Enhanced thermogenic responsiveness during chronic ephedrine treatment in man[1-3]

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ABSTRACT The thermogenic effect of a single oral dose of ephedrine (1 mg/kg body weight) was studied by indirect calorimetry in five women with 14% overweight before, during and 2 mo after 3 mo of chronic ephedrine treatment (20 mg, perorally, three times daily). Before treatment and 2 mo after its cessation a similar thermogenic response to ephedrine was observed. The total extra consumption of oxygen was 1.3 l before and 1.2 l after cessation of the chronic treatment. After 4 and 12 wk of treatment ephedrine elicited a more sustained response, the extra oxygen consumption in the 3 h following ephedrine intake being 7.0 and 6.9 l, respectively. The ratio of serum T_3 to T_4 increased significantly after 4 wk of treatment (15.6 ± 1.3 vs 19.4 ± 2.4; $p < 0.05$), but decreased below the initial value after 12 wk treatment. The mean body weight was significantly reduced after 4 and 12 wk of treatment (2.5 and 5.5 kg, respectively). An improved capacity for beta-adrenergic induced thermogenesis may be useful in the treatment of obesity. *Am J Clin Nutr* 1985;42:83–94.

KEY WORDS Brown adipose tissue, catecholamines, ephedrine, glucose, glycerol, nonesterified fatty acids, obesity, oxygen consumption, skeletal muscle, thermogenesis, thyrotropin, thyroid hormones

Introduction

A weight-reducing effect of ephedrine in human obesity has been demonstrated in a controlled clinical study (1). The effect was supposed to be elicited by reduction of the appetite. However, in single administration experiments in man ephedrine has also been shown to possess thermogenic properties (2–4). In both lean and obese rats and mice weight reduction during long-term ephedrine treatment are primarily due to an increased metabolic rate, rather than a reduction in food intake (5–7).

Since the thermogenic action of ephedrine may be useful in the treatment of human obesity, we need to know whether the thermogenic response to ephedrine is modified during prolonged administration.

In order to investigate the thermogenic and metabolic effects of long-term ephedrine treatment, the ephedrine-induced thermogenesis (EIT) was investigated before, during and after termination of 3 mo daily ephedrine administration in healthy women with a slight overweight, who claimed to have a weight problem despite a low food intake.

Methods

General

Five healthy female volunteers aging from 18 to 49 yr (mean 36 yr) were studied. They gave their informed consent according to the declaration of Helsinki 2. The protocol was approved by the Municipal Ethical Committee of Copenhagen.

The physical characteristics of the individual subjects are shown in **Table 1.** The percentages of overweight

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TABLE 1
Physical characteristics of the experimental subjects at the entry of the study

Subjects	Age	Height	Body fat content	Body weight	Overweight
	yr	*cm*	%	*kg*	%
BHa	45	158	32.1	58.5	14
BHe	31	180	31.6	77.0	15
MH	18	166	30.2	65.5	17
ER	49	170	33.2	68.8	15
BL	39	167	38.6	61.5	10
Mean ± SEM	36 ± 6	168 ± 4	33.1 ± 1.5	66.3 ± 3.2	14 ± 1

Body fat content and the percentage of overweight are calculated as described in the Methods section.

were calculated from their ideal body weights (8). Body fat content was estimated by measurement of skin fold thickness with a Harpender caliper (9).

All subjects had a family history of obesity, but none of diabetes mellitus. Two took anticonceptional pills, while the others did not take any medications.

Experimental protocol (Fig 1)

An initial clinical examination with measurement of blood pressure and pulse rate was performed. Each subject underwent a pretreatment control experiment (Fig 1), where the thermogenic response to an oral ephedrine load was measured (EIT_{c1}). The next day, subjects began taking ephedrine chloride (EFEDRIN, DAK-Laboratory, Copenhagen) 20 mg, one h before meals three times/day for three mo, ie 60 mg/day. After 4 and 12 wk of ephedrine administration the experiment was repeated (EIT_{4w} and EIT_{12w}, respectively). A similar experiment was carried out after 8 wk of ephedrine administration, but using placebo without informing the experimental subjects. Two mo after cessation of treatment, a final posttreatment control experiment was performed (EIT_{c2}).

The subjects were told to continue their eating habits, but no assessment of the energy intake was done. During treatment no ephedrine was taken on the morning of an experiment. Consumption of ephedrine was controlled by counting remaining tablets. As the basal metabolic rate varies with the menstrual cycle (10), the experiments for each subject were performed at about the same time in the cycle.

The subjects were lightly dressed and rested supine. The room temperature was 23–24°C. The experiments were commenced 8–9 AM after an overnight fast (at least 12 h). On the experimental days the subjects refrained from alcohol, coffee, tea and tobacco consumption. Oxygen consumption, carbon dioxide elimination and different metabolic and hormonal parameters were measured before and during EIT. Each EIT experiment consisted of respectively, a 30-min control period, ingestion of ephedrine chloride powder (DAK), 1 mg/kg body weight and a 3-h ephedrine stimulation period.

Preceeded by a 10-min adaptation, expiratory gas was collected in Douglas bags in 10-min periods twice during the control period and every 30 min up to 3 h after the ephedrine intake.

Venous blood was sampled at the end of each gas collection period and 45 and 75 min after ephedrine intake.

Analytical procedures

During adaptation and gas collection the subjects breathed through a low resistance one-way SCUBA mouthpiece. Expiratory gas was continuously analyzed

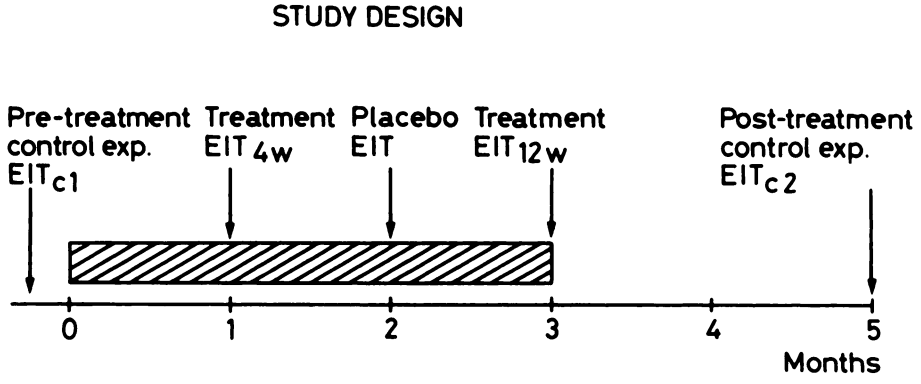

FIG 1. Experimental design. The hatched bar shows the period of chronic ephedrine treatment (20 mg ephedrine chloride orally three times/day). Each arrows indicate a thermogenesis experiment (EIT), where 1 mg ephedrine chloride or placebo powder/kg body weight was given perorally. c1: control 1; c2: control 2; 4w: 4 weeks; 12w: 12 weeks.

for oxygen and carbon dioxide with a Godart Rapox Oxygenometer and a Beckman LB-1 Medical Gas Analyzer. Respiratory steady state was assumed, when the end-expiratory CO_2 fraction was constant. Expiratory gas was collected in Douglas bags and analyzed for oxygen and carbon dioxide with Radiometer gas-electrodes connected to an acid-base analyzer (PHM 71, Copenhagen, Denmark) and the volume measured with a gas meter.

Through an indwelling Venflon cannula, blood was sampled without stasis from an antecubital vein in ice-cold syringes. The blood was then centrifuged at 4°C, and nonesterified fatty acids (NEFA) were immediately extracted and later determined as described in (11). Plasma sodium and potassium concentrations were determined by flame spectrophotometry. Plasma glucose was determined with the glucose oxidase method (12) and glycerol as described in (13). Serum thyroxine (T_4) and tri-iodothyronine (T_3) were measured by RIA (14). The tri-iodothyronine uptake test (T_3-resin-test) was performed as modified by Ames. Serum free thyroxine index (FT_4I) and free tri-iodothyronine index (FT_3I) were calculated as the product of the total serum T_4 or T_3 and multiplied by result of the T_3-test. Serum TSH was determined as described in (15). Plasma for determinations of catecholamines was preserved by addition of reduced glutathione and EGTA and stored at −50°C until analysis by radioenzymatic assay (16).

Statistics

A two-way analysis of variance for randomized blocks was performed to test differences between experimental periods within the same experiment as well as differences between responses to ephedrine at different times (17). The responses to ephedrine were estimated separately for each subject as the integrated areas under the response curves. A modified *t* test was applied to compare two means. A $p < 0.05$ was considered significant. All results are expressed as means ± SEM.

Results

Weight loss and side-effects

The body weight was reduced in all subjects, the average weight loss being 2.5 ± 0.2 kg ($p < 0.05$) and 5.5 ± 0.3 kg ($p < 0.01$) after 4 and 12 wk, respectively. Their overweight was similarly reduced from 14.2 ± 1.2% to 10.0 ± 1.5 and 6.2 ± 1.1% and the body fat content lowered by 3.5 ± 0.3 and 5.2 ± 0.3% of the body weight. Two months after cessation of ephedrine treatment there was an average regain of weight of 0.5 kg. Side effects were few. Only two subjects reported transient hand tremor the first 2–5 days.

The effects of ephedrine on blood pressure and pulse are shown in **Table 2.** The mean arterial blood pressure increased in the EIT_{c1} with 23 mmHg on an average one h after ephedrine intake ($p < 0.01$). During chronic treatment (EIT_{4w}) ephedrine increased only the mean blood pressure insignificantly (5 mmHg). No change in pulse rate could be detected. The blood pressure and pulse rate were not measured at other occasions.

Oxygen consumption and R

There was a transient rise in oxygen consumption in the EIT_{c1} experiment (**Fig 2**). It returned to control levels after 90 min and remained constant during the rest of the ephedrine stimulation period. A very similar pattern was seen in the EIT_{c2} experiment. In the EIT experiments during treatment the oxygen consumption showed a rise of similar magnitude but remained at the elevated level in the rest of the measuring period. This pattern was followed in all subjects. The oxygen consumption fell slightly during the placebo experiment. The baseline values were similar in all experiments, except for the EIT_{12w} where an 10% elevation was measured.

The oxygen consumption response, measured as the area under the oxygen consumption curve above baseline (0–180 min) were somewhat similar before and after treatment, 1.3 ± 1.1 and 1.2 ± 1.1 l, respectively (**Fig 3**). By contrast, the responses had increased markedly after 1 mo of treatment (7.0 ± 2.3 l, $p < 0.01$) as well as after 3 mo of treatment (6.9 ± 1.8 l, $p < 0.01$). These values correspond to 544 and 536% compared to the EIT_{c1} response, but represent an underesti-

TABLE 2
The effect of ephedrine on pulse rate and mean arterial blood pressure (MAP)

	Before treatment		During treatment (4 wk)	
	Baseline	60 min	Baseline	60 min
Pulse rate (min^{-1})	72 ± 4	70 ± 3 (NS)	75 ± 5	73 ± 4 (NS)
MAP (mmHg)	87 ± 3	110 ± 4 ($p < 0.01$)	82 ± 3	87 ± 5 (NS)

Results are quoted as means ± SEM.

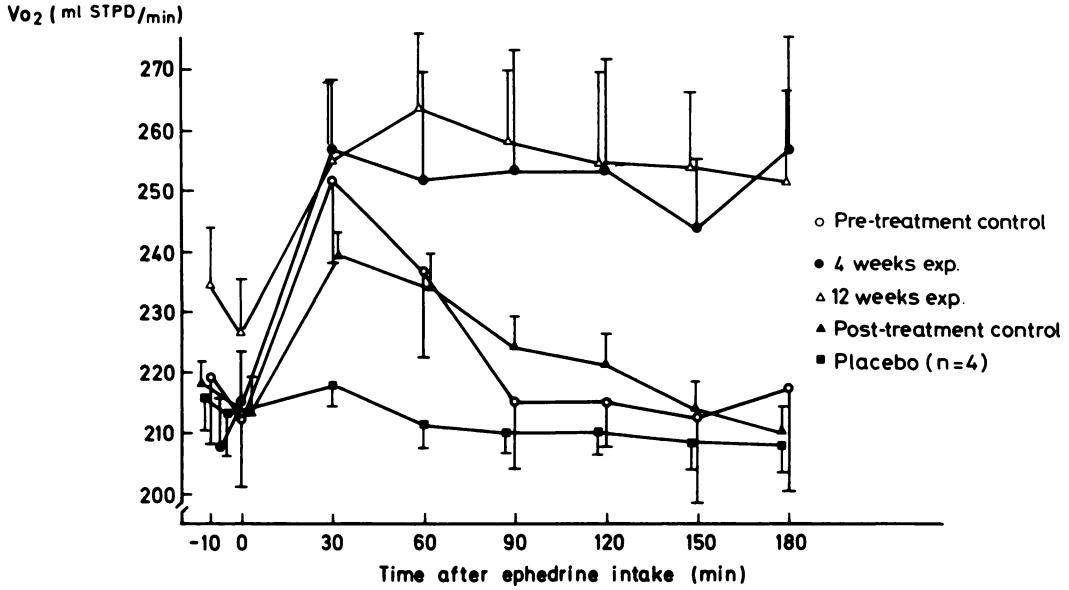

FIG 2. Oxygen consumption after 1 mg ephedrine orally/kg body weight in the experiments indicated in Figure 1 (n = 5, placebo study, n = 4). SEM is indicated on the figure.

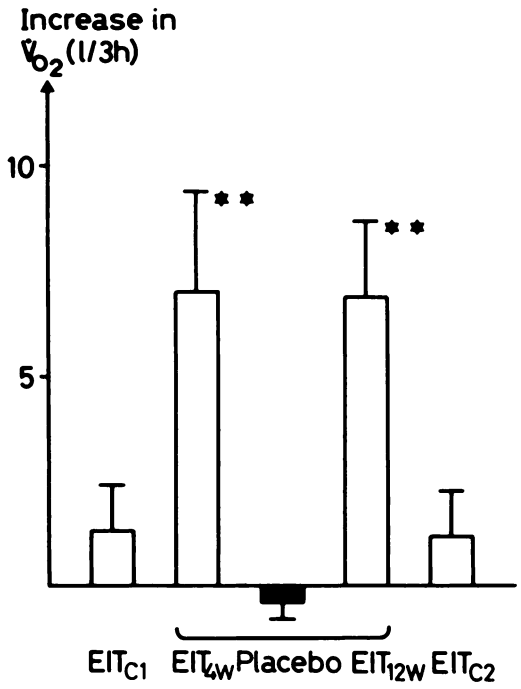

FIG 3. Increases in oxygen consumption after ephedrine administration. The black bar shows the response to placebo during chronic ephedrine treatment. ** Indicates the value is significantly different ($p < 0.01$) from the values obtained before as well as after cessation of treatment.

mation of the responses because the oxygen consumption had not returned to baseline levels at the end of these experiments. The baseline oxygen consumption was significantly elevated in EIT_{12w}. During all the EIT experiments including the placebo test, R fell from about 0.80–0.88 to 0.73–0.79 (**Fig 4**). No significant differences could be detected between the curves.

Plasma catecholamine concentrations

Figure 5 shows that plasma noradrenaline (NA) concentrations during the four EIT experiments (not measured in EIT_{4w}). In both the EIT_{c1} and EIT_{c2} experiments, ephedrine raised the plasma NA concentration significantly above baseline ($p < 0.01$). After 3 mo of treatment this response was abolished: the NA concentration remained unaltered like in the placebo experiments. The acute administration of ephedrine did not influence the plasma adrenaline levels (**Fig 6**). However, after 12 wk of treatment the plasma adrenaline level was significantly elevated compared with other times of measurement.

Plasma substrates concentrations

Ephedrine increased the plasma glucose concentration 10–20% in the EIT_{c1} and EIT_{c2},

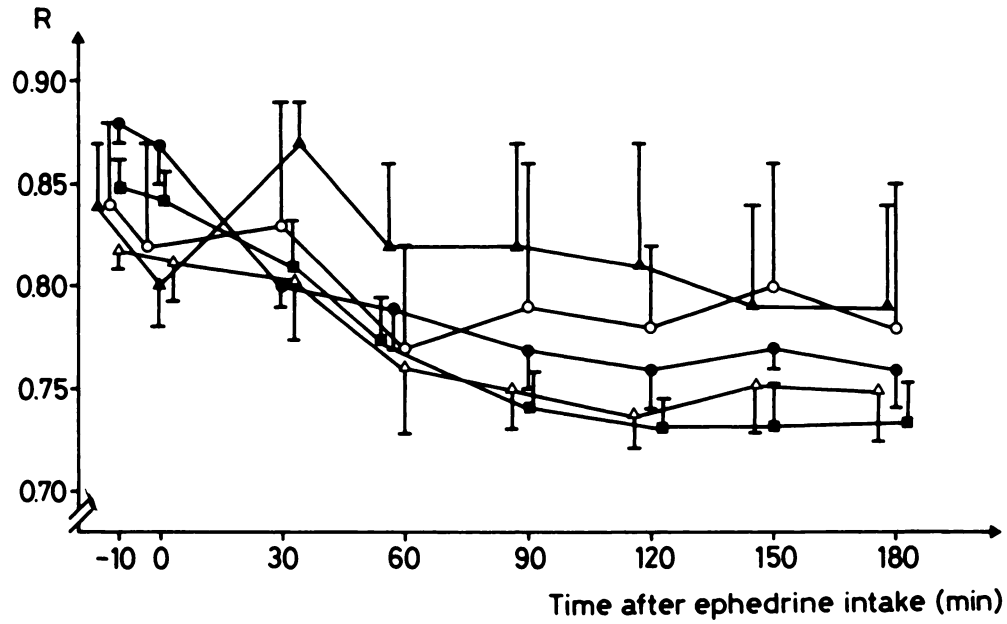

FIG 4. Changes in mean respiratory exchange ratio (R) elicited by ephedrine in the experiments indicated in Figure 1. Symbols as in Figure 2.

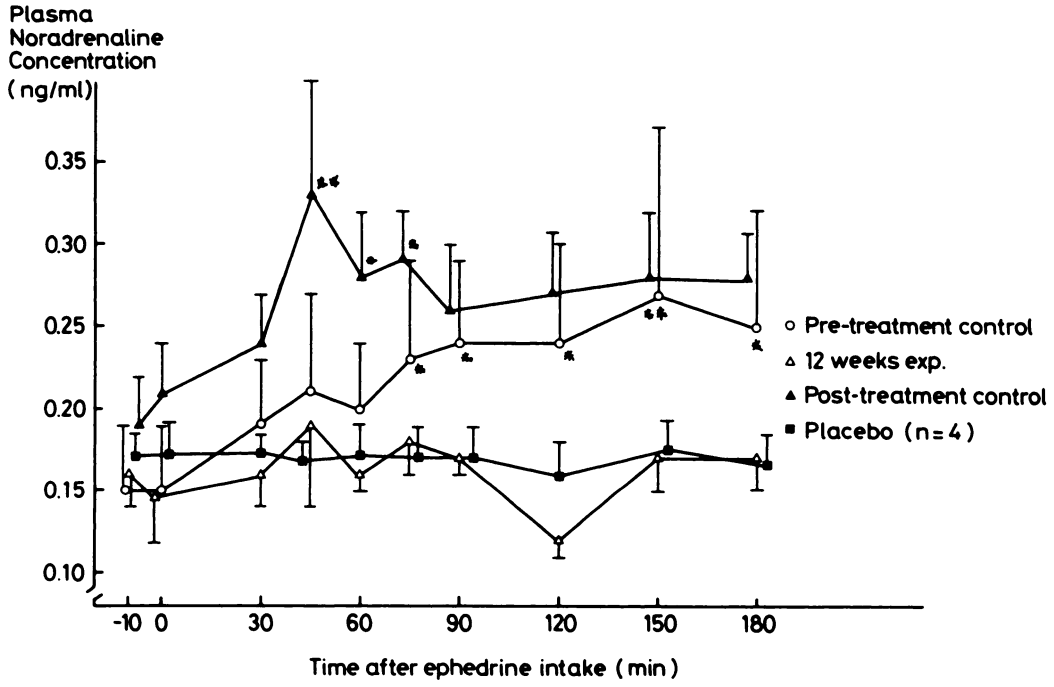

FIG 5. Changes in venous plasma noradrenaline concentration induced by ephedrine or placebo in the experiments shown in Figure 1. Symbols as in Figure 2. Values significantly increased above baseline are marked *, $p < 0.05$ and **, $p < 0.01$.

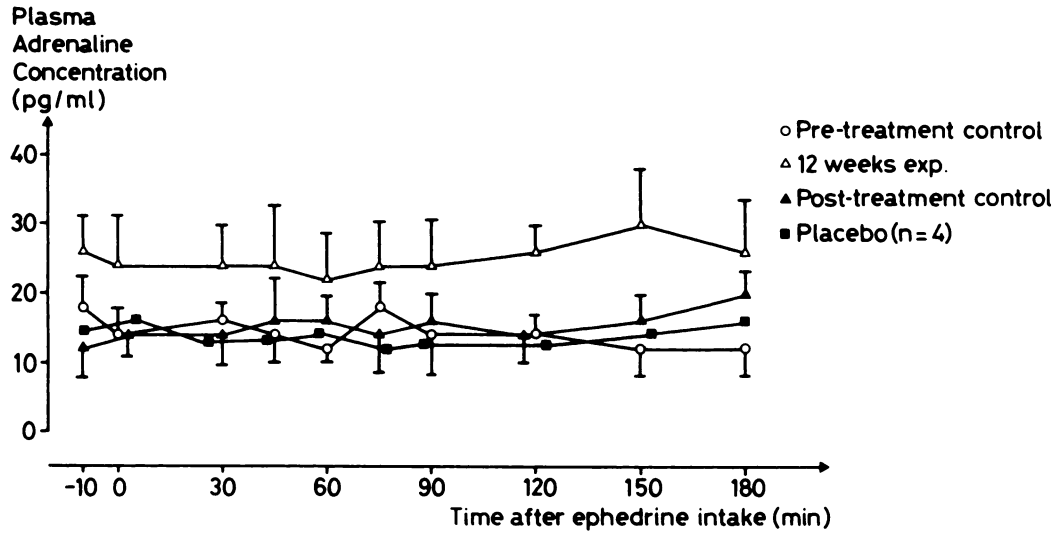

FIG 6. Venous plasma adrenaline concentrations after ephedrine or placebo in the experiments shown in Figure 1. Symbols as in Figure 2.

most markedly in the former (Fig 7). After 4 weeks of treatment (EIT_{4w}) the plasma concentration remained essentially constant, while it fell significantly during the EIT_{12w} experiment as well as during the placebo study. Thus tolerance gradually seems to develop to the hyperglycemic action of ephedrine during treatment of 3 mo duration. In all the EIT experiments (including the placebo one) plasma nonesterified fatty acids

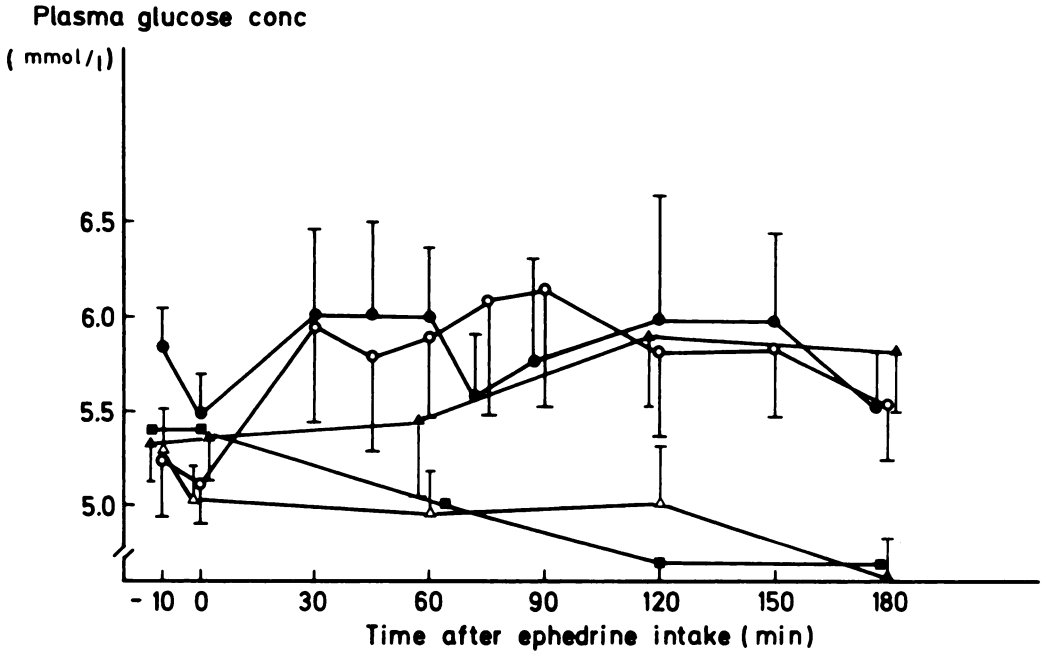

FIG 7. Changes in plasma glucose concentration induced by ephedrine or placebo in the experiments shown in Figure 1. Symbols as in Figure 2.

(NEFA) concentrations increased slightly (**Fig 8**), an observation in accordance with the fasting state of the subjects. The plasma glycerol concentration increased significantly only in the placebo EIT ($p < 0.01$) (**Fig 9**).

Plasma potassium and sodium concentrations

Before start of treatment, ephedrine reduced the plasma potassium concentration from 4.1 to 3.7 mmol/l ($p < 0.01$) (**Fig 10**). The responses were somewhat blunted during chronic administration and even 2 mo after cessation. In the placebo experiment the plasma potassium concentration increased significantly from 3.9 to slightly above 4.0 mmol/l. The plasma sodium concentration remained unaltered during all the experiments (data not shown).

Thyroid hormones

Chronic ephedrine treatment had no effect on serum TSH level (**Table 3**). Though not significant, the serum T_3 and FT_3I were slightly higher and T_4 concentration and FT_4I somewhat lower after 4 wk of treatment. When expressed as the ratio of serum T_3 to T_4, the changes reached significance ($p < 0.05$). However, the mean ratio fell significantly below the control levels after 12 wk of treatment ($p < 0.01$), primarily due to a reduction in serum T_3 level.

Discussion

The present study confirms the thermogenic effect of ephedrine in man previously reported (2–4). It further demonstrates, that this effect increases during prolonged ephedrine treatment. This sensitization to ephedrine is in contrast to the adaptation occurring to cardiovascular and other metabolic effects of ephedrine (18–21) and other beta-agonists (22) during chronic administration in man.

In rodents ephedrine and other beta-ago-

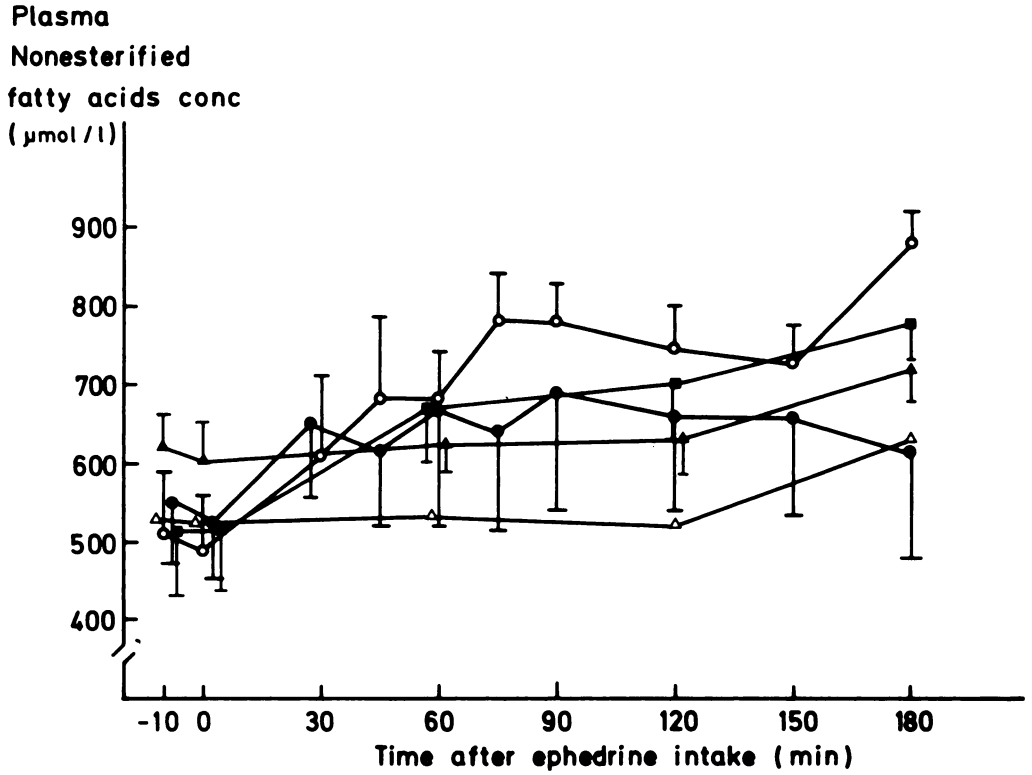

FIG 8. Changes in plasma nonesterified fatty acid concentration in the experiments shown in Figure 1. Symbols as in Figure 2.

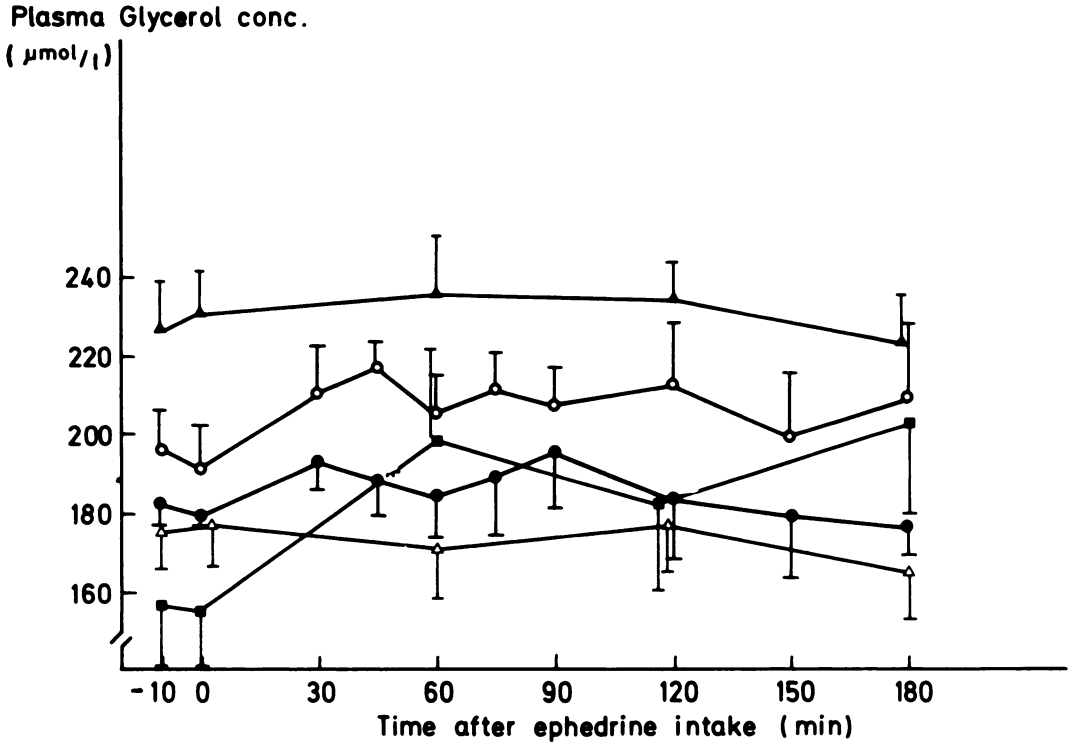

FIG 9. Plasma glycerol levels during stimulation with ephedrine or placebo in the experiments shown in Figure 1. Symbols as in Figure 2.

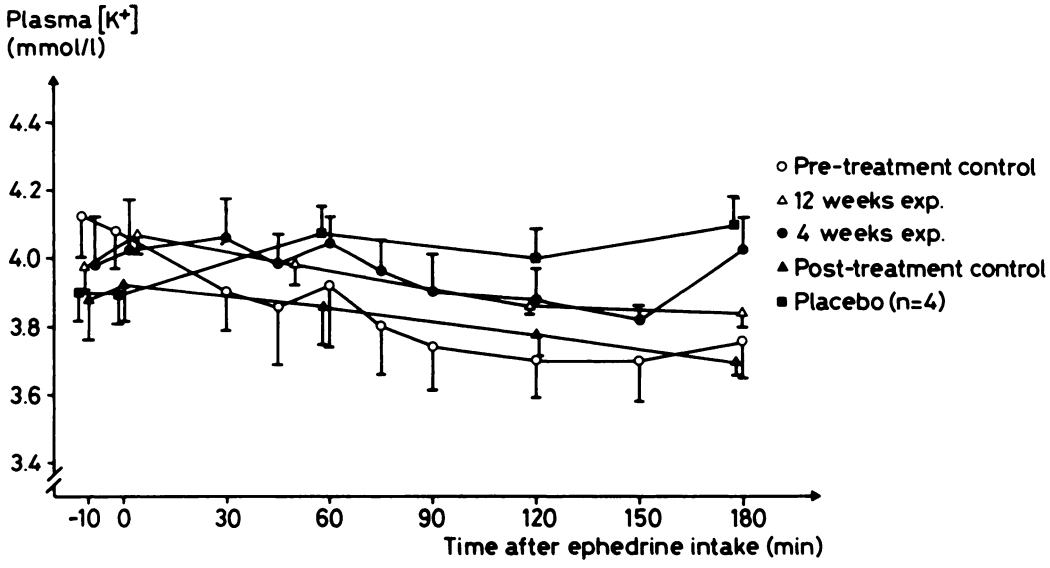

FIG 10. Changes in plasma potassium concentrations induced by ephedrine or placebo in the experiments shown in Figure 1. Symbols as in Figure 2.

TABLE 3
Serum concentrations of thyroid hormones before, during and after prolonged ephedrine treatment

	Before treatment	During treatment		After treatment
		4 wk	12 wk	
T_3 (ng/dl)	103 ± 15	109 ± 5	78 ± 15	100 ± 14
T_4 (μg/dl)	6.6 ± 0.6	5.9 ± 0.7	6.4 ± 0.6	6.6 ± 0.6
T_3:T_4 ratio × 10^3	15.6 ± 1.3	19.4 ± 2.4*	12.2 ± 2.0*	15.8 ± 1.4
FT_3I (arb U)	100.9 ± 9	111 ± 6	73 ± 17†	99 ± 13
FT_4I (arb U)	6.4 ± 0.4	5.9 ± 0.6	6.0 ± 0.7	6.5 ± 0.6
TSH (μU/ml)	3.3 ± 0.4	2.9 ± 0.1	3.8 ± 0.6	3.3 ± 0.3

FT_3I: serum free tri-iodothyronine index; FT_4I: Serum free thyroxine index. Results are presented as means ± SEM.
* $p < 0.05$; † $p < 0.01$.

nists stimulate the oxygen uptake of brown adipose tissue (BAT), the principal site of cold-induced and diet-induced thermogenesis (23–25). Furthermore, chronic administration of noradrenaline (26) or ephedrine (27), as well as cold adaptation (28) have been shown to sensitize rats and mice to the thermogenic effects of these stimulations. This sensitization is partly caused by a marked hyperplasia of BAT, with an increased mitochondrial concentration of the uncoupling protein, thermogenin (27, 29). Thus, noradrenaline seems to exert a trophic effect upon BAT in adult rodents (29).

In human subjects, an increased thermogenic response to noradrenaline has been reported in Korean women acclimated to severe cold-water stress (30). In patients with pheochromocytoma, an endocrine disorder characterized by high levels of circulating catecholamines, a high concentration of thermogenin has been reported in BAT (31, 32). It is conceivable that chronic ephedrine treatment may exert a similar trophic effect upon BAT. However, recent studies have not supported that BAT contributes to the thermogenesis induced by acute ephedrine administration in normal, adult humans (2, 33).

After two weeks of chronic treatment of humans with terbutaline, a beta-agonist, Scheidegger et al (34) found a blunted thermogenic response to an infusion of the unselective beta-adrenergic agonist, isoproterenol. This suggests that the thermogenic alterations induced by ephedrine treatment are not a consequence of chronic beta-2 adrenoceptor stimulation.

In man, skeletal muscle has recently been demonstrated as being an important site of thermogenesis induced by ephedrine (33). In rodents, an increased sensitivity of skeletal muscle to the thermogenic effect of catecholamines is also involved in the enhanced thermogenic capacity, which accompany conditions characterized by high circulating levels of catecholamines (35). How catecholamines exerts their thermogenic effect in skeletal muscle is yet unknown.

It has been suggested that the Na^+-K^+-pump may be of importance in thermogenesis induced by catecholamines. In all the EIT experiments (except the placebo) the rise in oxygen consumption was accompanied by a fall in plasma K^+ concentrations. This effect has also been observed after administration of adrenaline (36), terbutalin (37, 38) and orciprenalin (38), and the increased oxygen consumption has been interpreted as evidence of the stimulation of active Na^+-K^+ transport via beta-2 adrenoceptors (36–38). Clausen et al have recently demonstrated the presence of Na^+-K^+-pumps in human skeletal muscle (39). Since the hypokalemic effect of ephedrine was reduced rather than enhanced during chronic treatment, a sensitization of the Na^+-K^+-pump to the effect of ephedrine is not likely. This conclusion is supported by Buur et al, who have reported a suppressed adrenergic effect on active Na^+-K^+-transport in skeletal muscle in chronically terbutaline treated animals (40).

It has been proposed that the thermogenic action of catecholamines and related drugs might be due, at least in part, to an increased cycling of nonesterified fatty acids between triglyceride in adipose tissue and the liver (41, 42). The finding of fairly constant plasma glycerol concentrations after ephedrine ingestion does not support this theory.

Before and after chronic treatment ephed-

rine increased the plasma noradrenaline concentration in forearm venous blood, indicating an enhanced activity of the sympathetic outflow to the forearm muscles (43, 44). This observation is in accordance with a recent study, in which the lower extremity was shown to be a source of the noradrenaline released by ephedrine (33). During chronic treatment, no increase was seen in plasma noradrenaline concentration in the EIT experiments. This change could be due to a depletion of the neuronal noradrenaline stores resulting in a diminished release. If this is the case, the thermogenic effect of ephedrine could be exerted by its direct beta-agonistic properties. Alternatively, an increased noradrenaline removal from the circulation could explain the absence of the increase in plasma noradrenaline in the control experiments. The baseline oxygen consumption as well as the plasma adrenalin levels were significantly elevated after 12 wk of chronic treatment. Whether these changes are causally related requires further investigation.

Four wk of ephedrine treatment slightly elevates the serum T_3 concentration and significantly increases the T_3/T_4-ratio (Fig 9). These data are in accordance with the findings that 2 wk administration of terbutaline in man significantly increases the serum T_3 level and the ratio of serum T_3 to T_4 (33). In contrast to that study, we could not demonstrate a concomitant elevation of baseline oxygen consumption. Melander et al have shown that treating man with a sympathomimetic drug like amphetamine exert a stimulatory influence on the secretion of thyroid hormones (45). This effect appears to be mediated via beta-2-adrenoceptors in the thyroid gland (46). In the present study, the effect on the serum T_3/T_4 ratio was absent after 12 wk of chronic treatment when a significant reduction was seen, even compared to pre- and posttreatment levels.

A number of investigations have shown that some obese subjects have a reduced thermogenic response to beta-adrenergic stimulation (3, 47), and this has led to the hypothesis that at least some kinds of obesity might be due to an impaired thermogenesis (48, 49). A reduced diet-induced thermogenesis in obesity has been reported (49). Since the carbohydrate-induced thermogenesis seems to be mediated partly via beta-adrenergic receptors (50), a reduced thermogenic response to beta receptor stimulation might offer an explanation for the development of some kind of obesity.

If ephedrine treatment sensitizes—not only to the thermogenic effect of ephedrine—but also to thermogenesis elicited by biological catecholamines, it may increase energy expenditure by enhancement of food-induced thermogenesis, and thus become useful in the treatment of obesity.

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