Activation of antilipolytic $\alpha_2$-adrenergic receptors by epinephrine during exercise in human adipose tissue

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Several lines of evidence support the view that, during exercise, increased sympathetic nervous system (SNS) activity is responsible for the increase in lipid mobilization, since catecholamines are of major importance for the regulation of lipolysis in adipose tissue (AT; see Refs. 21 and 30) and for the increase of nonesterified fatty acid (NEFA) supply to the working muscle (7, 8, 17). During prolonged exercise, it is probable that other mechanisms reinforce the SNS-induced activation of lipolysis. They probably include a decrease of insulin, an increase in growth hormone and cortisol, and also a rise in plasma epinephrine (11, 14, 24). The specific role of these factors, particularly of epinephrine, in lipid mobilization during exercise is thus difficult to establish.

The coexistence of $\beta$-adrenergic receptors (AR) that increase and $\alpha_2$-AR that decrease the rate of lipolysis in human fat cells still raises questions about their physiological relevance. The presence of $\beta$- and $\alpha_2$-ARs has clearly been demonstrated by functional in vitro assays in isolated human fat cells and binding studies with selective ligands (9, 28, 30, 31). In human fat cells, where $\alpha_2$-AR outnumber $\beta$-AR, the preferential recruitment of the $\alpha_2$-AR, leading to an inhibition of lipolysis at lower catecholamine concentrations (10, 33), has been described in vitro. In addition, it has been shown that epinephrine is the amine with the highest affinity for fat cell $\alpha_2$-ARs (29). $\beta$-AR-stimulated lipolysis occurs at the highest concentrations of the amines. This dual effect of catecholamines on isolated human fat cells (i.e., antilipolytic and then lipolytic according to the concentration of the amine) was particularly striking in femoral adipocytes from overweight women (33) and was also observed in subcutaneous adipocytes from obese men (32). The physiological relevance of such in vitro responsiveness to catecholamines remains in doubt. Microdialysis appears to be an alternative method to study the lipolytic responses of AT in vivo to pharmacological drugs (2, 40) or during exercise (1, 11, 18). Although approaches based on the utilization of the microdialysis method have become considerably more numerous during the last years, studies concerning the action of the physiological amines (epinephrine and norepinephrine) toward $\beta$- or $\alpha_2$-adrenoceptor-mediated pathways in human subcutaneous AT have been scarcely reported.

The aim of the present study was to examine the influence of epinephrine lipolysis through the $\alpha_2$-adrenergic pathway during exercise. For that, healthy male subjects,fasted overnight, performed two bouts of prolonged exercise (60 min, 50% maximum $\text{O}_2$ uptake ($\text{V}_{\text{O}_2\text{max}}$)) separated by an equivalent period of rest.
model of the repeated exercise was selected because the two bouts are characterized by the same increase in plasma norepinephrine levels but different epinephrine responses (personal data), and thus the comparison of the responses to the two bouts provides an opportunity to discriminate, in physiological conditions, between the actions of the two catecholamines.

The present results showed that the higher exercise-induced epinephrine concentration in plasma during the second exercise promoted increased lipid mobilization as shown by an increase in plasma glycerol and NEFA concentrations and in extracellular glycerol concentration (measured with the microdialysis method). It was shown that glycerol output in subcutaneous AT was enhanced by the blockade of α-AR by phentolamine and that there was a relationship between the epinephrine levels and magnitude of the enhancement, i.e., the enhancement was higher during the second exercise when epinephrine levels increased more.

**MATERIALS AND METHODS**

**Subjects**

For in vitro studies on isolated fat cells, six nontrained men (mean age: 27 ± 2.1 yr) were selected. Their mean body weight was 72.5 ± 2.4 kg (range: 63–77 kg) and had been stable for at least 3 mo. Their body mass index (BMI) was 23.4 ± 0.7 kg/m² (range: 20.7–25.5 kg/m²). For dialysis studies, eight nontrained men (mean age: 22.3 ± 1.5 yr) were selected. Their mean body weight was 74.5 ± 2.2 kg (range: 70–81 kg) and had been stable for at least 3 mo before the beginning of the study. Their BMI was 23.9 ± 0.6 kg/m² (range: 21.3–25.3 kg/m²). All were drug free. One week before the investigation period, V˙O2max and heart rate were determined on an electrically braked bicycle ergometer (Ergometrics 800s; Ergoline, Jaeger, Germany) by use of an incremental work procedure (work rate increasing by 15 W/min) for the subjects that participated in the dialysis protocol. The rate of O2 consumption (V˙O2) was measured using a maximal velocity (V˙max) apparatus (Sensor Medics, Yorba Linda, CA), and the highest VO2 value was considered as VO2max. The mean VO2max was 46.4 ± 5.3 ml O2·kg⁻¹·min⁻¹ (range: 40.8–56.2 ml O2·kg⁻¹·min⁻¹). All subjects had given their informed consent before the study. The studies were performed according to the Declaration of Helsinki and were approved by the Ethical Committee of Prague, Faculty of Medicine (University Hospital).

**In Vitro Lipolysis Measurements**

A biopsy of abdominal subcutaneous AT was performed (after intradermal anesthesia with 1% lidocaine; Roger-Bellon, Neuilly-s-Seine, France) with a 2.3-mm-diameter needle. By successive suction, 200–300 mg of AT were drawn into a syringe. Biopsies were made between 8 and 9 AM after an overnight fast. Adipocytes were quickly isolated using the method previously described (4, 10) in a Krebs-Ringer bicarbonate-HEPES solution (pH = 7.4) containing 2% BSA, 6 mmol/l glucose (KRBA), and 0.5 mg/ml collagenase. Isolated adipocytes were washed three times, and the cells were used for lipolysis measurements in KRBA buffer. Concentration-response curves were obtained using isoproterenol (a nonselective β-AR agonist) and epinephrine alone or in the presence of 10 µmol/l RX-82,1002 (a selective α2-AR antagonist). All pharmacological compounds were added to a 5-µl volume at the start of the incubation performed with 2,000–3,000 isolated fat cells in a final volume of 100 µl KRBA. The incubation was run for 90 min, and 30 µl of infranatant were removed for the determination of glycerol (lipolytic index). Lipolytic activity was expressed as micromoles of glycerol released per milligram lipid for 90 min.

**In Vivo Experimental Protocols**

The subjects were investigated at 8 AM after an overnight fast and were placed in a semirecumbent position. Two microdialysis probes (Carnegie Medecin, 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) into the abdominal subcutaneous AT at a distance of 10 cm immediately to the right of the umbilicus. The probes were separated by 5 cm and were connected to a microinjection pump (Harvard apparatus; SARL, Les Ulis, France). One probe (A) was perfused with Ringer solution (139 mmol/l sodium, 2.7 mmol/l potassium, 0.9 mmol/l calcium, 140.5 mmol/l chloride), and the second (B) was infused with Ringer plus 0.1 mmol/l phentolamine (α-AR antagonist). This nonselective α1/α2-antagonist is the only agent allowed in microdialysis assays in humans. The two perfusate solutions were supplemented with ethanol (1.7 g/l). Ethanol was added to the perfusate to estimate changes in the blood flow, as previously described (2, 3, 13, 20). After a 30-min equilibration period, a 30-min fraction of dialysate was then collected at a flow rate of 0.5 µl/min. Next, the perfusion was set at 2.5 µl/min for the remaining experimental period. The calibration procedure using various perfusate rates was applied for interstitial glycerol concentration in AT and was previously described by our group (2, 3, 13, 30). This time-consuming method was not used in this study. A simplified technique was used. The estimated extracellular glycerol concentrations were calculated by plotting (after log transformation) the concentration of glycerol in the dialysate measured at 0.5 and 2.5 µl/min against the perfusion rates. The values of extracellular glycerol concentrations found in the present study fit with previous determinations in lean subjects (2, 22, 23, 34).

After the calibration of the probes, the subjects performed an exercise for 60 min with an imposed power corresponding to 50% of their VO2max on the cycle ergometer. The heart rate was continuously monitored with a Baumann BHL 6000 cardiometer during the exercise. V˙O2 was measured regularly using a V˙max apparatus (Sensor Medics). Next, the subjects were allowed to rest in the semirecumbent position for 60 min, after which they performed a new 60-min exercise with an imposed power such that their heart rate was kept constant and similar to that recorded during the first exercise bout. Finally, the subjects rested again for 60 min. Water intake was allowed ad libitum during the exercise and recovery periods.

During the whole experimental period, including resting periods, 15-min fractions of dialysate were collected from the probes. At the corresponding times (i.e., every 15 min), 5 ml of blood were collected from an indwelling polyethylene catheter inserted into an antecubital vein. The catheter was kept patent by slow infusion of saline. Blood was collected on 50 µl of an anticoagulant and antioxidant cocktail (Immunotech, Marseille, France) to prevent oxidation of catecholamines and was immediately spun down in a refrigerated centrifuge. The plasma was stored at −80°C until analysis.

**Drugs and Biochemical Determinations**

Isoproterenol hydrochloride (Isuprel) and phentolamine methanesulfonic acid (Regitine) were obtained from Sterling Winthrop (Clichy, France) and Giba-Geigy (Reuil-Malmaison, France).
In vitro effects of increasing concentrations of isoproterenol and epinephrine alone in the presence of the selective α2-AR antagonist (RX-82,1002) are depicted in Table 1. A significant lipolytic effect of isoproterenol (a β-AR agonist) was observed with 0.01 µmol/l, the maximal effect being reached with 0.1 µmol/l. Epinephrine was devoid of lipolytic effect until 1 µmol/l, and a significant increase in glycerol production was observed only with 10 µmol/l. A clear increase in the lipolytic effect of epinephrine was observed when RX-82,1002 was added to the incubation medium. Epinephrine-induced glycerol release was significant with 0.1 µmol/l, and the maximal effect (obtained with 1 µmol/l epinephrine) was similar to that of isoproterenol.

In Vivo Results

General observations. Perceived exertion was not augmented by the second bout of exercise by the subjects. The power developed was regularly adjusted to maintain the heart rate constant over each exercise bout. Values of heart rate and \( \dot{V}O_2 \) measured during the last 5 min of each exercise period, i.e., \( t = 55 \)–60 min and 175–180 min, were 136 ± 3 and 141 ± 4 beats/min (not significant) and 1.45 ± 0.07 and 1.33 ± 0.05 l/min (not significant), respectively. The power developed during the second exercise bout was significantly lower (102 ± 7 and 85 ± 6 W, respectively).

Plasma catecholamine concentrations. At rest, plasma norepinephrine and epinephrine concentrations were 192 ± 38 and 59 ± 21 pg/ml, respectively (Fig. 1). Half-way through the period of exercise (\( t = 30 \) min), the plasma norepinephrine concentration rose (482% of the basal values) and did not change significantly (551%) until the end of exercise (\( t = 60 \) min). At the end of the recovery period (\( t = 120 \) min), norepinephrine concentration decreased to a value (227 ± 36 pg/ml) that did not differ from that measured in basal conditions (\( t = 0 \) min). No differences were found in the time course of plasma norepinephrine concentration increment during the second bout of exercise. The increments were 463 and 557% at 150 and 180 min, respectively, and were no different (\( P = 0.54 \)) from that measured during the first exercise bout. The plasma epinephrine concentration rose to 147% of the basal values after 30 min of exercise and rose progressively (\( P = 0.01 \)) until the end of exercise (271%). During recovery, the epinephrine concentration decreased to a value that did not differ at \( t = 120 \) min (61 ± 20 pg/ml) from that measured in basal conditions (\( t = 0 \) min). During the second exercise bout, the plasma epinephrine concentrations (measured at \( t = 150 \) and 180 min) dramatically rose to values significantly higher than those measured during the first bout of exercise. The corresponding increments were 236 and 496% at \( t = 150 \) and 180 min, respectively. The AUC calculated for the norepinephrine and epinephrine increase in plasma during the second exercise bouts showed significantly higher values for epinephrine (6,637 ± 960 vs. 2,586 ± 526 pg·ml\(^{-1}·60\) min\(^{-1} \); \( P = 0.001 \)) but not for norepi-
Plasma NEFA and glycerol levels and extracellular glycerol concentration in AT. During the baseline period, plasma glycerol and NEFA concentrations were 52 ± 5 and 337 ± 41 µmol/l, respectively (Fig. 3). The corresponding baseline extracellular glycerol concentrations in subcutaneous AT were not significantly different in probe A infused with Ringer alone (185 ± 35
µmol/l) and probe B infused with phentolamine (229 ± 28 µmol/l).

Plasma NEFA concentrations were unchanged all along the first exercise period. After 15 min of recovery, NEFA concentration increased significantly and then decreased to values different from those found in basal conditions at t = 0 min. During the second exercise bout, plasma NEFA concentration increased significantly starting from 15 min and gradually rose during the exercise period (Fig. 3A).

Starting from 30 min into the first exercise, the extracellular glycerol concentration increased significantly in probe A. Plasma glycerol increased significantly 15 min after the beginning of exercise. Next, both the plasma and extracellular glycerol concentrations steadily increased. At the end of exercise, the increases were ~125 and 172% in plasma and the extracellular compartment, respectively. The extracellular glycerol concentration (calculated from probe B where phentolamine was added) increased significantly starting from 15 min during the exercise. At the end of the exercise, the increase was ~235%. Although the extracellular glycerol concentration was higher in probe B, no significant difference was found when compared with values obtained with probe A (calculated AUC are 16.956 ± 5.566 vs. 9.448 ± 2.428 µmol·l⁻¹·60 min⁻¹; P = 0.07). During the recovery period, plasma glycerol concentration (66 ± 6 µmol/l), as well as extracellular glycerol concentrations calculated from probes A and B (209 ± 66 and 223 ± 28 µmol/l, respectively), fell steadily to reach a level at t = 120 min not different from that measured before exercise (t = 0 min).

During the second bout of exercise, the glycerol concentration in plasma and the extracellular compartment calculated from probe A rose significantly starting from 15 min of exercise and continued to rise during the exercising period. A significant increase in glycerol concentrations in plasma and in the extracellular compartment was observed when compared with the glycerol increment measured during the first exercise bout. At the end of exercise, the percentage increase was ~360 and 464% in plasma and in the extracellular compartment, respectively. A similar qualitative response was obtained when considering probe B, which was infused with phentolamine (Fig. 3B). The glycerol concentration in the extracellular compartment increased significantly from 15 min into the second exercise, and a significant increase of extracellular glycerol concentrations was observed when compared with the glycerol increment measured during the first exercise bout. However, the addition of phentolamine in probe B significantly increased extracellular glycerol concentrations when compared with the glycerol increment measured in control probe A and during the second exercise bout (calculated AUC are 33.911 ± 9.182 vs. 16.304 ± 3.030 µmol·l⁻¹·60 min⁻¹; P = 0.03).

Ethanol outflow-to-inflow ratio in AT. Ethanol outflow-to-inflow ratios (expressed as a percentage, i.e., the ethanol concentration measured in the dialysate/ the ethanol concentration measured in the perfusate × 100) in the dialysate from probes A and B are depicted in Fig. 4. In the two resting periods (t = 0 and 120 min), the ethanol outflow-to-inflow ratio did not differ between probe A (59.4 ± 3.0 and 60.1 ± 3.0, respectively) and probe B (54.3 ± 2.7 and 55.8 ± 2.9, respectively). No significant variation of the ethanol outflow-to-inflow ratio was observed either during the first or the second exercise session in probe A. In probe B, the ethanol outflow-to-inflow ratio decreased during the two exercise bouts, with the magnitude of the decrease being similar in the two bouts.

DISCUSSION

The present study reveals that epinephrine contributes to exercise-induced lipolysis, although the existence of α₂-AR-mediated counteraction was clearly revealed with our protocol. The coexistence of lipolytic β-ARs and antilipolytic α₂-ARs in human fat cells has been largely demonstrated through in vitro studies on isolated fat cells and binding studies (30, 31). The rate of lipolysis, through activation or inhibition of the adenyl cyclase, is relevant from this dual action of catecholamines on lipolysis (30, 31). In human subcutaneous fat cells in which α₂-ARs numerically predominate over β-ARs (33), the recruitment of the α₂-ARs, leading to epinephrine inhibition of lipolysis, has been described in vitro. Epinephrine is the preferential amine for fat cell α₂-adrenergic receptors, suggesting that it is probably involved more than norepinephrine in the control of lipolysis through the α₂-adrenergic pathway (29). The physiological relevance of such in vitro α₂-AR responsiveness to catecholamines is not clearly understood. Previous studies using microdialysis have led to conflicting results. Using local administration of phentolamine, one study has shown that resting lipolysis was modulated by α₂-adrenergic inhibition, whereas the α₂-adrenergic mechanism did not modulate lipolysis during exercise (1). On the contrary, Hellström et al. (18) showed that phentolamine potentiated exercise-induced lipolysis in men (but not in women). However,
in these studies, the contribution of epinephrine to the lipolytic responses to α2-adrenergic blockade was not assessed.

The first part of the present study, carried out in vitro, demonstrated the effect of the blockade of α2-ARs on epinephrine-induced lipolysis in the fat cells from young healthy subjects used in the present study. Two points arise from these results. First, they demonstrate the relative effect of catecholamines on α2- and β-ARs, and the results fit with previously reported in vitro observation demonstrating that epinephrine has a higher affinity for α2-AR than for β-ARs (29). Epinephrine had no lipolytic effect on fat cells below concentrations of 1 µmol/l, whereas a lipolytic action of isoproterenol (a nonselective β-AR agonist) was obtained with 0.01 µmol/l. The lipolytic action of epinephrine was enhanced after blockade of α2-ARs. These in vitro findings demonstrate that the control of lipolysis through the dual action of catecholamines on β- and α2-ARs is operational in fat cells from young healthy subjects and in older and/or obese subjects (32, 33).

They also justify research into the involvement of α2-ARs, and particularly the role of epinephrine, in the control of lipolysis in vivo in young male subjects.

Exercise is a physiological stimulus for the activation of both the SNS and the adrenal medulla. The challenge of the experiment was to find exercise conditions inducing similar activation of the SNS and a different secretion of epinephrine. For that, an experimental protocol using two successive repeated exercise bouts, separated by an appropriate resting period, in fasting subjects was used. Determining the appropriate conditions of the two exercise bouts (intensity, duration, and recovery period) was the object of preliminary investigations.

Previous studies (26) have shown that successive exercise bouts (50% \( V_{O2max} \), 30 min) separated by 30-min resting periods progressively increased \( V_{O2} \), heart rate, and body temperature. To avoid such a drift in responses, in our study, the second exercise bout was performed with a \( V_{O2} \) intensity similar to that measured during the first exercise. \( V_{O2} \) was not different in the two bouts of exercise, indicating that the two bouts were performed at identical relative intensities. The same relative intensity of the two exercise bouts was a condition enabling the comparison of the hormonal response to each bout, because it was shown that the hormonal response to exercise is determined by the relative rather than absolute intensity of exercise (15, 25). It is noticeable that, in these conditions, the power developed during the second exercise was significantly lower than that measured during the first bout.

Hence, the activation of the SNS (assessed by plasma norepinephrine levels) was of similar amplitude during the two exercise bouts, whereas the second exercise led to a higher activation of the adrenal medulla (assessed by plasma epinephrine levels). In fact, the enhanced exercise-induced increase in plasma epinephrine levels during the second exercise bout might be caused by the decrease in plasma glucose level (15) occurring in the second but not in the first exercise bout. Plasma glycerol and NEFA concentrations were higher during the second exercise bout, showing an enhancement of lipolysis in the AT. This enhanced lipolysis could be the direct consequence of the more pronounced epinephrine secretion. However, the exercise-induced reduction in plasma insulin concentration was also enhanced during the second exercise bout. It is well known that plasma insulin concentration decreases during exercise (21), reflecting the adrenergic-dependent inhibition of insulin secretion through activation of α2-AR located on the pancreatic β-cells (35). Epinephrine is the most efficient agonist for pancreatic α2-ARs (35). Thus the greater decrease in plasma insulin levels observed during the second bout of exercise, associated with the higher plasma epinephrine concentrations, could explain the observed higher lipolytic rate. There is no demonstration that a decrease of glucose uptake by fat cells leads to hormone-sensitive lipase activation and increased lipolysis.

Concerning local lipolytic responses in the subcutaneous AT (assessed by extracellular glycerol concentration), striking differences appeared in extracellular glycerol concentration in the presence of the α-AR antagonist phentolamine (Fig. 3). Extracellular glycerol concentration in AT (calculated from control probe A) was higher during the second exercise bout, suggesting an enhancement of the lipolytic rate in this tissue. This increased lipolytic response could be attributable to the higher plasma epinephrine levels observed during the second exercise, which reached the subcutaneous AT. Stalknecht et al. (37, 39) showed that, when epinephrine is infused intravenously in humans at doses giving plasma concentrations quite similar to those seen during exercise, its extracellular concentration in abdominal subcutaneous AT (evaluated by microdialysis) varies in parallel with the concentration measured in the plasma. Interestingly, one of the main results of our study is the finding that local α-adrenergic blockade enhances the glycerol output from AT (calculated from probe B perfused with phentolamine). This effect did not reach a significant level during the first exercise bout but was significant during the second. Plasma epinephrine concentrations were twofold higher during the second exercise than during the first, whereas the exercise-induced increase in plasma norepinephrine levels was similar. Thus the increased extracellular glycerol concentration in the presence of phentolamine could be due to the local suppression of the α2-adrenergic antilipolytic component of epinephrine on fat cells.

Local blood flow has been shown to influence glycerol levels in AT (12, 16). During exercise, the increase in extracellular glycerol concentration could be due to changes in blood flow in the AT. The measurement of ethanol escape through the dialysis probe is a validated nonquantitative method to estimate the changes in vascular tone in AT (2, 3, 16). In agreement with others (18, 36), the stability of the ethanol outflow-to-inflow ratio found in probe A during the two exercise bouts indicated that vascular tone was not changed during the exercise. It has previously been demonstrated that
β-AR stimulation increases and that α-AR stimulation decreases local blood flow in AT (2, 3, 16, 27, 34), whereas insulin (at various plasma levels realized by a multistage euglycemic hyperinsulinemic clamp) does not modify the local blood flow in AT (38). When the α-ARs were blocked by phentolamine (probe B), the exercise-induced decrease in the outflow-to-inflow ratio suggests an increase in blood flow in AT probably due to the β-adrenergic vasodilating component of catecholamine after α-AR blockade. It is a situation that could diminish glycerol output in the probes. Nevertheless, as shown in Fig. 4, the exercise-induced decrease in ethanol outflow/inflow was of similar amplitude during the two exercise bouts in the probe perfused with phentolamine. This suggests that the increase of interstitial glycerol in probe B (with phentolamine) was influenced in the same manner during the two exercise bouts and that the β-AR-induced vasodilation is quite similar in both conditions. Consequently, the higher response observed during the second exercise bout indicates an enhancement of β-adrenergically mediated lipolysis in AT, which is unmasked after blockade of α2-ARs. The disinhibition of lipolysis after α2-adrenergic blockade was higher during the second bout of exercise, i.e., in the situation of higher epinephrine levels. This suggests that epinephrine is the hormone responsible for the α2-mediated antilipolytic action during exercise.

Our study demonstrates the physiological relevance of β- and α2-AR interplay in the control of lipolysis in subcutaneous AT, during exercise in humans. The exercise-induced lipolysis has been shown to be specific in respect to region and gender (1, 18). Therefore, it is important to note that the results of the present study are specific for male subjects and for the subcutaneous abdominal region. The study suggests for the first time that epinephrine has a specific role in vivo in the control of lipolysis in human subcutaneous AT through activation of antilipolytic α2-ARs. It also updates numerous former in vitro studies that propose that the activation of α2-ARs by epinephrine could play an important role in the control of lipolysis in AT, specially in abdominal subcutaneous fat deposits (33, 19). If abdominal subcutaneous fat reflects what goes in the intra-abdominal fat, as proposed by some authors, it would be of interest to study the involvement and the importance of the epinephrine-induced β- vs. α2-AR activation in AT in obese subjects during exercise. The activation of antilipolytic α2-ARs by epinephrine could be an important inhibitory factor for lipid mobilization in subcutaneous AT in exercising obese subjects, the AT of which expresses a higher α2-AR component in vitro (32). This should be the subject of our forthcoming studies.

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