At baseline, 2 weeks, and 8 weeks, blood samples were drawn pretreatment for measurement of GH, insulin-like growth factor I (IGF-I; also measured at 1 week), IGF-binding protein-3 (IGFBP-3), free fatty acids (FFA), glycerol, and β-hydroxybutyrate. Eight-hour profiles of GH, PRL, and cortisol were performed after the first intake of study drug and after tablet intake at 2 and 8 weeks. At baseline, 2 weeks, and 8 weeks, 24-h urine was collected, an oral glucose tolerance test (OGTT) was performed, basal metabolic rate (BMR) and total body nitrogen (TBN) were measured, and body composition was evaluated by dual energy x-ray absorptiometry (DEXA) and a four-compartment model. Abdominal computed tomography scans were conducted at baseline and 8 weeks. Daily caloric intake was assessed at baseline, 4 weeks, and 8 weeks. Body weight measurements and laboratory assessments were performed weekly.

Eight-hour serum profiles of GH, PRL, and cortisol were determined after an overnight fast. Venous blood samples were drawn before treatment and 30, 60, 90, 120, 240, and 480 min after administration of the daily dose of MK-677 or placebo. The area under the curve (AUC) for each hormone was calculated using the trapezoidal rule.

Total body fat and fat-free mass (FFM) were assessed with DEXA measurements, using software version 1.31 for the Lunar DPX-L (Scanexport Medical, Helsingborg, Sweden). The scanner (system no. 7156) had precision errors of 1.7% for total body fat and 0.7% for FFM, as determined by duplicate examinations in 10 healthy subjects.

The four-compartment model used is based on total body potassium (TBK) and total body water (TBW) assessments as previously described by Bruce *et al.* (19). TBK was assessed using a whole body counter [coefficient of variation (CV) = 2.2%], and TBW was determined by the isotope dilution of tritiated water (CV = 3.2%).

Visceral fat mass was determined by means of a Philips Tomoscan 350 (Philips Medical Systems, Eindhover, the Netherlands) using the following settings: 120 kV, 300 mA, and 12-mm slice thickness. Five scans were conducted while the subject remained in a recumbent position, as described previously by Chowdbury *et al.* (20). Images from the computed tomography scanner were transferred to a Philips Stand Alone Viewing System (SAVS) analyzing unit. Total abdominal visceral fat volume was then determined (20). Sagittal diameter was measured at the L4–L5 level.

TBN was measured by *in vivo* neutron activation as previously described (21, 22). The measurement error was approximately ±4% (21, 22).

BMR was determined by indirect calorimetry, using a computerized, ventilated, open hood system (Deltatrac, Datex, Helsinki, Finland). The measurements were made in the morning after an overnight fast and after at least 15 min of rest in the supine position. Respiratory data were collected each minute for 30 min. The calculations used were described by Ferrannini (23). The overall SE of a single determination was 4%, as calculated from 2 determinations on consecutive days in 20 healthy subjects. The technical error of the system, verified at specified intervals by calibrated ethanol combustion experiments, was approximately 3%.

Daily caloric intake was evaluated using standardized, self-administered dietary questionnaires, as described by Lindroos *et al.* (24).

OGTTs using 75 g glucose dissolved in water were performed after an overnight fast. Venous blood samples were drawn for glucose and insulin determinations at 0, 30, 60, 90, and 120 min.

Biochemical assays

Serum GH was determined by a polyclonal antibody-based immunoradiometric assay (Pharmacia, Uppsala, Sweden). The detection limit of the assay was 0.3 mIU/L, and the total CV was 5.3% for a serum pool with 19.8 mIU/L. Serum IGF-I was measured by RIA after acid-ethanol extraction (Endocrine Sciences, Calabasas Hills, CA). At mean serum IGF-I concentrations of 26, 299, and 330 μg/L, the within-assay CVs were 20%, 5.9%, and 5.6%, respectively. At mean serum IGF-I concentrations of 24, 279, and 307 μg/L, the between-assay CVs were 28%, 7.7%, and 8.2%, respectively. Serum IGFBP-3 was measured by RIA (Endocrine Sciences). The intraassay CV was 5.1%, and the interassay CV was 7.8% at a mean serum IGFBP-3 concentration of 2.7 mg/L. Serum PRL was measured by RIA (Diagnostic Products Corp., Los Angeles, CA), with a total CV of 6%. Serum cortisol was determined by RIA (Farmos Diagnostica, Turku, Finland), with a total CV of 6%. Urinary free cortisol was measured by RIA after extraction and chromatography (Endocrine Sciences). Urinary 17-hydroxycorticosteroids were measured as Porter-Silber chromogens after enzymatic hydrolysis and purification (Endocrine Sciences). Serum insulin was determined by RIA (Phadebas, Pharmacia, Sweden), and blood glucose was measured using the glucose-6-phosphate dehydrogenase method (Kebo Laboratory, Stockholm, Sweden). Plasma FFA and glycerol were measured using enzymatic methods (NEFAC, Wako, Neuss, Germany; and Boehringer Mannheim, Mannheim, Germany, respectively). Plasma β-hydroxybutyrate was determined enzymatically as described by Li *et al.* (25).

Statistical analysis

The descriptive statistical results are presented as the mean and SEM. Where appropriate, a logarithmic transformation was performed before statistical analysis. Logarithmically transformed data (peak GH, GH AUC, serum IGF-I, and IGFBP-3) are presented as the geometric mean ± SEM. Unpaired *t* tests were used to assess between-group differences. Differences in baseline were accounted for by analyzing the percent change from baseline for all variables except the hormone profiles, for which the absolute values were analyzed. Within-group differences were analyzed using paired *t* tests. Correlations were calculated using Pearson's linear regression coefficient. A two-tailed $P < 0.05$ was considered significant.

Results

The two groups were matched with regard to mean age, weight, height, BMI, and waist/hip ratio (Table 1).

Compliance and side-effects

Compliance data were available for all 24 subjects and indicated greater than 99% compliance. MK-677 treatment was generally well tolerated. Five subjects had clinical and/or laboratory adverse experiences with MK-677 administration that the investigator considered drug related; all were of mild intensity, and none required medical treatment. One subject in the treatment group had transient gastritis at 4 weeks and transient mild sweating at 6 weeks, and 1 subject had a glucose concentration of 10 mmol/L after 6 weeks of MK-677 treatment, which spontaneously decreased 1 week later. Three subjects in the treatment group had asymptomatic, transient increases in ALT and/or AST.

GH-IGF-I axis (Table 2 and Fig. 1)

Peak serum GH and serum GH AUC after MK-677 administration were significantly increased compared with those after placebo treatment throughout the study period (Table 2). In the treatment group, peak serum GH and serum GH AUC were significantly reduced after 2 weeks of treatment compared to the results after the first dose of MK-677 ($P < 0.01$ and $P < 0.001$, respectively), but there were no significant differences between 2 and 8 weeks. Serum IGF-I and IGFBP-3 were both significantly increased throughout the study period ($P < 0.001$ and $P \leq 0.001$, respectively; Fig. 1). There was a significant positive correlation between baseline serum IGF-I and IGFBP-3 ($r = 0.57$, $P < 0.01$), and a marginally significant positive correlation ($r = 0.56$, $P < 0.06$) was found in the MK-677 treatment group between the increases in serum IGF-I and IGFBP-3 at 8 weeks of treatment.

TABLE 1. Baseline characteristics of the cohort or 24 obese males treated with MK-677 25 mg or placebo daily for 8 weeks

Subject characteristics	MK-677	Placebo
Age (yr)	36.8 (2.7)	39.0 (2.4)
BW (kg)	99.3 (2.3)	103.4 (2.1)
Ht (cm)	176.0 (2.1)	178.6 (1.4)
BMI (kg/m^2)	32.0 (0.4)	32.5 (0.5)
Waist/hip ratio	1.04 (0.02)	1.00 (0.01)
Serum IGF-I (μg/L)	150.3 (12.1)	156.4 (8.2)
Serum IGFBP-3 (mg/L)	2.8 (0.1)	2.8 (0.1)

All values are presented as the mean (±SEM). No statistically significant differences were found between the MK-677 group and the placebo group using unpaired *t* tests.

PRL and cortisol (Table 2)

Peak serum PRL and serum PRL AUC were significantly higher in the treatment group than in the placebo group after the first administration of MK-677 ($P < 0.001$). These increases after the initial dose of MK-677 were significantly greater than the increases after multiple doses of MK-677. After 2 and 8 weeks of treatment, only PRL AUC remained increased *vs.* that after placebo administration ($P = 0.01$).

Peak serum cortisol and serum cortisol AUCs were significantly increased compared with those after placebo treatment after the first administration of MK-677 ($P < 0.001$). After 2 and 8 weeks of treatment, there were no significant differences compared with placebo values (Table 2). No significant effects were elicited by MK-677 on urinary free cortisol and 17-hydroxycorticosteroids (Table 2).

TABLE 2. Serum peak and AUC values of GH, PRL, and cortisol and 24-h urine collections of free cortisol and 17-hydroxycorticosteroids (17-OHCS) during 2 months of treatment with MK-677 (25 mg) or placebo daily in obese males

Variable	Initiation of treatment	2 weeks	8 weeks	Reference range
Peak GH (mIU/L)				
MK-677	65.4 (13.1)[a]	17.0 (3.3)[a]	14.3 (3.9)[a]	No reference range exists
Placebo	2.0 (0.8)	1.5 (0.8)	0.9 (0.4)	
GH AUC (mIU·h/L)				
MK-677	144.4 (32.1)[a]	33.1 (5.0)[a]	29.0 (7.5)[a]	No reference range exists
Placebo	7.1 (2.2)	5.8 (2.3)	3.8 (1.0)	
Peak PRL (mIU/L)				
MK-677	737 (59)[a]	358 (24)	372 (35)	<300
Placebo	224 (29)	290 (51)	282 (50)	
PRL AUC (mIU·h/L)				
MK-677	3565 (259)[a]	2135 (157)[a]	2015 (196)[b]	No reference range exists
Placebo	1097 (143)	1261 (170)	1252 (162)	
Peak cortisol (nmol/L)				
MK-677	634 (34)[a]	329 (21)	357 (30)	200–800
Placebo	313 (20)	329 (28)	296 (15)	
Cortisol AUC (nmol·h/L)				
MK-677	3439 (235)[a]	1977 (109)	2129 (129)	No reference range exists
Placebo	1901 (108)	1971 (116)	1806 (90)	
Urinary free cortisol/creatinine ratio (10^{-6})				
MK-677	26.2 (3.0)	17.7 (2.0)	21.4 (3.3)	No reference range exists
Placebo	18.5 (2.6)	14.9 (2.2)	15.4 (1.3)	
17-OHCS/creatinine ratio (10^{-3})				
MK-677	6.0 (0.5)	6.2 (0.7)	6.8 (0.6)	No reference range exists
Placebo	3.8 (0.3)	3.6 (0.4)	4.1 (0.4)	

The hormonal profiles were performed after tablet intake, whereas the urine collections were made before tablet intake. All values are presented as the mean (SEM). *P* values are based on a between-group analysis of the absolute values for the hormonal profiles. For the urine collection values, a between-group analysis of the percent change from baseline was performed. Note that GH peak and AUC values are presented as the geometric mean.

[a] $P < 0.001$.

[b] $P \leq 0.01$.

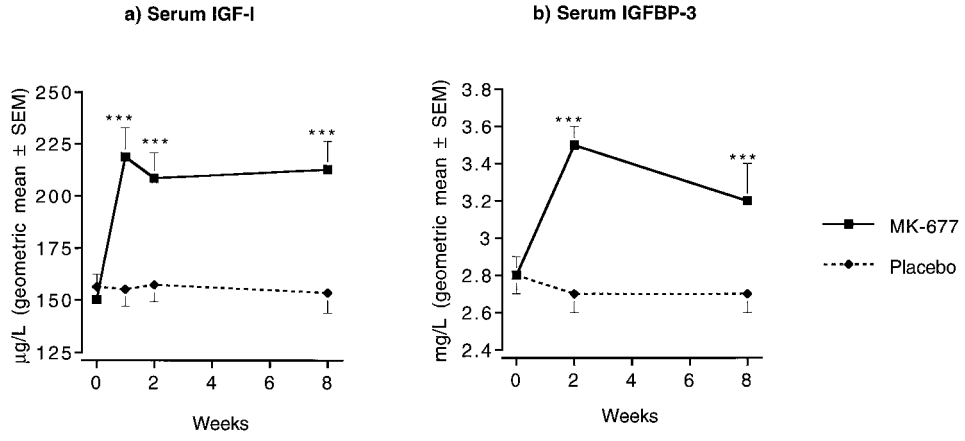

FIG. 1. Serum concentrations of IGF-I and IGFBP-3 during 2-month treatment with MK-677 (25 mg) or placebo daily in obese males. The *vertical bars* indicate the SE for the mean values shown. *P* values are based on a between-group analysis of percent change from baseline. ***, $P \leq 0.001$.

TABLE 3. Body weight, sagittal diameter, abdominal visceral fat volume, total body nitrogen (TBN), total body water (TBW), total body potassium (TBK), blood pressure, and heart rate during 2 months of treatment with MK-677 (25 mg) or placebo daily in obese males

Variable	Baseline	2 weeks	8 weeks
BW (kg)			
MK-677	99.3 (2.3)	100.9 (2.3)[a]	102.0 (2.4)[b]
Placebo	103.4 (2.1)	102.8 (1.9)	103.1 (1.8)
Sagittal diameter (cm)			
MK-677	26.2 (0.4)	ND	26.2 (0.7)
Placebo	24.8 (0.4)	ND	25.0 (0.4)
Visceral fat vol (L)			
MK-677	5.54 (0.58)	ND	5.32 (0.59)
Placebo	4.79 (0.40)	ND	4.75 (0.39)
TBN (kg)			
MK-677	1.85 (0.06)	1.91 (0.05)	1.92 (0.06)
Placebo	2.02 (0.06)	1.96 (0.08)	2.07 (0.06)
TBW (kg)			
MK-677	50.6 (1.9)	54.6 (1.2)	55.2 (1.6)
Placebo	53.4 (1.0)	56.0 (1.7)	55.8 (1.5)
TBK (mmol)			
MK-677	4390 (134)	4493 (138)[b]	4539 (129)[c]
Placebo	4778 (122)	4694 (141)	4739 (127)
Systolic blood pressure (mm Hg)			
MK-677	131.2 (3.2)	129.1 (1.9)	134.1 (4.7)
Placebo	124.4 (3.1)	126.5 (3.4)	134.2 (3.4)
Diastolic blood pressure (mm Hg)			
MK-677	78.8 (3.4)	79.0 (2.5)	83.7 (3.2)[c]
Placebo	80.6 (2.1)	78.8 (2.7)	79.0 (2.7)
Heart rate (beats/min)			
MK-677	58.6 (2.7)	62.5 (3.6)	61.3 (3.0)[c]
Placebo	60.0 (2.5)	62.5 (2.3)	55.9 (1.8)

Values are presented as the mean (±SEM). *P* values are based on a between-group analysis of the percent change from baseline. ND, Not determined.

[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.

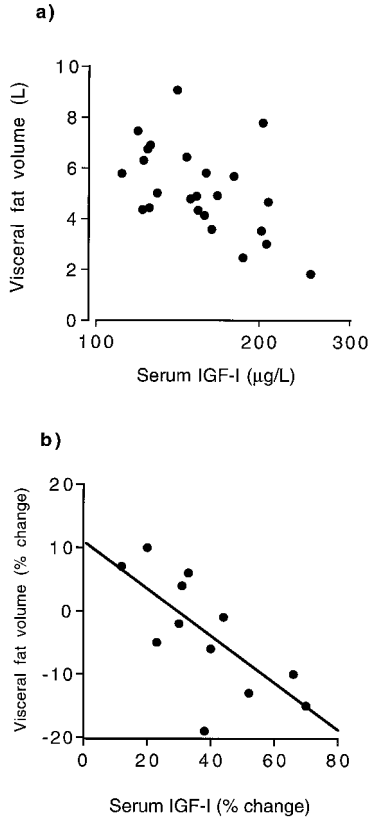

FIG. 2. Correlations a) in the total study population at baseline, between serum IGF-I and visceral fat volume ($r = -0.5$; $P < 0.01$); and b) in the MK-677 treatment group, between the percent change in serum IGF-I and the percent change in visceral fat volume at the end of the study period ($r = -0.7$; $P < 0.01$). Note the logarithmic scale for the *x*-axis in a.

Body composition, blood pressure, and BMR (Table 3 and Figs. 2–4)

The treatment group showed a weight gain of 2.7 kg at 8 weeks of MK-677 treatment ($P < 0.01$ *vs.* placebo; Table 3). At the poststudy visit 1 week after the end of treatment, BW was still significantly increased compared to baseline values in the treatment group (1.8 kg), although this did not achieve statistical significance compared with the change in BW in the placebo group. Sagittal diameter, visceral fat volume, TBN, and TBW did not change, whereas TBK was increased in response to treatment (Table 3). Systolic blood pressure was not changed, whereas diastolic blood pressure and heart rate were increased by MK-677 at 8 weeks ($P < 0.05$ *vs.* placebo; Table 3).

At baseline, visceral fat volume correlated negatively with serum IGF-I ($r = -0.5$; $P < 0.01$; Fig. 2a), and in the MK-677 treatment group, a strong negative correlation was found between the percent change in visceral fat volume and the percent change in serum IGF-I at the end of the study period ($r = -0.7$; $P < 0.01$; Fig. 2b).

FFM increased about 3 kg in the treatment group compared with that in the placebo group ($P < 0.01$; Fig. 3a). In contrast, total body fat, as assessed from DEXA measurements, was not changed by MK-677 treatment (Fig. 3b). BCM derived from the four-compartment model increased about 1 kg ($P < 0.05$) in the treatment group (Fig. 3c). No significant effects were elicited by MK-677 treatment on total body fat when derived from the four-compartment model (Fig 3d).

BMR was increased by MK-677 at 2 weeks of treatment ($P = 0.01$ compared with placebo) even after correction for the increase in FFM ($P < 0.05$; Fig. 4).

Glucose homeostasis (Table 4)

No significant effects were seen on fasting blood glucose, serum insulin, or insulin AUC after OGTT. However, the 2-h concentration of blood glucose during the OGTT was increased at both 2 and 8 weeks of treatment, and blood glucose AUC and the 2-h serum insulin during OGTT were increased after 2 weeks, but not after 8 weeks, of treatment (Table 4).

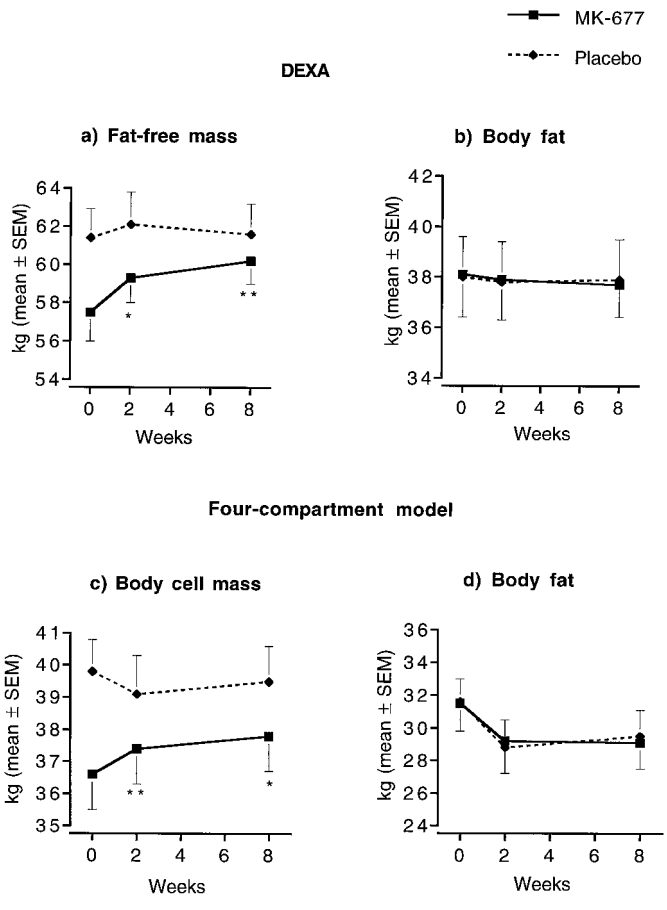

FIG. 3. Body composition during 2-month treatment with MK-677 (25 mg) or placebo daily in obese subjects. a and b show FFM and body fat, respectively, as assessed by DEXA. c and d show body cell mass and body fat, respectively, as calculated using the four-compartment model. The *vertical bars* indicate the SE for the mean values shown. *P* values are based on a between-group analysis of the percent change from baseline. *, $P < 0.05$; **, $P < 0.01$.

Daily caloric intake and plasma concentrations of FFA

Total daily caloric intake, as assessed using dietary questionnaires, remained unchanged during the study (data not shown). Daily intakes of fat, protein, and carbohydrates were also not changed by MK-677 (data not shown). Fasting concentrations of FFA, glycerol, and β-hydroxybutyrate were not changed by MK-677 compared to baseline values or compared to placebo values (data not shown).

Discussion

We have shown that 2-month treatment of healthy obese males with the oral GH secretagogue MK-677 produced a significant GH response throughout the study period, capable of increasing serum IGF-I and IGFBP-3 and FFM. BMR was increased at 2 weeks, but not at 8 weeks. Body fat was not significantly changed. Diastolic blood pressure and heart rate were increased at 8 weeks. The effects on cortisol secretion were transient, whereas a minor increase in PRL levels was found throughout the study period. Basal values of fasting blood glucose and insulin were unchanged, but the OGTT showed an impairment of glucose homeostasis at 2 weeks and, with some attenuation, at 8 weeks of treatment.

Previously, short term administration of GHRP-6 (26), hexarelin (5), and nonpeptide substance L-692,429 (27) as well as 2 weeks of MK-677 treatment (8) have been found to increase GH secretion. In the present study, GH levels were increased by MK-677 treatment throughout the 8-week study period, even though the GH response to MK-677 was lower at 2 and 8 weeks compared to the initial response. It is possible that the negative feedback that IGF-I exerts on GH secretion (28) could explain this dampening in GH response to MK-677 administration. Such a mechanism would also be supported by the constant level of increased serum IGF-I found throughout the study. A homologous desensitization after infusion of GHRP has previously been reported (29, 30). It is unknown whether desensitization contributed to the decrease in the GH response between initiation and 2 weeks of treatment in this study. In any case, the response to oral MK-677 was not abolished even after 8 weeks of treatment, which may also indicate that MK-677 does not deplete the pituitary reserve of GH, possibly because of a stimulatory effect on GH synthesis.

Previously, single dose administration of GH secretagogues (5, 26, 27) and 2-week treatment with MK-677 (8) produced small increases in PRL levels. In the present study, a similar initial increase in PRL was found, but at 2 and 8 weeks, only the PRL AUC, not peak PRL, remained increased. These findings indicate that there is a minor effect on PRL secretion that persists after 8 weeks of treatment, possibly the result of MK-677 affecting pituitary somatomammotrops (31, 32).

The present study confirms that the stimulatory effect of GHRP-related compounds on cortisol secretion is transient. Increased cortisol levels have been noted after single dose administration of GHRPs (26, 27), but not after 1 (7) or 2 (8)

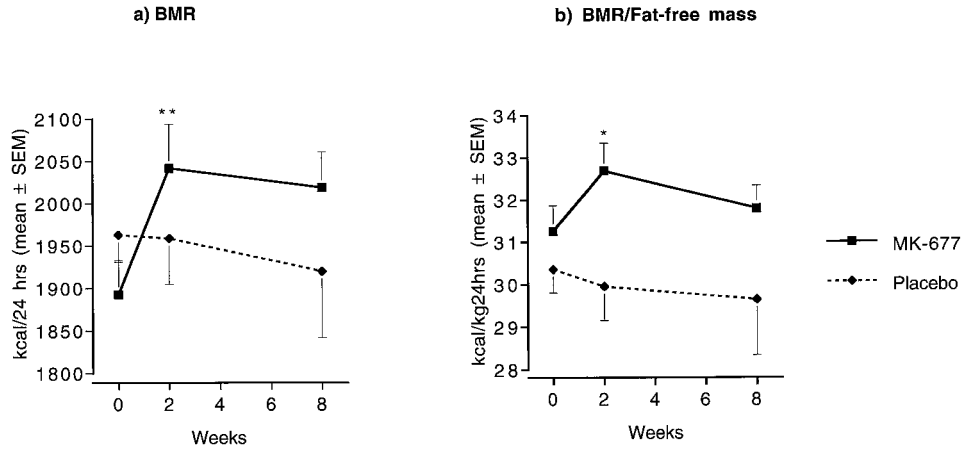

FIG. 4. BMR (a) and BMR corrected for the increase in FFM (b) during 2-month treatment with MK-677 (25 mg) or placebo daily in 24 obese males. The *vertical bars* indicate the SE for the mean values shown. *P* values are based on a between-group analysis of the percent change from baseline. *, $P < 0.05$; ** $P = 0.01$.

TABLE 4. Effects of 2 months of treatment with MK-677 (25 mg) or placebo daily in obese males on oral glucose tolerance test

Variable	Baseline	2 weeks	8 weeks
Basal blood glucose (mmol/L)			
MK-677	4.2 (0.1)	4.3 (0.2)	4.3 (0.2)
Placebo	4.3 (0.2)	4.2 (0.1)	4.3 (0.1)
Blood glucose 120 (mmol/L)			
MK-677	5.2 (0.3)	7.8 (0.7)[a]	7.0 (0.7)[b]
Placebo	6.4 (0.5)	5.4 (0.6)	6.2 (0.6)
Blood glucose AUC (mmol·h/L)			
MK-677	13.3 (0.8)	15.2 (1.2)[c]	14.9 (1.2)
Placebo	13.9 (0.7)	13.0 (0.8)	13.9 (0.9)
Basal insulin (mIU/L)			
MK-677	14.2 (2.0)	19.4 (2.9)	16.4 (2.5)
Placebo	11.6 (1.1)	12.9 (1.3)	12.2 (1.1)
Insulin 120 (mIU/L)			
MK-677	54.4 (10.2)	92.6 (12.6)[b]	77.0 (14.3)
Placebo	59.5 (7.7)	45.6 (7.4)	68.2 (12.0)
Insulin AUC (mIU·h/L)			
MK-677	126 (21)	155 (14)	141 (17)
Placebo	114 (12)	125 (14)	136 (16)

All values are presented as the mean (±SEM). *P* values are based on a between-group analysis of percent change from baseline. Note that serum levels of insulin are given. Blood glucose 120 and insulin 120 are the respective values 2 h after oral administration of a 75-g glucose solution. Blood glucose AUC and insulin AUC also refer to the OGTT.

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

weeks of MK-677 treatment. In the present study, an increase in serum cortisol was demonstrated after the first MK-677 administration, but no increase was found at 2 and 8 weeks. Moreover, urinary cortisol was unchanged throughout the study. These results are clinically important with regard to the safety of MK-677, as visceral obesity is accompanied by relative hypercortisolism (33).

An anabolic effect was seen on FFM in the treatment group, with a maximum increase of 3 kg measured by DEXA scan, corresponding to the increase in body weight of this cohort. This was expected from experience with GH treatment of GH-deficient adults (15) and elderly subjects (34, 35). The increase in FFM is not explained by an increase in body water, since TBW estimations did not show any significant difference between the groups. However, it is possible that the decrease in body weight in the treatment group from the study end to the poststudy visit (0.9 kg) at least in part can be explained by loss of water. It is also possible that different estimations of body water can explain part of the difference (1.5 kg) between DEXA and the four-compartment model in estimating the increases in FFM and body cell mass, respectively.

Body fat was unchanged, which was unexpected based on the results of previous studies of GH treatment of GH-deficient adults (15) and obese males (18). GH induces lipolysis with an increase in FFA levels (36), but no increase in FFA levels or glycerol was observed in this study to support increased lipolysis with MK-677 treatment. Previously, continuous infusion of GH has been shown to produce a greater reduction in total body fat than sc GH injections in a study of GH-deficient adults (37). Therefore, it is possible that the GH secretory pattern produced by MK-677 is less effective in inducing lipolysis and body fat reduction.

A strong negative correlation was found between the changes in serum IGF-I and visceral fat in the treatment group. Correlation analysis showed that a greater than 30–35% increase in serum IGF-I was needed to reduce visceral fat mass. This suggests that a higher dose of MK-677, resulting in enhanced levels of serum GH and IGF-I, may cause a reduction in visceral fat. In obese males, GH treatment reduces the visceral fat mass over a 9-month period (18), and it is possible that a more prolonged MK-677 treatment period could cause a decrease in visceral fat.

GHRH stimulates food intake in rats (38), and it has recently been found that the newly developed GHRP KP-102 stimulates feeding in rats (39). GHRP-6 injection activates neuropeptide Y cells in the rat arcuate nucleus (40), which could indicate a positive effect on appetite (41). It is difficult to explain our present findings of increases in body weight, FFM, and BMR in combination with unchanged body fat without a concomitant increase in food intake. The dietary questionnaires used, however, did not indicate any such effect, but they may not be sufficiently sensitive.

The increase in diastolic blood pressure found after treatment with a GH secretagogue in the present study is unexpected, as GH treatment has been shown to reduce peripheral vascular resistance (42). However, the current study was

conducted in a relatively small number of subjects, and the effect of MK-677 on blood pressure should be confirmed in a larger study. It cannot be excluded that longer term treatment with MK-677 could affect blood pressure in a more favorable way if a reduction of visceral fat is achieved.

Past studies have shown an increase in BMR during GH treatment of GH-deficient adults (15). We observed an increase in BMR at 2 weeks of treatment even when corrected for the increase in FFM. However, there was no significant increase in BMR at study end. This could be explained by the lower GH response to MK-677 at 2 and 8 weeks of treatment compared to the response at the first administration. In a 9-month study of GH treatment of obese males, a similar decrease in BMR responsiveness was observed (43). Therefore, it is possible that a down-regulation of the initial increase in BMR occurs during long term GH or MK-677 treatment of obese subjects, an effect not seen with GH treatment in adult GH deficiency.

Fasting levels of glucose and insulin were unchanged in the present study, but the OGTT demonstrated an impaired glucose homeostasis after 2 and 8 weeks of MK-677 treatment. The tendency to an improvement from 2 to 8 weeks of treatment is probably not explainable by changes in GH secretion, because the GH response to MK-677 was similar at 2 and 8 weeks of treatment. A similar pattern has been observed in a study of GH deficiency, in which an initial deterioration of insulin resistance was restored to baseline values after 6 months of GH treatment (44). Skeletal muscle is the major site of glucose disposal (45), IGF-I stimulates glucose transport into skeletal muscle *in vitro* (46), and GH treatment of hypophysectomized rats increases the proportion of insulin-sensitive type I muscle fibers (47). Therefore, the increase in FFM found in the present study or any related changes in muscle metabolism or morphology that may have occurred might help to explain the improvement in glucose homeostasis between 2 and 8 weeks of treatment.

We concluded that 2-month treatment with the oral GH secretagogue MK-677 was generally well tolerated in healthy obese males. MK-677 treatment elicited a significant GH response, followed by increases in serum IGF-I and IGFBP-3, whereas effects on cortisol secretion were transient. Changes in body composition and energy expenditure were of an anabolic nature, with a sustained increase in FFM and a transient increase in BMR. Further studies are needed to evaluate whether body fat can be affected by a higher dose of or more prolonged treatment with MK-677.

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