Exercise-induced lipid mobilization in subcutaneous adipose tissue is mainly related to natriuretic peptides in overweight men

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1Département Obésité et Métabolisme, Institut National de la Santé et de la Recherche Médicale, Unité 858, Institut de Médecine Moléculaire de Rangueil; 2Faculté de Médecine de Toulouse Service de Pharmacologie, Centre Hospitalier Universitaire; 3Hôpitaux Purpan et Larrey, Toulouse, France; 4Institut National de la Santé et de la Recherche Médicale, Franco-Czech Laboratory for Clinical Research on Obesity, Prague, Czech Republic; and 5Centre d’Investigation Clinique, Hôpital Purpan, Toulouse, France

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Exercise-induced lipid mobilization in subcutaneous adipose tissue is mainly related to natriuretic peptides in overweight men. Am J Physiol Endocrinol Metab 295: E505–E513, 2008. First published June 17, 2008; doi:10.1152/ajpendo.90227.2008.—Involvement of sympathetic nervous system and natriuretic peptides in the control of exercise-induced lipid mobilization was compared in overweight and lean men. Lipid mobilization was determined using local microdialysis during exercise. Subjects performed 35-min exercise bouts at 60% of their maximal oxygen consumption under placebo or after oral tertatolol (α-β-adrenergic receptor (AR) antagonist). Under placebo, exercise increased dialysate glycerol concentration (DGC) in both groups. Phenotolamine (α-AR antagonist) potentiated exercise-induced lipolysis in overweight but not in lean subjects; the α2-antilipolytic effect was only functional in overweight men. After tertatolol administration, the DGC increased similarly during exercise no matter which was used probe in both groups. Compared with the control probe under placebo, lipolysis was reduced in lean but not in overweight men treated with the β-AR blocker. Tertatolol reduced plasma nonesterified fatty acids and insulin concentration in both groups at rest. Under placebo or tertatolol, the exercise-induced changes in plasma nonesterified fatty acids, glycerol, and insulin concentrations were similar in both groups. Exercise promoted a higher increase in catecholamine and ANP plasma levels after tertatolol administration. In conclusion, the major finding of our study is that in overweight men, in addition to an increased α2-antilipolytic effect, the lipid mobilization in subcutaneous adipose tissue that persists during exercise under β-blockade is not dependent on catecholamine action. On the basis of correlation findings, it seems to be related to a concomitant exercise-induced rise in plasma ANP when exercise is performed under tertatolol intake and a decrease in plasma insulin.

microdialysis; tertatolol; atrial natriuretic peptide; insulin

THE REGULATION OF HUMAN ADIPOSE TISSUE LIPOLYSIS during exercise was previously attributed to both the increase in catecholamine levels and the simultaneous decrease in plasma insulin concentration (12, 16, 17). In fat cells, lipolysis is activated through stimulation of β-adrenergic receptors (AR) and inhibited through α2-AR stimulation (2, 21). The simultaneous activation of both receptors modulates the intracellular cAMP concentration, which activates cAMP-dependent protein kinase, leading to the phosphorylation and activation of perilipin and hormone-sensitive lipase (Ref. 22). Moreover, we have shown that natriuretic peptides (NPs) are potent activators of lipolysis in human fat cells and specifically in primates (29, 31). Atrial natriuretic peptide (ANP) stimulates fat cell plasma membrane receptors (NPR-A subtype) bearing intrinsic guanylyl cyclase activity and an increase intracellular levels of cGMP that activates a cGMP-dependent protein kinase (PKG), PKG-dependent phosphorylation of perilipin and hormone-sensitive lipase stimulates lipolysis (30). NPs are potent lipolytic agents on isolated fat cells from subcutaneous adipose tissue (SCAT). The lipolytic efficacy of this cardiac-derived peptide hormone has been confirmed several times after intra-venous administration. When intravenously administered at pharmacological doses in humans (h), hANP promotes a strong lipid-mobilizing effect that is independent of the activation of the sympathetic nervous system (SNS; Ref. 11). A similar lipid-mobilizing response occurred when hANP was perfused through a microdialysis probe inserted in SCAT. Moreover infusion of hANP, within a concentration range currently observed in humans, increases lipid mobilization from adipose tissue and plasma nonesterified fatty acids (NEFA) levels (5). Circulating ANP concentrations rise during short-exercise bouts; the plasma concentrations of ANP increase two- to threefold (26). The physiological relevance of the ANP-dependent lipolytic pathway was demonstrated in young men performing physical exercise (26). Nevertheless, it is unknown if this ANP-dependent effect operates similarly in overweight and obese patients who also exhibit an imbalance between β- and α2-AR response in SCAT. An increment of the α2-AR component promotes a reduction of the β-AR responsiveness in the obese (34); the effects of ANP remain to be established. Previous reports (14, 1, 26) have focused attention on the fact that β-AR blockade does not fully inhibit exercise-induced lipolysis at low and moderate intensities of exercise in lean subjects. Nevertheless, administration of oral tertatolol, associated with local concomitant α- and β-AR-blockade, has previously been shown to completely block catecholamine action in situ (26). These results suggest that another lipolytic pathway operates to explain the lipid mobilization remaining under β-blockade; the ANP-dependent pathway could be a good candidate to explain the results.

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The aim of the present study was to compare the relative contribution of catecholamines, ANP, and insulin in the control of lipid mobilization during exercise in overweight men; a lean group was included to perform a comparison in similar conditions. Exercise, which is known to promote SNS activation, NP release, and reduction of plasma insulin levels (10, 26), was used to promote lipid mobilization. For that, healthy male men fasted overnight performed a 35-min exercise bout at 60% of their non-β-blocked maximal oxygen consumption (V\(_{\text{O}_2\text{max}}\)) 120 min after oral administration of tertiatolol (a non selective β-AR antagonist) or placebo. In both conditions, exercise-induced lipid mobilization was assessed in SCAT, using in situ microdialysis, under local α-AR-blockade alone in one microdialysis probe and both α- and β-AR-blockade in another probe during the exercise bout. The study was expected to delineate the specific contribution of catecholamines ANP and insulin in the control of lipid mobilization in SCAT in overweight men. Since in previous studies performed in lean subjects the protocols differed from those selected here, we included a group of lean subjects to compare the responses in overweight and lean subjects performing strictly similar exercise challenges (26).

**SUBJECTS AND METHODS**

**Subjects.** Nine healthy young lean and nine healthy overweight men without hypertension, who had not been enrolled in any other pharmacological or nutritional protocol prior to the study, were recruited according to their body mass index (BMI; e.g., they were considered overweight for a BMI between 25 to 30 and cutoff for lean recruited according to their body mass index (BMI; e.g., they were considered overweight for a BMI between 25 to 30). Selection of the men was based on a screening evaluation of their detailed medical history, a physical examination, and several blood chemistry analyses. Insulin sensitivity was assessed by homeostasis assessment of insulin resistance (HOMA-IR) calculated according the formula: HOMA-IR = [(fasting glucose (mmol/l) × fasting insulin (\(\mu\)M/mL))/22.5 (23). One week before the investigation period, the maximal oxygen consumption (V\(_{\text{O}_2\text{max}}\)) was determined on an electric brake cycle ergometer (Ergometrics 800i Ergoline) by use of an incremental procedure (work rate increasing by 30 W/3 min). V\(_{\text{O}_2\text{max}}\) was measured using an Oxycor Pro (Jaeger), and the highest V\(_{\text{O}_2}\) value was considered as V\(_{\text{O}_2\text{max}}\). Under treatment with tertiatolol, subjects exercised at the same V\(_{\text{O}_2}\) that was 60% of their non-β-blocked V\(_{\text{O}_2\text{max}}\). Fat mass and lean mass were measured using a total body Dual-Energy X-ray Absorptiometer (Lunar-DPX). The Ethical Committee of the Faculty of Medicine of Toulouse approved the study. All the subjects gave their informed consent for the experimental conditions after a detailed explanation.

**Table 1. Characteristics of lean and overweight subjects**

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Overweight</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>28.4±1.9</td>
<td>31.7±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.7±2</td>
<td>173.6±1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.1±2.5</td>
<td>82.2±3.0</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>22.9±0.8</td>
<td>27.3±0.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>10.8±1.2</td>
<td>21.6±1.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fat free mass, kg</td>
<td>55.1±1.6</td>
<td>54.1±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Muscle, kg</td>
<td>29.1±0.9</td>
<td>30.1±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>V(_{\text{O}_2})max, l/min</td>
<td>3.49±0.13</td>
<td>3.30±0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal workload, W</td>
<td>241.0±6.1</td>
<td>233.3±10</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.79±0.13</td>
<td>1.80±0.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

BMI, body mass index; HOMA-IR, homeostasis assessment of insulin resistance. P value is comparison between lean and overweight subjects.

**Table 2. Basal dialysate glycerol values and ethanol ratio in control probe, probe with phentolamine alone, or probe associated with propranolol in lean and in overweight subjects 120 min after placebo or tertiatolol administration**

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Overweight</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control probe</td>
<td>95.6±17.2</td>
<td>78.2±6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>83.7±11.7</td>
<td>89.5±8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Phentolamine + propranolol</td>
<td>101±15.8</td>
<td>92.7±10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Tertiato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control probe</td>
<td>81.9±10.7</td>
<td>90.0±13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>75.9±8.1</td>
<td>88.3±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Phentolamine + propranolol</td>
<td>83.9±16.3</td>
<td>76.9±13.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Ethanol ratio, %**

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Overweight</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control probe</td>
<td>42.7±7.5</td>
<td>64.9±6.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>42.1±7.7</td>
<td>66.8±6.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Phentolamine + propranolol</td>
<td>51.9±7.4</td>
<td>62.0±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Tertiato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control probe</td>
<td>41.7±8.1</td>
<td>69.2±4.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>43.7±6.4</td>
<td>67.8±7.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Phentolamine + propranolol</td>
<td>56.1±8.8</td>
<td>67.3±5.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Design of the study.** Subjects were investigated at 8 AM after an overnight fast for 2 days separated by 1 wk according to a double-blind randomized crossover procedure. The subjects entered the Center of Clinical Investigation at 8.00 AM and were maintained in a semi-recumbent position. An indwelling polyethylene catheter was inserted into the antecubital vein for blood sampling. At 8.30 AM, three microdialysis probes (Carnegie Medicin, Stockholm, Sweden) of 20 × 0.5 mm and 20,000 molecular weight cutoff were inserted percutaneously after epidural anesthesia (200 µl of 1% lidocaine, Roger-Bellon, Neuilly-sur-Seine, France) into the SCAT at a distance of 10 cm from the umbilicus. Immediately after, the subjects absorbed a placebo or 5 mg tertatolol, and then, the exercise bouts began 120 min later. The probes were connected to a microperfusion pump (Harvard apparatus; S.A.R.L., Les Ulis, France) and perfused at 2.5 µl/min with Ringer solution (in mmol/l: 139 sodium, 2.7 potassium, 0.9 calcium, 140.5 chloride, and 2.4 bicarbonate). Ethanol (1.7 g/l) was added to the perfusate to estimate changes in the local blood flow, as described previously (9). One control probe was perfused with Ringer’s solution alone. The second probe was perfused with 100 µmol/l phentolamine (an α12-AR antagonist); it is the only α-AR antagonist tolerated for use in such clinical studies. The third probe was perfused with 100 µmol/l phentolamine plus 100 µmol/l propranolol (a nonselective β-AR antagonist).

After a 90-min equilibration period, two 15-min fractions of the outgoing dialysate were collected in all probes to determine basal glycerol output (i.e., basal lipolysis). Then, the subjects performed an exercise period for 35 min with a load corresponding to 60% of their V\(_{\text{O}_2\text{max}}\) measured under placebo (i.e., in non-β-blocked situation) on the cycle ergometer. Dialysate was collected at 20 and 35 min and every 15 min during a 30-min recovery period. Heart rate was continuously monitored with a Polar Accurex Plus cardiometer. At rest and during exercise, blood pressure was measured with an exercise-adapted monitor (Tango Stress Test BP Monitor; Suntech Medical Instruments, Raleigh, NC). Water intake was allowed ad libitum during the exercise bouts and recovery periods. Before, during, and after exercise bouts, 5 ml of blood were collected from the catheter for endocrine and metabolic parameter.
determination. For catecholamine determinations, a supplementary blood sample was collected in with 50 μl of sodium metabisulfite at 100 μM (i.e., 50 μl/1.5 ml of plasma) to prevent the oxidation of catecholamines and it was immediately centrifuged in a refrigerated centrifuge. The plasma was stored at −80°C until analysis.

Drugs and analytical methods. Phentolamine methanesulfonate (Regitine), propranolol (Avlocardyl), and tertatolol (Artex) were obtained from Novartis (Reuil-Malmaison, France), Zeneca Pharma (Cergy, France), and Therva Medical (Neuilly-sur-Seine, France), respectively. Sodium metabisulfite came from Sigma-Aldrich (St. Quentin Fallavier, France). Glycerol in dialysate and in plasma was analyzed with an ultra-sensitive radiometric method (7). Ethanol in dialysate and perfusate (5 μl) was determined with an enzymatic method (4). Plasma glucose and NEFA were determined with a glucose-oxidase technique (Biotrol, Paris, France) and an enzymatic procedure (Wako, Unipath, Dardilly, France), respectively. Plasma insulin concentrations were measured using RIA kits from ICN Pharmaceuticals (Orsay, France). Plasma epinephrine and norepinephrine were assayed in 10-ml aliquots of plasma by high-pressure liquid chromatography using electrochemical (amperometric) detection. Plasma cortisol was determined using a RIA method (CISBIO International, Gif sur Yvette, France), and lactate was evaluated using an enzymatic/colorimetric dosage (BioMerieux, Marcy l’Etoile, France). Plasma collected on EDTA (1 mg/ml) plus aprotinin (5 μmol/ml) was used for ANP and growth hormone (GH) determinations using radioimmunoassay kits from Peninsula Laboratories (San Carlos, CA).

Statistical analysis. All values are means ± SE. The responses to exercise were analyzed by two-way repeated-measures ANOVA. Extracellular concentration response-curves were calculated as the mean integrated changes over baseline values. See Figs. 1–4 and Tables 1–4 for significance values. P < 0.05 was considered statistically significant.

RESULTS

Effect of placebo administration on dialysis glycerol concentration during exercise. After placebo administration and at rest, the mean basal dialysis glycerol concentration (DGC) values did not differ in the control probe and that with phentolamine alone or associated with propranolol in lean or in overweight men (Table 2).

Exercise increased DGC in all the probes. The DGC increase had a tendency to be higher in lean than in overweight subjects in the control probe, but the difference did not reach significance (88.3 ± 14.9 and 68.4 ± 15.3 μmol/l, respectively; P = 0.09). The presence of 100 μmol/l phentolamine in the perfusate significantly increased glycerol release in overweight but not in lean men (Figs. 1 and 2). In lean men, the residual DGC

![Fig. 1. A: dialysate glycerol from subcutaneous adipose tissue (SCAT) at rest, during exercise [35 min, 60% maximal oxygen consumption (VO2max)], and during the recovery period in lean subjects after placebo or tertatolol administration. Probes were perfused with Ringer, with Ringer + phentolamine, and with Ringer + phentolamine + propranolol. B: mean of dialysate glycerol increase during the exercise bouts. Data are means ± SE. *P < 0.05, compared with similar probes after tertatolol administration. #P < 0.05, compared with the control probe or the phentolamine probe.](http://ajpendo.physiology.org/)
increment, determined from the probe supplemented with propranolol, was significantly reduced compared with the control probe (36%) and the probe with phentolamine (31%) (Fig. 1). In overweight men, the addition of propranolol did not reduce significantly the exercise-induced DGC increase compared with the control probe, while a significant reduction (42%) of DGC was observed compared with the probe with phentolamine (Fig. 2).

Effect of tertatolol administration on DGC during exercise. Selection of tertatolol dose and the time course of its utilization were defined according to the results of a previous investigation (3). After oral intake of 5 mg tertatolol (120 min), mean basal DGC values did not differ in the control probe and the probes with phentolamine alone or associated with propranolol in lean or in overweight men. Moreover, the basal DGC were not different from those found after placebo administration no matter which probe was used (Table 2).

During exercise (i.e., performed at 60% of the nonblocked VO2max), no difference in DGC increase was found between the three probes in both groups (Figs. 1 and 2). In lean men, the mean increase of DGC in control probe was reduced under tertatolol compared with placebo administration (57.8 ± 8.2 and 88.3 ± 14.9 μmol/l, respectively; P < 0.05). A similar reduction was also observed in the probe added with phentolamine (65.1 ± 13.2 and 94.2 ± 6.9 μmol/l, respectively; P < 0.01), but no significant change appeared in the probe containing phentolamine and propranolol. In contrast, in overweight men, the mean increase in DGC in the control probe after tertatolol administration was not different compared with the control probe under placebo administration (67.1 ± 19.7 and 68.4 ± 15.3 μmol/l, respectively). A reduction of DGC was only observed when the probes added with phentolamine were compared (68.6 ± 12.4 and 96.9 ± 19.8, respectively; P < 0.05). In the probe containing phenotolamine and propranolol, a tendency to an increased DGC (73.9 ± 10 and 50.1 ± 13.6, the increase being not significant; P = 0.10) was observed after tertatolol administration.

Local blood flow in SCAT. Changes in local blood flow occurring in SCAT microcirculation during exercise were evaluated using the method based on the measurement of ethanol escape from the microdialysis probes (9). Ethanol outflow-to-inflow was expressed as a percentage, (i.e., the ethanol concentration in the dialysate divided by the ethanol concentration in the perfusate ×100); a higher ethanol ratio corresponds to the lower ethanol washout and to a lower regional adipose tissue blood flow (ATBF). At rest, the average ethanol ratio

![Fig. 2](image-url)
was not different in the control probe and the probe with phentolamine or with phentolamine plus propranolol and no difference was found in any groups (Table 2). Significantly higher ethanol ratio values were observed in overweight men (a result suggesting a lower blood flow). During the exercise bouts, no significant changes in ethanol ratio were observed in all probes either after placebo or tertatolol administration (not shown).

**Plasma determinations.** In both groups, plasma NEFA and glycerol concentrations at rest were reduced 120 min after

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**Fig. 3.** Plasma glycerol and nonesterified fatty acids (NEFA) concentrations measured at rest, during exercise (35 min, 60% VO\(_{2\max}\)), and during the recovery period in lean and overweight subjects after placebo or tertatolol administration. Data are means ± SE. *P < 0.02, compared with values measured at rest.

**Fig. 4.** Plasma insulin and glucose concentrations measured at rest, during exercise (35 min, 60% VO\(_{2\max}\)), and during the recovery period in lean and overweight subjects after placebo or tertatolol administration. Data are means ± SE. *P < 0.02, compared with values measured at rest.
Plasma ANP levels were increased after tertatolol administration, the increase being higher in the lean than in the overweight men (Table 3). A positive correlation between plasma ANP levels and DGC values was observed in the lean (r = 0.55; P = 0.02) as well as in the overweight (r = 0.49; P = 0.02) subjects. Plasma cortisol values increased during exercise, and no differences were observed in all groups of subjects and treatments. Finally, after placebo or tertatolol administration, plasma lactate concentrations at rest were similar in both groups and no differences were found in the exercise-induced lactate increase according to the group or the treatment (Table 3).

**Cardiovascular data.** Heart rate and systolic and diastolic blood pressure were not different in both groups. In the resting state, tertatolol administration lowered heart rate and systolic and diastolic blood pressure. During exercise, heart rate increased after placebo or tertatolol administration but remained lower under tertatolol treatment. A similar pattern of changes was observed with systolic blood pressure. Finally, whatever the treatment, the diastolic blood pressure evolution was similar (Table 4).

**DISCUSSION**

The present study reveals that a large part of the exercise-induced lipid mobilization in SCAT of overweight men was not modified by a simultaneous local α- and β-AR-blockade or the oral administration of a β-AR blocker (i.e., tertatolol); the existence of a non-AR component is thus suspected. In addi-
The lipid-mobilizing response induced by exercise under combined AR blockade (α2/β-AR) was not different from the control probe. The complete blockade of fat cell AR receptors did not suppress the exercise-induced lipolysis in both groups. Propranolol, at the concentration used (100 μmol/l), fully suppressed the lipolytic effect of a high concentration of isoproterenol (nonselective β-AR agonist) infused locally in SCAT (26). Thus exercise-induced extracellular glycerol increase in the probe perfused with propranolol cannot be attributed to stimulation of fat cell β-ARs by the catecholamines released during exercise. This residual lipid mobilization under local blockade of effectors of the AR system has previously been attributed to ANP-mediated lipolysis (26). Acute exercise increases the cardiac filling pressure and end-diastolic volume that promote the release of ANP by the right atria of the heart.

Tertatolol, which exerted the expected cardiovascular effects in our study (Table 4), has been shown to enhance exercise-induced ANP secretion (3). Oral tertatolol was also shown to totally suppress the isoproterenol-induced DGC increase promoted by a local administration of the β-AR agonist (26). The enhancement of ANP release by the heart explains the exercise-induced increase in the plasma concentration of ANP observed after β-blockade in both groups of subjects (Table 3). An exercise-dependent increase in DGC persisted in SCAT after tertatolol administration. Nevertheless, the comparison of exercise-induced lipid mobilization under tertatolol treatment in both groups of subjects shows that residual lipid mobilization resistant to β-AR blockade is higher in the overweight subjects. This suggests that it is a non-AR pathway that plays the major role in the control of exercise-induced lipid mobilization in SCAT of the overweight men. On the contrary, and as previously shown, catecholamines are partially involved in the control of exercise-induced lipid mobilization in lean men (1, 14, 26, 37). Our results fit with previous results considering the effect of β-AR blockade on lipid mobilization. One study has shown that during endurance exercise no significant decrease in plasma glycerol and NEFA concentrations is found after β-adrenoceptor blockade (19). Another group (38), clearly showed that β-AR blockade does not inhibit exercise-induced lipolysis at low and moderate intensities of exercise as formerly believed. We have provided arguments to demonstrate that it is the ANP-dependent pathway that could explain the lipid mobilization observed in such conditions. Unfortunately, our conclusion based on correlative data suffers a major limitation due to that observed after placebo treatment in overweight men. This result clearly reveals the existence of another mechanism that is more efficient in the overweight than in the lean subject.

Investigation of lipid mobilization in SCAT was done using in situ microdialysis. Its regulation at rest and during exercise was investigated using pharmacological antagonist compounds targeting α2-ARs (phentolamine) or both β- and α2-ARs (association of propranolol plus phentolamine). The exercise-induced increase in extracellular glycerol concentration was lower in overweight men (Fig. 2) but was enhanced by infusion of phentolamine. This effect was not observed in lean men (Fig. 1). This kind of response (Fig. 1) has previously been observed in obese patients (34). Differences in the responses between lean and overweight are easily interpretable. Exercise promotes an increase in sympathetic nervous outflow and epinephrine (Table 3). Epinephrine is known to exhibit a higher affinity for α2-ARs than norepinephrine (33); it preferentially activates the antilipolytic α2-AR in SCAT during exercise. Several data have underlined that α2-ARs largely outnumber β-ARs in subcutaneous adipocytes and that α2-AR density correlates with fat cell size (2).
(PTH) stimulates lipolysis in vitro in human fat cells (6, 35, 36). However, its lipolytic effect is weak and it is only obtained with high concentrations of the hormone. Moreover, moderate exercise had no action or slightly increased in PTH plasma concentration (15). GH is secreted during exercise (20, 32). The time course of appearance of the lipolytic effect of GH is long in human fat cell incubations in vitro. Intravenous administration of hGH exerts delayed action on lipolysis and lipid mobilization in humans. A significant effect is only observed 2 h after injection (13, 24, 25). Thus involvement of GH-related lipolytic effects cannot be proposed to interpret the lipid mobilization promoted by exercise in the present study. The plasma cortisol concentration rose during exercise. The effects of cortisol on lipolysis have only been demonstrated in fat cells preincubated for several hours to days (27). The morning rise in cortisol was proposed to regulate lipolysis in SCAT (28). Therefore, it is unlikely that the exercise-induced rise in plasma cortisol participates in lipid mobilization during the short-term exercise bouts.

The interpretation of changes in extracellular glycerol concentration in SCAT should take into account ATBF changes. For example, if ATBF is reduced by a vasoconstriction, a rise in glycerol concentration will occur in the interstitial space of the tissue. In our study, local ATBF was evaluated by the validated ethanol escape method (9). As previously found, it was observed that ATBF is decreased in overweight men under placebo and tertatolol treatment compared with lean men (i.e., this fact is assessed by the higher ethanol ratio). In both groups, and in both treatment conditions, no change in ATBF was observed during exercise as shown previously (32). Consequently, under our working conditions with rather short duration of exercise bouts, the difference in exercise-induced lipolysis between the lean and overweight subjects cannot be attributed to major changes in local blood flow.

At rest, basal venous glycerol and NEFA concentrations have a tendency to be higher in overweight but the differences are not significant. During exercise, the working skeletal muscle oxidizes NEFA released from adipose tissue and the plasma NEFA concentrations remained not far different from baseline. A weak significant decrease was only observed 20 min after the beginning of exercise in both groups and also after tertatolol or placebo treatment (Fig. 4). This transitory difference could be explained by the occurrence of slight differences in the kinetics of NEFA mobilization, recycling through reesterification and utilization. The exercise-induced increase in plasma glycerol concentration was similar in both groups. Under tertatolol administration, the exercise-induced increase in plasma glycerol is significantly reduced in both groups when compared with placebo. Nevertheless, a progressive exercise-induced increase in plasma glycerol concentration was observed after tertatolol administration during the exercise bouts. This increase in plasma glycerol reflects the occurrence of a lipid mobilization (38). The most evident argument for the existence of an exercise-induced lipid mobilization is the rebound in plasma NEFA concentrations occurring at the end of the exercise bouts. This rebound is classically attributed to a simultaneous persistence of lipolysis and a reduction of NEFA utilization or reesterification by the skeletal muscles during the 15–30 min after the end of exercise (16, 32).

To conclude, exercise (35 min at 60% VO₂max) induces SNS activation (assessed by an increment of plasma catecholamine levels) with a concomitant decrease in insulin and an enhanced ANP release by the heart leading to increased plasma levels of ANP. When SNS activation-dependent events are considered, the functionality of the α2AR-mediated antilipolytic effect is revealed in overweight men during exercise, while being absent in lean subjects. Concerning β-AR responses, in lean men, the exercise-induced lipid mobilization in SCAT is reduced by ~48% after tertatolol administration. In lean men, exercise-induced lipid mobilization is due to the combined action of catecholamines and ANP. The major finding in overweight men is that during the exercise bouts selected in the present study, the exercise-induced lipid mobilization in SCAT is unchanged after tertatolol administration; it is not SNS related. Based on correlative findings revealing a positive correlation between plasma ANP levels and glycerol release in lean and overweight subjects, the residual lipid-mobilizing effect observed when exercise is performed under tertatolol intake could reasonably be associated with a concomitant rise in plasma ANP during exercise in lean. The action is stronger in the overweight, since the whole lipid-mobilizing response is resistant to tertatolol blockade. The major limitation of the strength of our results to be irrefutable is due to the lack of a NPR-A receptor antagonist usable in clinical studies. Finally, the contribution of the modulator antilipolytic action of insulin on lipid mobilization (related to the exercise-induced decrease in plasma insulin concentrations) cannot be completely excluded.

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