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Acute effect of L-796568, a novel β_3-adrenergic receptor agonist, on energy expenditure in obese men

Objective: **Our objective was to investigate the thermogenic efficacy of single oral doses of the novel β_3-adrenergic receptor agonist L-796568 [(*R*)-*N*-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]-phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans.**
Methods: **Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, and blood pressure were measured at baseline and during the 4-hour period after administration.**
Results: **Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concentrations. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found.**
Conclusions: **Single-dose administration of 1000 mg of the novel β_3-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of β_3-adrenergic receptor agonists in humans without significant evidence for β_2-adrenergic receptor involvement. (Clin Pharmacol Ther 2002;71:272-9.)**

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The prevalence of obesity is increasing in many countries all over the world.[1] The health risks associated with obesity, such as type 2 diabetes, hypertension, coronary artery disease, gallbladder disease, and arthritis, form a serious public health problem for the years to come if no effective strategies to prevent and treat it are developed.[1] Comprehensive weight management programs, including a reduction of energy intake through an energy-restricted diet and an increase in energy expenditure through increased levels of physical activity in combination with a behavior modification program, have been developed. In many cases such programs lead to considerable short-term weight loss. However, long-term maintenance of the reduced weight often fails to occur. Current pharmacologic approaches to the treatment of obesity focus on reinforcement of these programs and they have been shown to improve long-term weight maintenance success.[2,3] The pharmacologic agents currently available for the management of obesity (orlistat and sibutramine) are effective through decreased nutrient absorption and appetite suppression, respectively. The approach of increased energy expenditure has been less well explored.

The peripheral sympathetic nervous system plays an important role in the regulation of energy expenditure.[4] Stimulation of sympathetic activity results in an

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increase of resting energy expenditure in humans, which is mediated by β-adrenergic receptors.[5] Both β_1- and β_2-adrenergic receptors lead to thermogenesis on stimulation.[6,7] Obesity appears to be associated with a blunted response to sympathetic stimulation that is probably caused mainly by β_2-adrenergic receptor malfunction.[7,8] However, treatment of obesity with the classic nonselective or β_2-selective agonists is not possible, because of the many unacceptable side effects of these drugs.

The discovery of a third β-adrenergic receptor subtype in humans, which in animal models has been shown to stimulate lipolysis in brown and white adipose tissue and lead to thermogenesis in brown adipocytes, has opened new possibilities for treatment of human obesity by selective β_3-adrenergic receptor stimulation. In humans the presence of β_3-adrenergic receptor mRNA has been shown in brown and white adipose tissue and the gall bladder, colon, stomach, small intestine, prostate gland, and heart but not in skeletal muscle or the liver, lung, kidney, thyroid, or lymphocytes.[9-12] One study has more recently provided evidence for the presence of the β_3-adrenergic receptor protein in human gastrocnemius muscle and the right atrium.[13] Although most of the currently available β_3-adrenergic receptor agonists are only weak partial agonists of the human β_3-adrenergic receptor and usually not very selective, a functional role for the β_3-receptor in adipocyte lipolysis has been suggested by studies in isolated human omental and subcutaneous fat cells[14,15] and in vivo in microdialysis studies with such agonists.[16-18] Because these drugs are not available for intravenous or oral administration in humans, their thermogenic efficacy is unknown. Indirect studies that used combinations of different sympathomimetics and blockers to dissect out the contribution of the β_3-receptor to human thermogenesis have yielded inconsistent results.[19-22]

L-796568 [(*R*)-*N*-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] is a newly developed β_3-adrenergic receptor agonist with high affinity (concentration that produces 50% of the maximum possible response [EC_{50}], 3.6 ± 2.2 nmol/L) and efficacy (94% ± 10% of maximal cyclic adenosine monophosphate accumulation by isoproterenol [INN, isoprenaline]) for the cloned human β_3-adrenergic receptor transfected in Chinese hamster ovary cells.[23] L-796568 is a weak partial agonist at the human β_1-receptor and β_2-receptor, with EC_{50} values of 4.8 and 2.4 μmol/L, respectively, and efficacy of 25% of isoproterenol activity.[23] Phase I human studies showed that L-796568 was well tolerated in doses up to 1500 mg. Administration of L-796568 therefore allows us to study, for the first time, the effects of a specific human β_3-adrenergic receptor agonist on in vivo lipolysis and thermogenesis in humans. This study was designed to investigate the thermogenic efficacy of single oral doses of 250 and 1000 mg L-796568 in obese men.

METHODS

Subjects. Twelve healthy, nonsmoking male volunteers between 18 and 45 years old (mean ± SD, 34.4 ± 5.8 years) were included in the study. All of the subjects had maintained a stable weight (±4 kg) and had a body mass index between 28 and 34 kg/m^2 (mean ± SD, 30.7 ± 2.1 kg/m^2). None of the volunteers had participated in an organized weight loss program during the previous 3 months. All had normal blood pressure measurements (90 to 150 mm Hg systolic and 50 to 95 mm Hg diastolic blood pressure) and resting heart rates (<90 beats/min). Habitual heavy consumers of coffee (>4 cups per day) were excluded. Current or anticipated use of any prescription or nonprescription drugs was not allowed.

Experimental protocol. The study was a 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo in a balanced fashion. All drug supplies were provided as a "double dummy," so investigators and subjects were blinded to the treatment regimen. A washout period of 6 to 8 days between study periods allowed plasma levels of L-796568 to dissipate. Prestudy procedures included a medical history and a physical examination that included vital signs, determination of body mass index, measurement of thyroid function parameters, a safety laboratory panel for blood and urine, and a 12-lead electrocardiogram (ECG).

On the test days the subjects came to the laboratory in the morning after an overnight fast. Urine was collected for the safety panel. Subjects rested in a semirecumbent position, and a catheter was inserted into a forearm vein of each subject for blood sampling (100 minutes before dosing). Continuous heart rate and blood pressure monitoring was started, and heart rate and blood pressure were registered at 65 and 20 minutes before dosing. At 10 minutes before dosing, blood samples were taken for plasma catecholamine concentration (heparinized tubes that contained glutathione), plasma free fatty acids and glycerol concentration (ethylenediaminetetra-acetic acid tubes), plasma potassium (lithium-heparin tubes), and serum leptin concentration (serum tubes), as well as for the safety laboratory panel.

At 0 minutes before dosing, another blood sample was obtained for free fatty acids and glycerol concentration and for serum leptin concentration. After all blood was drawn, the catheter was flushed with saline solution. Ear temperature was determined at 60 minutes before dosing. Energy expenditure was measured for 30 minutes, from 60 minutes before dosing to 30 minutes before dosing, as a predose baseline.

After the baseline measurements, each subject was given a single oral dose of the study drug (250 mg or 1000 mg L-796568 or placebo) with 240 ml water and continued to fast and rest in a semisupine position for 4 hours. During this period, energy expenditure was measured during the last 20 minutes of each half hour. The first 10 minutes of each half hour was used for either blood sampling or calibration or both. Blood pressure and heart rate continued to be monitored and were recorded every 30 minutes. Blood samples for potassium, free fatty acids, and glycerol were obtained at 1, 2, 3, and 4 hours after dosing. Blood samples were obtained 1.5 and 4 hours after dosing for plasma catecholamines and 4 hours after dosing for leptin. The catheter was flushed with saline solution after each blood sample was drawn. Four hours after dosing, ear temperature was measured and a 12-lead ECG was obtained.

Methods. Energy expenditure was determined by indirect calorimetry with use of a ventilated hood system. Flow through the hood was set at approximately 50 L/min and was measured with a dry gas meter (Maastricht: Schlumberger, Dordrecht, The Netherlands; Copenhagen: Oxycon-beta, Mijnhardt, The Netherlands). $\dot{V}O_2$ and $\dot{V}CO_2$ were determined every 15 seconds from flow through the hood and the difference in oxygen (Maastricht: paramagnetic oxygen analyzer, Servomex, Crowborough, United Kingdom; Copenhagen: Oxycon-beta) and carbon dioxide (Maastricht: paramagnetic CO_2 analyzer, Servomex; Copenhagen: Oxycon-beta) concentrations between ingoing and outgoing air. Identical calibration procedures were used in the two centers. Respiratory quotient was calculated as $\dot{V}CO_2/\dot{V}O_2$. Energy expenditure was calculated from $\dot{V}O_2$ and $\dot{V}CO_2$ with the abbreviated Weir formula.[24]

Blood pressure and heart rate were measured with a semiautomated device (Maastricht: Omron 705 CP, Hamburg, Germany; Copenhagen: digital blood pressure meter model UA-743, A & D Company, Tokyo, Japan). Heart rate monitoring was performed by means of a 3-lead ECG monitor (Maastricht: Cardiolife, Nikon-Kohden, Tokyo, Japan; Copenhagen: Diascope 2, model 211, Simonsen & Weel, Copenhagen, Denmark). The 12-lead ECG was registered by means of a Cardiette Daedalus View H, H&C Medical Devices, Cavareno, Italy (Maastricht), or a Microsmart MC, Marquette Hellige, Freiburg, Germany (Copenhagen).

Analytic methods. Blood for serum leptin was allowed to clot at least 30 minutes and was then centrifuged for 15 minutes at 1200*g* at room temperature. All other blood samples were centrifuged immediately at 4°C for 15 minutes at 1200*g* except for the sample for potassium, which was centrifuged at room temperature. Plasma and serum were stored at –80°C until analysis.

Plasma free fatty acids,[25] glycerol,[26] potassium (direct potentiometry with an ion-selective electrode), and serum leptin[27] were analyzed at the Department of Clinical Chemistry, Academic Hospital of the Free University of Brussels (Brussels, Belgium). Plasma catecholamine concentrations (norepinephrine and epinephrine) were analyzed at the Department of Human Biology in Maastricht by HPLC with electrochemical detection by use of a kit from Recipe (München, Germany).[28]

Data analysis. Data are presented as mean values ± SD, unless stated otherwise. For all variables, mean values at baseline (ie, predose for each treatment period) and at 4 hours after dosing were calculated. Within-treatment changes from baseline to 4 hours after dosing were computed by subtracting the baseline value from the 4-hour postdose value [Δ4-0 h]). In addition, mean energy expenditure during the 4-hour postdose period (mean 0-4 h) and 1-hour peak values were calculated for energy expenditure (for each treatment the two 20-minute measurements within each hour were averaged and the highest 1-hour mean value was chosen as the 1-hour peak value). The 3 treatments were compared by ANOVA for repeated measures (baseline values, 4-hour postdose values, and changes over the 4-hour postdose period [Δ4-0 h]). In case of a significant overall ANOVA outcome ($P < .050$), post hoc comparisons between the 250- and 1000-mg doses of L-796568 and placebo were performed by paired *t* tests. Within-treatment differences between the 4-hour postdose and baseline measurements were analyzed by paired *t* tests. A *P* value <.050 was considered to be statistically significant.

RESULTS

L-796568 was generally well tolerated in this study. Side effects were reported by 7 subjects, were of mild to moderate intensity, and had disappeared within 24 hours. No tremor was reported. No significant changes in safety laboratory parameters or urine composition were found in any subjects during the course of the study, except in 1 subject in whom low total cholesterol was found that appeared to be unrelated to the drug. At baseline there were no statistically significant differences for any of the variables among conditions.

Table I. Values of all variables (mean ± SD) at baseline (0 h) and at 4 hours after dosing (4 h) and the change during the 4-hour postdose period (Δ4-0 h)

Variable and treatment	*0 h*	*4 h*	*Δ4-0 h*
Energy expenditure (kJ/min)			
Placebo	6.05 ± 0.55	6.14 ± 0.59	0.09 ± 0.36
250 mg	6.11 ± 0.53	6.16 ± 0.48	0.06 ± 0.21
1000 mg	5.97 ± 0.58	6.43 ± 0.52**	0.46 ± 0.31**
ANOVA	*P* = .38	*P* < .050	*P* < .001
Ear temperature			
Placebo	36.6°C ± 0.5°C	36.7°C ± 0.7°C	0.13°C ± 0.40°C
250 mg	36.5°C ± 0.4°C	36.7°C ± 0.6°C	0.15°C ± 0.48°C
1000 mg	36.4°C ± 0.5°C	36.8°C ± 0.5°C	0.33°C ± 0.22°C
ANOVA	*P* = .35	*P* = .80	*P* = .19
Plasma free fatty acids (mmol/L)			
Placebo	0.341 ± 0.115	0.542 ± 0.144	0.183 ± 0.138
250 mg	0.303 ± 0.123	0.585 ± 0.115	0.283 ± 0.166
1000 mg	0.327 ± 0.100	0.780 ± 0.185**	0.444 ± 0.224**
ANOVA	*P* = .63	*P* < .001	*P* < .010
Plasma glycerol (μmol/L)			
Placebo	48.0 ± 17.3	60.8 ± 17.9	11.6 ± 21.4
250 mg	41.1 ± 9.6	63.4 ± 13.8	23.1 ± 14.8*
1000 mg	41.4 ± 10.1	78.7 ± 20.7**	36.3 ± 19.6**
ANOVA	*P* = .20	*P* < .001	*P* < .001
Respiratory quotient			
Placebo	0.803 ± 0.062	0.793 ± 0.034	–0.010 ± 0.035
250 mg	0.834 ± 0.052	0.796 ± 0.027	–0.038 ± 0.034
1000 mg	0.818 ± 0.040	0.783 ± 0.015	–0.035 ± 0.040
ANOVA	*P* = .26	*P* = .39	*P* = .08
Plasma potassium (mmol/L)			
Placebo	4.01 ± 0.24	3.97 ± 0.21	–0.04 ± 0.14
250 mg	4.10 ± 0.28	3.87 ± 0.14	–0.23 ± 0.24
1000 mg	4.18 ± 0.59	3.94 ± 0.14	–0.24 ± 0.55
ANOVA	*P* = .56	*P* = .22	*P* = .29
Heart rate (beats/min)			
Placebo	62.8 ± 11.1	59.4 ± 12.5	–3.5 ± 7.1
250 mg	60.3 ± 8.1	62.0 ± 7.0	1.5 ± 5.7
1000 mg	61.2 ± 8.2	61.4 ± 9.0	–0.2 ± 4.4
ANOVA	*P* = .43	*P* = .62	*P* = .14
Systolic blood pressure (mm Hg)			
Placebo	128.6 ± 6.6	130.1 ± 12.6	1.1 ± 10.0
250 mg	132.4 ± 6.2	135.6 ± 12.2*	3.2 ± 8.6
1000 mg	126.8 ± 9.7	139.1 ± 13.0**	12.2 ± 14.2**
ANOVA	*P* = .16	*P* < .050	*P* < .010
Diastolic blood pressure (mm Hg)			
Placebo	82.9 ± 6.7	85.7 ± 7.6	2.6 ± 5.8
250 mg	85.5 ± 7.1	87.3 ± 10.0	1.8 ± 6.1
1000 mg	81.9 ± 6.8	88.8 ± 10.5	6.8 ± 8.6
ANOVA	*P* = .12	*P* = .29	*P* = .13
Plasma norepinephrine (ng/L)			
Placebo	262 ± 70	271 ± 92	9.0 ± 54.1
250 mg	258 ± 108	278 ± 113	20.5 ± 64.1
1000 mg	289 ± 90	324 ± 129	34.8 ± 114.5
ANOVA	*P* = .29	*P* = .16	*P* = .69
Plasma epinephine (ng/L)			
Placebo	28 ± 14	38 ± 20	9.8 ± 21.0
250 mg	27 ± 21	32 ± 19	4.9 ± 12.3
1000 mg	28 ± 14	30 ± 14	2.2 ± 17.9
ANOVA	*P* = .97	*P* = .21	*P* = .43
Serum leptin (μg/L)			
Placebo	12.6 ± 7.6	11.8 ± 6.7	–0.78 ± 1.61
250 mg	14.0 ± 7.4	12.8 ± 6.6	–1.18 ± 1.17
1000 mg	11.9 ± 6.7	11.0 ± 6.9	–0.87 ± 0.54
ANOVA	*P* = .18	*P* = .10	*P* = .70

ANOVA *P* value refers to overall between-groups ANOVA outcome.
*$P < .05$, **$P < .001$, versus placebo (post hoc paired *t* tests).

Thermogenic effects. The changes in energy expenditure from baseline during the 4-hour postdose period are shown in Fig 1. At 4 hours after dosing, energy expenditure was significantly different among the 3 conditions ($P < .05$, between-treatments overall ANOVA; Table I). Energy expenditure increased significantly from baseline to 4 hours after dosing (by 0.46 ± 0.31 kJ/min, 7.8%) after the 1000-mg dose ($P < .001$, within-treatment paired *t* test). No statistically significant changes were found after the 250-mg dose (0.06 ± 0.21 kJ/min, 1.0%; $P = .35$, within-treatment paired *t* test) or after placebo (0.09 ± 0.36 kJ/min, 1.5%; $P = .41$, within-treatment paired *t* test). The changes differed significantly among the 3 conditions ($P < .001$, between-treatments overall ANOVA; $P < .001$ for 1000 mg versus placebo; $P = .67$ for 250 mg versus placebo; Table I). Comparison of the 1-hour peak energy expenditures or mean energy expenditure during the period from baseline to 4 hours after dosing among the 3 treatments did not yield statistically significant differences ($P = .32$ for 1000 mg versus placebo; $P = .88$ for 250 mg versus placebo; between-treatments overall ANOVA).

Ear temperature values at different time points are shown in Table I. No statistically significant differences were found at any time point, and the 4-hour postdose changes did not differ among treatments ($P = .19$, between-treatments overall ANOVA).

Metabolic effects. The plasma concentrations of free fatty acids and glycerol showed a dose-dependent increase during the 4-hour postdose period (Fig 2), which differed statistically significantly among conditions ($P < .010$ for Δ4-0 h, between-treatments overall ANOVA). The changes after the 250-mg dose (0.283 ± 0.166 mmol/L for Δ4-0 h free fatty acids; 23 ± 15 μmol/L for Δ4-0 h glycerol) and after the 1000-mg dose (0.444 ± 0.224 mmol/L for Δ4-0 h free fatty acids; 36 ± 20 μmol/L for Δ4-0 h glycerol) differed significantly from those after placebo (0.183 ± 0.138 mmol/L for Δ4-0 h free fatty acids; 12 ± 21 μmol/L for Δ4-0 h glycerol) (Δ4-0 h free fatty acids: $P < .010$, between-treatments overall ANOVA; $P = .09$ for 250 mg versus placebo; $P < .005$ for 1000 mg versus placebo; Δ4-0 h glycerol: $P < .001$, between-treatments overall ANOVA; $P < .050$ for 250 mg versus placebo; $P < .005$ for 1000 mg versus placebo; Table I).

The respiratory quotient at 4 hours after dosing did not differ statistically significantly among treatments ($P = .39$, between-treatments overall ANOVA; Table I), although there was a tendency toward a reduction in the respiratory quotient after the 250-mg (–0.038 ± 0.034) and 1000-mg (–0.035 ± 0.040) doses compared with placebo (–0.010 ± 0.035), but the difference among treatments did not reach statistical significance (Δ4-0 h respiratory quotient: $P = .08$, between-treatments overall ANOVA). Plasma potassium concentrations showed no statistically significant changes during any of the treatments (Table I).

Cardiovascular effects. There were no statistically significant differences in heart rate between the 3 treatments at any time point, and the changes during the 4-hour postdose period did not differ significantly. At 4 hours after dosing, there was a statistically significant difference in systolic blood pressure among treatments ($P < .050$, between-treatments overall ANOVA; Table I). The increase in systolic blood pressure during the 4-hour postdose period was 1.5 ± 10.4 mm Hg after placebo, 3.2 ± 8.7 mm Hg after 250 mg L-796568, and 12.2 ± 13.7 mm Hg after 1000 mg L-796568 ($P < .005$, between-treatments ANOVA; $P = .41$ for 250 mg versus placebo; $P < .010$ for 1000 mg versus placebo; Table I). No statistically significant differences in diastolic blood pressure were observed during the study period (Table I).

Hormonal effects. No differences in plasma norepinephrine, epinephrine, or serum leptin concentrations were found among treatments during the 4-hour study period (Table I).

DISCUSSION

Despite the very clear role of β_3-adrenergic receptors in the regulation of energy expenditure in several animal models, their importance in human thermogenesis has not yet been convincingly shown. Several β_3-adrenergic receptor agonists have been tested in humans, but because of their poor selectivity and efficacy, the results so far have not been convincing.[29-32] In contrast to these compounds, L-796568 is both a highly selective and a highly effective agonist of the human β_3-adrenergic receptor in vitro.[23] This study clearly showed that L-796568 also has lipolytic and thermogenic activity in vivo after single-dose administration to obese men. At 4 hours after administration, the 1000-mg dose had increased energy expenditure by about 8%. The time to peak plasma concentration of L-796568 has been shown to be about 4 to 5 hours.[33] In this study the plasma concentration of L-796568 therefore probably had not reached its peak in all individuals after the 4-hour period, and a further thermogenic effect by L-796568 after 4 hours is likely.

In vitro the EC_{50} of L-796568 for stimulation of the human β_3-adrenergic receptor was 3.6 nmol/L. The EC_{50} values of L-796568 for human β_1-adrenergic receptor (4770 nmol/L) and β_2-adrenergic receptor stimulation (2405 nmol/L) were much higher than

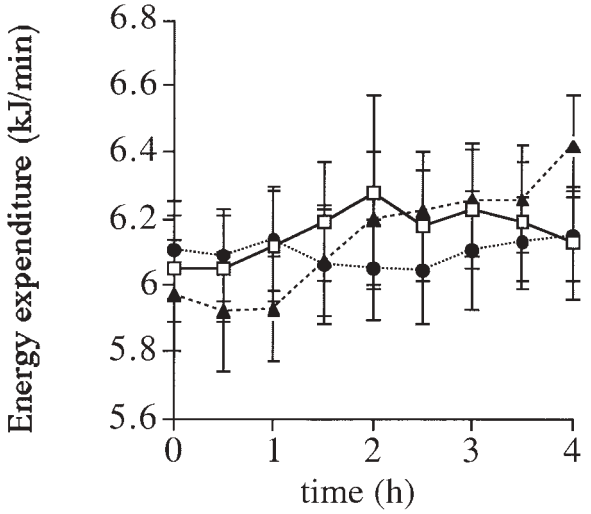

Fig 1. Energy expenditure (mean ± SEM) after placebo *(squares),* 250 mg L-796568 *(circles),* and 1000 mg L-796568 *(triangles).*

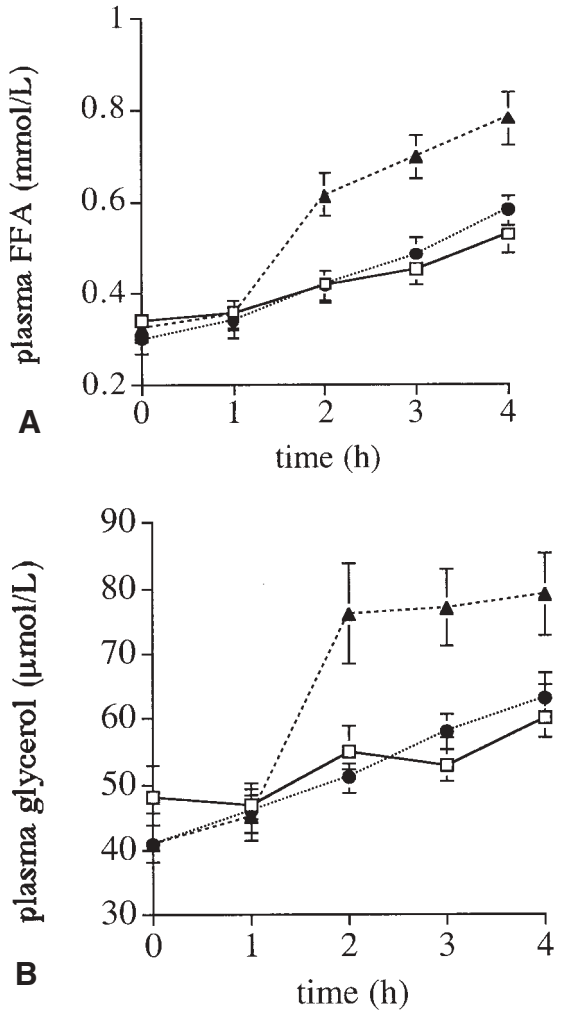

Fig 2. Mean ± SEM plasma free fatty acid concentrations (FFA; **A**) and glycerol concentrations **(B)** after placebo *(squares),* 250 mg L-796568 *(circles),* and 1000 mg L-796568 *(triangles).*

those for human β_3-adrenergic receptor stimulation.[23] In another study it was found that the peak plasma concentration of L-796568 was about 28.5 nmol/L after a single 250-mg dose and about 89.4 nmol/L after a single 1000-mg dose in lean healthy volunteers (Merck Research Laboratories. Data on file). Both concentrations were well above the EC_{50} of β_3-adrenergic receptor stimulation, and the highest concentration was still >25-fold lower than the EC_{50} for β_2-adrenergic receptor stimulation and >50-fold lower than the EC_{50} for β_1-adrenergic receptor stimulation. However, a significant contribution of β_2- or β_1-adrenergic receptor-mediated stimulation cannot be fully excluded only on the basis of comparisons with in vitro EC_{50} values. Tremor and hypokalemia, indicators of β_2-adrenergic receptor stimulation, were not evident and it is unlikely that the effects of L-796568 were the result of stimulation of sympathetic nervous system activity because plasma catecholamine concentrations did not change.

Several in vitro studies have shown that human subcutaneous adipose tissue and especially omental adipose tissue express functional β_3-adrenergic receptors.[14,15] Microdialysis studies have shown that these receptors are also functional in situ.[16-18] This study confirms that systemic administration of a β_3-adrenergic receptor agonist is also capable of stimulating lipolysis in vivo. In a recent study we showed that increased plasma concentrations of free fatty acids induced thermogenesis in lean and obese subjects in the absence of stimulation by the sympathetic nervous system.[33] It is therefore conceivable that the thermogenic response after L-796568 administration is caused by the β_3-adrenergic receptor-mediated stimulation of lipolysis and does not involve any further β_3-adrenergic receptor-mediated effects.

Systolic blood pressure increased significantly after L-796568. In the absence of an increase in heart rate, this suggests increased contractility of the heart or an increase in total peripheral resistance. However, diastolic blood pressure did not increase significantly, which does not support an increase in peripheral resistance. Moreover, in vivo and in vitro experiments in different animal species suggest a vasodilatory effect

of β_3-adrenergic agonists.[34] The presence of β_3-adrenergic receptors in the human heart has been reported for the right atrium[13] and for the ventricular endomyocardium.[12] To date, the functional role of the atrial β_3-adrenergic receptors is unclear. Stimulation of the ventricular β_3-adrenergic receptors produces a negative inotropic effect in animals and in human ventricular endomyocardial biopsies.[12,34] On the basis of these findings, a role for the up-regulation of β_3-adrenergic receptors in human heart failure as a protection against further myocyte damage has been proposed.[34] However, a negative inotropic effect of stimulation of β_3-adrenergic receptors is not in line with the increase in systolic blood pressure that was observed in this study. On the basis of these data, an increased contractility of the heart as a result of β_1-adrenergic receptor stimulation by L-796568 cannot be fully excluded. However, the pattern of changes of the different variables after L-796568 is not identical to that after specific β_1- (or β_2)-adrenergic receptor stimulation.[33]

In conclusion, single-dose administration of 1000 mg of the novel β_3-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of β_3-adrenergic receptor agonists in humans, without significant evidence for β_2-adrenergic receptor involvement. Involvement of β_1-adrenergic receptor stimulation could not be fully excluded but seems to be unlikely in view of the higher EC_{50} for human β_1-adrenergic receptor stimulation than for human SYMBOLB_3-adrenergic receptor stimulation in vitro and the plasma concentrations likely to be present.

We thank Jos Stegen for his analysis of the plasma catecholamines.

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