# Metabolic and Hormonal Responses to Adrenoceptor Antagonists in 48-Hour–Starved Exercising Rats

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**The influence of 48 hours of starvation on sympathoadrenal regulation of nutrient utilization was investigated in rats. To assess the role of α- and β-adrenoceptors, rats were studied during alpha- and beta-blockade. Energy metabolism was measured using indirect calorimetry before, during, and after moderate swimming exercise (~60% maximal $O_2$ consumption [$V_{O_2}max$]). Additionally, blood samples were taken for determination of nutrient and hormone concentrations. In 48-hour–starved rats, under baseline conditions, there was a reduction in energy expenditure (EE) accompanied by a shift toward fat oxidation (fat-ox) in comparison to fed rats. Exercise-induced responses in EE, fat-ox, and carbohydrate oxidation (CHO-ox) did not differ from those in fed rats. In starved rats, a stronger response to exercise of the sympathoadrenal system was observed. In comparison to control 48-hour–starved rats, blockade of α- and β-adrenoceptors led to a reduction in the exercise-induced increase in EE and fat-ox. The rate of CHO-ox was slightly reduced after blockade of either adrenoceptor type. Alpha-blockade prevented the exercise-induced increase in blood glucose. Plasma free fatty acid (FFA) was not affected. Blood lactate, plasma insulin, norepinephrine (NOR), and epinephrine (EPI) were increased after alpha-blockade. Due to beta-blockade, exercise-induced increases in glucose and FFA were prevented. Blood glucose even declined below the baseline value. EPI showed an exaggerated increase, and NOR showed a smaller increase. Results obtained in starved rats support the idea that alpha-adrenoceptor blockade–induced changes in energy metabolism are the result of a diminished oxygen supply due to diminished circulation. In the case of beta-blockade, changes in energy metabolism are mainly induced by a decrease in energy substrate availability.**



FORMER STUDIES in our laboratories showed that in rats, α- and β-adrenoceptors play an important part in the regulation of energy substrate and oxygen availability during exercise.[1,2] It was recognized that due to α-adrenoceptor stimulation, the sympathetic system partakes in redistribution of cardiac output to the working muscles by causing vasoconstriction in the visceral vascular bed.[1] In addition, hepatic glycogenolysis is increased by α-adrenoceptor stimulation.[3,4] β-Adrenoceptors have been shown to play an important part in the supply of nutrients, in addition to their function in the regulation of cardiac performance and distribution of systemic blood flow.[1,2] Stimulation of $\beta_2$- and $\beta_3$-adrenoceptors has been reported to result in increased rates of glycogenolysis in muscles[5] and of lipolysis in white adipose tissue,[6] respectively.

Exercise is accompanied by a strong activation of the sympathoadrenal system (for review, see Galbo[7] and Scheurink and Steffens[8]). In starved animals, the sympathoadrenal system may be stimulated even more than in fed rats to prevent hypoglycemia, with hepatic glycogen being nearly depleted.[9,10] Hepatic glycogen has been reported to be the major source of blood glucose.[11] Depletion of hepatic glycogen stores, as occurs during starvation, will therefore reduce the availability of blood glucose.[10] Since nonactive muscle cells in 48-hour food-deprived rats still contain 70% of the amount of glycogen present in muscle cells of nondeprived rats, glycogenolysis in these cells may contribute to save blood glucose.[10] The adrenal medulla may be stimulated because epinephrine (EPI) elicits glycogenolysis in muscle cells via its $\beta_2$-adrenoceptor effect.[5] Further depletion of hepatic glycogen stores during exercise in starved rats will therefore be prevented. In addition, lactate formed in active muscle cells may serve as an important precursor of glucose in the liver, which contributes also to save liver glycogen stores. The reduced blood glucose availability and increased free fatty acid (FFA) availability may result in a reduction in carbohydrate oxidation (CHO-ox).

Adrenoceptor blockade in starved rats may produce important information about the significance of hepatic glycogen in the supply of nutrients to the working muscles. This applies especially to beta-blockade, in which muscle glycogenolysis is prevented, leading to increased uptake from the blood to cover the need for glucose in muscle cells. Therefore, in this study the influence of 48 hours of starvation on sympathoadrenal regulation of energy metabolism during swimming exercise was investigated. Exercise was performed with and without blockade of α- or β-adrenoceptors. Energy metabolism was determined by indirect calorimetry under baseline conditions, during swimming, and during recovery. The contribution of CHO-ox and fat oxidation (fat-ox) to total energy expenditure (EE) was calculated from oxygen consumption ($V_{O_2}$) and carbon dioxide production ($V_{CO_2}$). In addition, blood samples were taken for determination of energy substrate and hormone concentrations.

## MATERIALS AND METHODS

### Animal Care and Surgery

Male Wistar rats weighing 375 to 425 g at the beginning of the study were used. They were housed individually in Plexiglas (Rohm & Haas, Philadelphia, PA) cages (25 × 25 × 30 cm) at room temperature (21° ± 2°C) and had continuous access to food (Hope Farms, Woerden, The Netherlands) and water unless otherwise stated. Animals were maintained on a 12-hour light-dark cycle (7

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*Submitted October 17, 1994; accepted February 16, 1995.*

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*0026-0495/95/4410-0018$03.00/0*

AM to 7 PM light) and were handled and weighed every morning at 9 AM. All animals were provided with an indwelling silicon catheter in the right jugular vein, with the tip at the entrance of the right atrium; the other end was externalized on top of the skull.[12] This method allows frequent sampling of well-mixed central venous blood in unanesthetized, undisturbed, freely moving rats.[13] Surgery was performed under ether anesthesia. Experiments started when the animals had regained preoperative body weight, but at least 1 week of recovery was allowed. To avoid novelty stress, rats were habituated to the experimental conditions in four to five training sessions, in which duration of the swimming exercise was gradually increased.[14,15]

### *Exercise and Gas Analysis*

The experiments were performed in an airtight Plexiglas swimming pool, which was provided with a metabolic chamber at its upper side.[16] The bottom of the chamber was a movable resting platform that could be lowered to the bottom of the pool, so that the rat was forced to swim for keeping its head in the metabolic chamber. During swimming, a water current of 0.22 m/s was maintained. The temperature of the water was 32° ± 1°C. Untreated, fed rats swimming under these conditions perform at a level of approximately 60% maximal $\dot{V}O_2$ ($\dot{V}O_2max$).[16] Airflow through the metabolic chamber was 4.5 L/min. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured using an $O_2$ analyzer (Ametek S3A, Pittsburgh, PA) and a mass spectrometer (Balzers QMG 511, Liechtenstein), respectively, combined with a gas flow meter. Before each experiment, the measuring system was calibrated as described previously.[16] In studies using indirect calorimetry, degradation of proteins can be calculated from nitrogen excreted with urine. In short-term experiments and especially during swimming, collection of urine is hardly possible. Therefore, EE, CHO-ox, and fat-ox were calculated according to the method reported by Lusk,[17] without taking proteins into account. Although this procedure introduces a slight error in the absolute rates of EE, CHO-ox, and fat-ox, changes in these quantities are reliably measured, as shown, for instance, in the determination of exercise- and drug-induced changes.[1,16]

### *Blood Sampling and Chemical Determinations*

During an experiment, 18 blood samples of 0.7 mL were withdrawn for determination of glucose and lactate concentrations in whole blood and concentrations of FFA, insulin, EPI, and norepinephrine (NOR) in plasma. For blood sampling, a polyethylene tube (length 400 mm, OD 1.25 mm, and ID 0.75 mm) was connected to the outlet of the catheter, pierced through a passage in the hood of the metabolic chamber, and sealed airtight with modeling clay. After a sample was taken, 0.7 mL citrated (0.6% citrate) blood obtained from permanently cannulated, 48-hour–starved donor rats was reinfused. Between withdrawal of successive blood samples, the tip of the catheter was filled with 6% citrate solution as an anticoagulant; citrate was used instead of heparin to avoid activation of endothelial lipase.

After withdrawal, blood samples were transferred to chilled (0°C) centrifuge tubes containing 11 μL EDTA solution (70 g/L) as anticoagulant and antioxidant. Blood glucose was determined by an enzymatic photometric method (Sigma, St Louis, MO) using 75 μL blood. Lactate level was measured by an automated enzymatic method in 20 μL blood (Kontron 640, Milan, Italy). The remaining blood was centrifuged for 12 minutes at 2,600 × *g* and 4°C. Plasma (100 μL) was taken for determination of EPI and NOR and stored at −80°C till handling. Catecholamines were determined by high-performance liquid chromatography with electrochemical detection.[18] The remaining plasma was stored at −30°C until further handling. FFA level was measured in 25 μL plasma by an enzymatic photometric method (WAKO, Osaka, Japan). Rat-specific plasma immunoreactive insulin was determined by means of a radioimmunoassay (NOVO, Copenhagen, Denmark), and guinea pig serum M8309 served as antiserum. Duplicate assays were performed on 25-μL plasma samples. Bound and free $^{125}$I-labeled insulin was separated using a polyethylene glycol solution.[19]

### *Adrenoceptor Antagonists*

Phentolamine (Regitine; Ciba Geigy, Basel, Switzerland) in a total dose of 0.9 mg and timolol (Merck, Sharp, & Dohme, Rahway, NJ) in a total dose of 0.7 mg were used as alpha- and beta-blocking agents, respectively. These doses result in effective blockade of peripheral α- and β-adrenoceptors.[1,2] The blocking agents were administered together with donor blood after blood sampling at the points in time and in the amounts shown in Fig 1. Animals received the α-blocker, β-blocker, or solvent, saline (9 g/L), in random order with at least 1 week between consecutive experiments.

### *Experimental Protocol*

Approximately 48 hours before the start of an experiment, food was removed from the animal's home cage. On an experimental day, gas analyzers were calibrated first, and then the animal was placed into the metabolic chamber on top of the swimming pool and connected to the polyethylene tube for blood sampling. The experiment was started when both $\dot{V}O_2$ and $\dot{V}CO_2$ had stabilized. This took approximately 1.5 hours. At time 0, the platform was lowered to the bottom of the swimming pool, forcing the rat to swim. At 20 minutes, the platform was raised to enable the rat to leave the water. An infrared lamp was switched on to prevent cold stress. Blood samples were taken to determine hormone and energy substrate concentrations under baseline conditions, during exercise, and during recovery at the points in time shown in Fig 1. Experiments were performed between 12 noon and 4 PM, ie, in the light period.

### *Statistics*

Data obtained in starved rats without adrenoceptor blockade are expressed as the mean value over 10-minute periods. These data are compared with data obtained in fed rats taken from an earlier report.[16] For comparison of data obtained after adrenoceptor blockade with data obtained without adrenoceptor blockade, data are expressed as the mean change ± SE over 10-minute periods, taking the values in period $t = 20 - 11$ minutes (ie, period −2, Fig 1) before swimming as the baseline. ANOVA and the Mann-

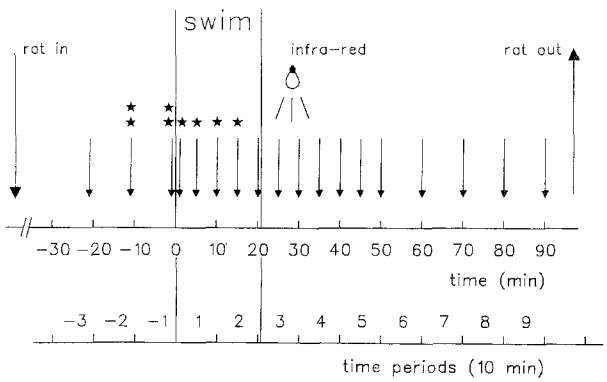


**Fig 1. Experimental protocol. Arrows denote withdrawal of blood samples. *Donation of 12.5% of the total dose of the blocking agent.**

Whitney $U$ test were applied to determine any differences between experiments. Within an experiment, Wilcoxon's matched-pairs signed-rank test was used to compare data obtained at each moment relative to the baseline level at $t = -11$ minutes for blood components or period −2 (Fig 1) for data obtained by indirect calorimetry. The level of significance was set at $P$ less than .05.

## RESULTS

### *Influence of Starvation*

Results obtained in starved rats are presented in Table 1 and Figs 2, 3, and 4 in comparison to those obtained in ad libitum–fed rats presented in a previous report.[16] Under baseline conditions, the starved group of animals had a lower rate of EE than the fed group. The rate of fat-ox was significantly increased in the starved group, and the rate of CHO-ox was significantly decreased. Blood glucose and lactate concentrations were lower after 48 hours of starvation, and plasma FFA was higher. NOR was decreased under baseline conditions, but this decrease only reached the level of significance in period −1. Insulin was decreased after starvation.

During steady-state exercise, ie, period 2 during swimming, no difference in EE between the two groups was observed. The exercise-induced increase in CHO-ox and fat-ox was similar in the two groups. However, the net rate of CHO-ox remained significantly lower in the starved group, and fat-ox remained higher. Blood glucose increased less during swimming in the starved group than in the fed group. The exercise-induced increase in lactate, FFA, EPI, and NOR was more pronounced in the starved group. In the starved group, no exercise-induced effect on insulin was recognized. In the fed group, insulin decreased to the level of the starved group.

During recovery, EE was similar in the two groups, except for period 9, in which EE was significantly higher in the fed group. As in baseline conditions and during swimming, CHO-ox was lower and fat-ox higher after starvation. In both groups, blood glucose and plasma FFA returned to baseline values. Lactate was significantly higher during steady-state swimming and the first two periods of recovery in the starved group than in the fed group. In the last period of the experiment, lactate was decreased in comparison to levels in the fed group. As in baseline conditions, insulin was lower after starvation than in fed animals.

### *Influence of Adrenoceptor Blockade After Starvation*

Baseline values (±SE) for EE, CHO-ox, fat-ox, blood glucose and lactate, plasma FFA, EPI, NOR, and insulin for the experiments with alpha- or beta-adrenoceptor blockade are presented in Table 1. Results obtained after adrenoceptor blockade were compared with results obtained in 48-hour–starved rats without adrenoceptor blockade. No significant differences between baseline values of the groups with adrenoceptor blockade and the control group were found, except for the lower plasma insulin concentration in the experiment with beta-blockade. Results obtained during the exercise period are shown in Figs 5, 6, and 7. In Fig 5 are presented the mean changes (±SE) from baseline for EE, CHO-ox, and fat-ox, in Fig 6 the mean changes in blood glucose, plasma lactate, and FFA, and in Fig 7 the mean changes in plasma EPI, NOR, and insulin in the control experiment and in experiments with peripheral alpha- or beta-adrenoceptor blockade.

Blockade of α-adrenoceptors caused a significantly reduced increase in EE during swimming and the first three periods thereafter in comparison to the experiment in starved rats without adrenoceptor blockade (Fig 5). No significant differences were observed for CHO-ox during steady-state swimming (period 2). The exercise-induced increase in fat-ox was significantly reduced (period 2). It remained reduced for the first three periods of recovery. In period 9, fat-ox was significantly higher than it was without adrenoceptor blockade. Blood glucose (Fig 6) was significantly lower than in the control experiment in periods 2 through 6. Lactate showed an extra increase after alpha-blockade from period 2 throughout the experiment. Plasma FFA levels were significantly increased in period −1 and significantly decreased in periods 3 through 6. Alpha-

**Table 1. Baseline Values of EE, CHO-ox, Fat-ox, Blood Glucose, Blood Lactate, Plasma FFA, Plasma Catecholamines, and Plasma Insulin**

| Variable | Fed Control (n = 17) | 48-Hour–Starved Control (n = 10) | β-Blockade (n = 9) | α-Blockade (n = 8) |
|---|---|---|---|---|
| EE (W/kg) | 5.27 ± 0.13 | 4.46 ± 0.13* | | |
| | | 4.91 ± 0.14 | 4.75 ± 0.16 | 4.89 ± 0.16 |
| CHO-ox (mg/kg · min) | 8.5 ± 0.8 | 0.5 ± 0.3* | | |
| | | 0.5 ± 0.4 | 0.1 ± 0.2 | 0.4 ± 0.4 |
| Fat-ox (mg/kg · min) | 4.4 ± 0.3 | 6.8 ± 0.2* | | |
| | | 7.4 ± 0.3 | 7.4 ± 0.3 | 7.5 ± 0.2 |
| Glucose (mmol/L) | 6.08 ± 0.14 | 4.34 ± 0.16 | 4.09 ± 0.16 | 4.54 ± 0.28 |
| FFA (mmol/L) | 0.32 ± 0.0 | 0.67 ± 0.04 | 0.69 ± 0.04 | 0.69 ± 0.04 |
| Lactate (mmol/L) | 1.2 ± 0.1 | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.8 ± 0.1 |
| EPI (ng/L) | 22 ± 3 | 43 ± 8 | 34 ± 8 | 53 ± 13 |
| NOR (ng/L) | 136 ± 37 | 80 ± 23 | 87 ± 14 | 101 ± 21 |
| Insulin (mU/L) | 47 ± 4 | 25 ± 4 | 15 ± 3 | 28 ± 5 |

NOTE. Values are the mean ± SE measured in period −2, ie, 20 − 11 minutes before swimming, for data obtained by indirect calorimetry. Values for concentrations of energy substrates, catecholamines, and insulin are the mean ± SE obtained at $t = -11$ minutes. Data for the control group are derived from a previously published study.[16]

*Values calculated with the animal's body weight before the starvation period.

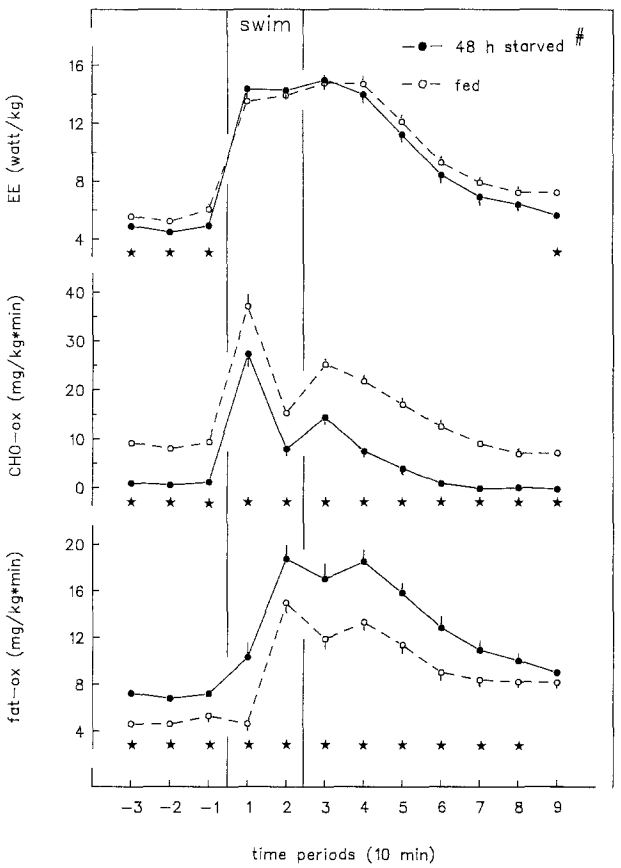


**Fig 2. Effect of 48 hours of starvation on EE, CHO-ox, and fat-ox in comparison to levels in ad libitum–fed rats. Data presented for the control group are derived from a previously published study.[16] Data are expressed as the mean ± SE over 10-minute time intervals. #Values calculated with the animal's body weight before the period of starvation. *Significant differences in comparison to the control experiment ($P < .05$).**

adrenoceptor blockade led to a significantly more pronounced exercise-induced increase in EPI (Fig 7). EPI remained significantly augmented throughout the experiment. NOR was significantly increased in comparison to the experiment without adrenoceptor blockade in periods 1 through 9. Insulin was significantly increased, in comparison to the baseline level and the control experiment, from the first injection of the α-blocker (period −1) till period 7.

In comparison to the experiment in starved rats without adrenoceptor blockade, beta-blockade caused a significantly reduced increase in EE during swimming (periods 1 and 2) and in periods 3 through 6 and 8 during recovery (Fig 5). The increase in CHO-ox was significantly reduced in the experiment with beta-blockade in comparison to the control experiment in periods 1, 3, 4, and 5. After beta-blockade, fat-ox was lower than in the control experiment in periods 2 through 6 and 8. Blood glucose was lower after beta-blockade than in the control experiment in periods 1 through 5 (Fig 6). The exercise-induced increase in FFA was prevented after beta-blockade. After swimming, FFA remained lower than in the control experiment for another two periods. Beta-adrenoceptor blockade led to a significantly more pronounced increase in EPI (Fig 7). EPI remained augmented throughout the experiment. NOR showed a reduced increase in periods 1 through 4 of the experiment with beta-blockade. Insulin showed no decrease from the baseline level during exercise after beta-blockade.

## DISCUSSION

### *Starvation*

Data obtained by indirect calorimetry used for the comparison between fed and starved rats were calculated using body weights of the animals before the period of starvation. This enables a fair comparison between starved and fed animals to be made, since the decline in body mass during 48 hours of starvation is mainly due to the loss of nonmetabolizing mass (feces, water, and fat).[20] The mean loss in body mass was 9.1% of the prestarvation mass. Data obtained by indirect calorimetry used to identify changes induced by adrenoceptor blockade were calculated using body weights of the animals after starvation, ie, actual body weights at the beginning of the experiment.

Starvation for 48 hours resulted in a slight decrease in EE under baseline conditions. The rate of fat-ox was increased, and CHO-ox was decreased. Concentrations of blood glucose and lactate were decreased, whereas plasma FFA

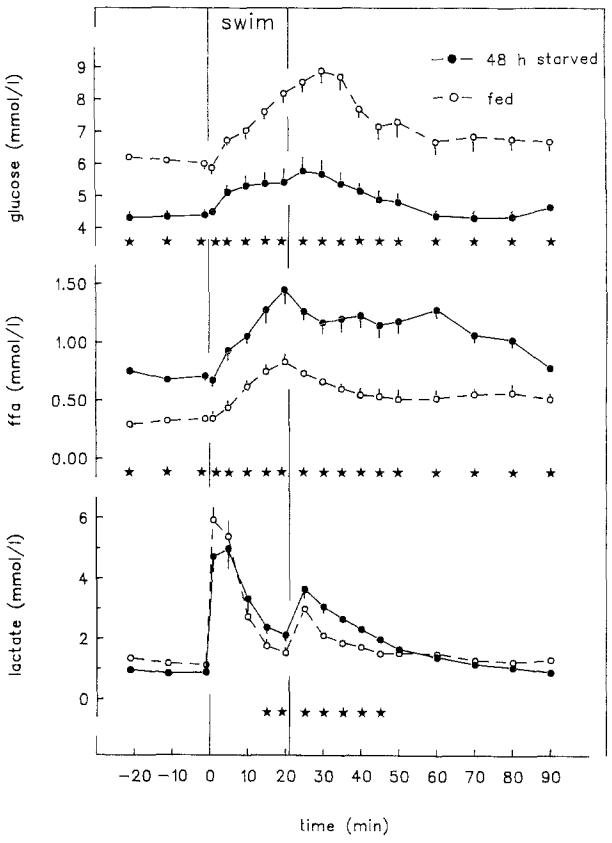


**Fig 3. Effect of 48 hours of starvation on glucose, FFA, and lactate concentrations. Data presented for the control group are derived from a previously published study.[16] Data are expressed as the mean ± SE. *Significant differences in comparison to ad libitum–fed rats ($P < .05$).**

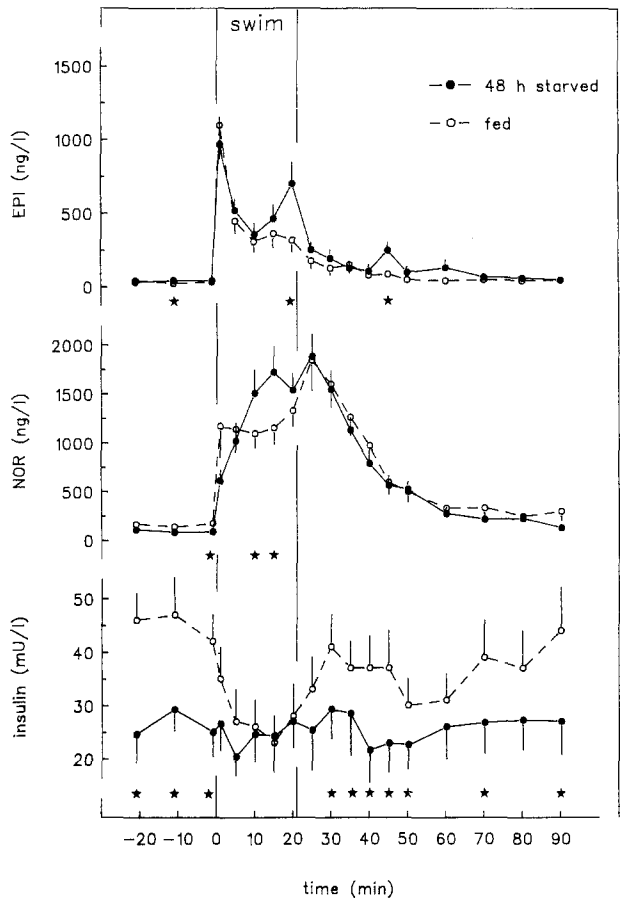


**Fig 4. Effect of 48 hours of starvation on NOR, EPI, and insulin concentrations. Data are expressed as in Fig 3.**

was increased. Baseline concentrations of NOR were slightly decreased, and EPI was not affected. Insulin was decreased after starvation.

The observed changes in baseline energy metabolism may be the result of a decreased setpoint for body temperature.[20] In addition to this reduction in body temperature, the starvation-induced decrease in insulin concentration may play an important part, with insulin being a stimulator of EE.[21] The starvation-induced decrease in insulin may be the result of decreased insulin release from pancreatic β cells due to the absence of stimulation by the effects of food intake[22] and to a starvation-induced decrease in β-cell responsiveness.[23] Since insulin has a strong antilipolytic action and is a potent stimulus for FFA uptake by adipose tissue,[24] the decrease in insulin after fasting may explain the elevated plasma FFA concentration. Another consequence of starvation is an increase in the basal rate of lipolysis in white adipose tissue,[24,25] which also increases FFA concentration. Since availability of FFA under baseline conditions determines its utilization,[26,27] the rate of fat-ox increases during starvation. Consequently, blood glucose, the main energy source for the central nervous system, is spared.

Exercise-induced increases in EE, CHO-ox, and fat-ox (Fig 2) are similar in both groups of animals. Thus, it appears that exercise-induced changes in energy metabolism are superimposed on baseline metabolism. The reduced blood glucose concentration seems to have no effect on the exercise-induced increase in CHO-ox. Sonne et al[10] reported a decrease in blood glucose turnover in 48-hour–fasted running rats, showing that the exercise-induced demand for carbohydrates may be satisfied by an increased rate of muscle glycogenolysis. After 48 hours of food deprivation, the liver is nearly depleted of glycogen. Muscle cells, on the other hand, still contain a considerable amount of glycogen, which may serve as a carbohydrate source. Muscular glycogenolysis is apart from the contraction-related $Ca^{2+}$ release dependent on stimulation of $\beta_2$-adrenoceptors on the cell membrane.[5] EPI, a potent $\beta_2$-adrenoceptor agonist, is increased during swimming after starvation in comparison to levels in the fed group and causes muscle glycogenolysis. The increase in muscle glycogenolysis, both in active[28] and inactive[29,30] muscle groups, leads to increased lactate production, as indicated by increased plasma lactate levels in the second period of

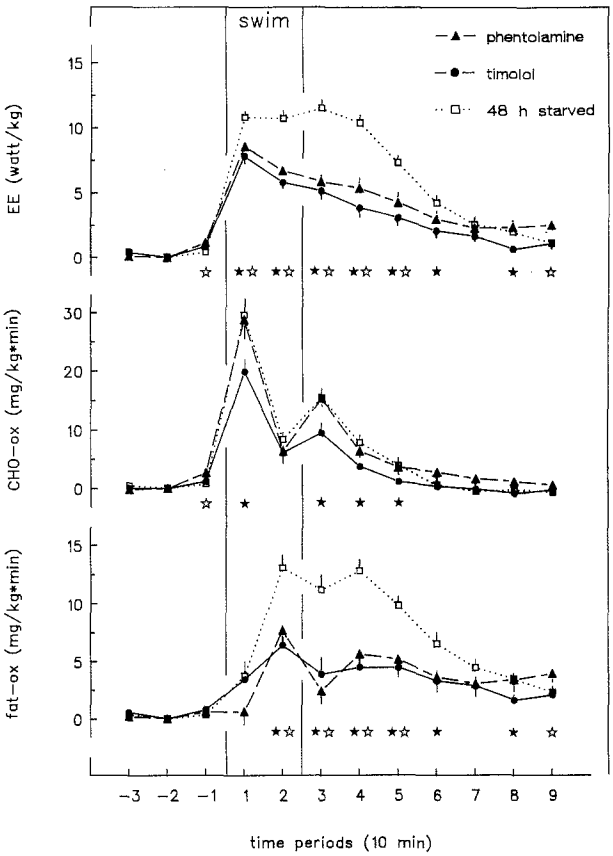


**Fig 5. Effect of intravenous administration of the α-adrenoceptor antagonist phentolamine (0.9 mg) and the β-adrenoceptor antagonist timolol (0.7 mg) on EE, CHO-ox, and fat-ox in 48-hour–starved rats versus untreated 48-hour–starved rats. Data are expressed as the mean change ± SE over 10-minute periods (Fig 1) from baseline levels. Baseline levels were measured over period −2, ie, 20 11 minutes before swimming, and before any blocking agent was administered. Open and closed asterisks denote significant differences between experiments with alpha-blockade and control experiments and between experiments with beta-blockade and control experiments, respectively ($P < .05$).**

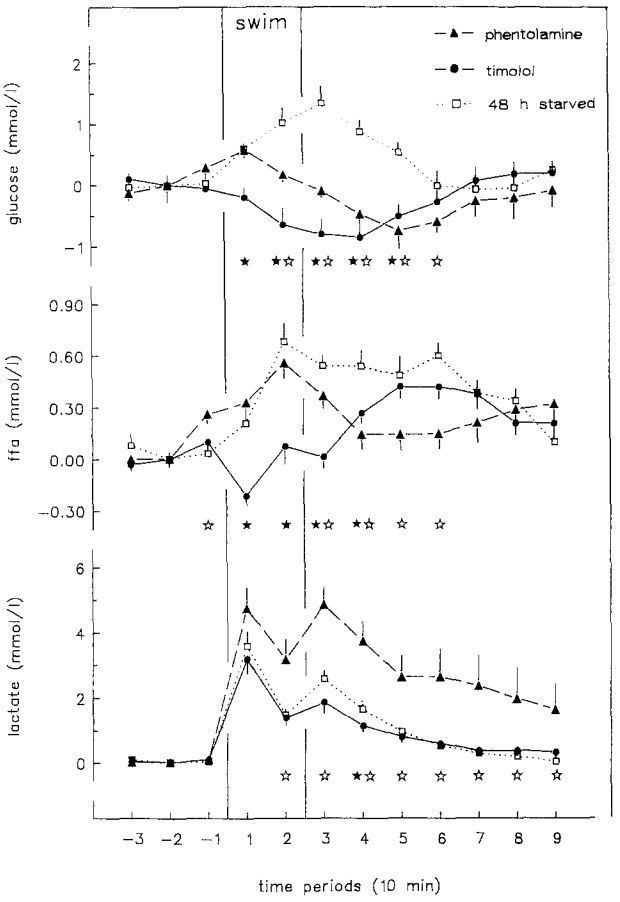


**Fig 6. Effect of intravenous administration of the α-adrenoceptor antagonist phentolamine (0.9 mg) and the β-adrenoceptor antagonist timolol (0.7 mg) on blood glucose and lactate and plasma FFA in 48-hour–starved rats as compared with untreated 48-hour–starved rats. Data are expressed as in Fig 5.**

swimming. This lactate serves as the main gluconeogenetic substrate in exercise,[31,32] and since renal glucose production is negligible in rats, it serves as an important factor in replenishing the nearly depleted hepatic glycogen stores.[9,10]

NOR was decreased under baseline conditions in the starved group, indicating decreased sympathetic output. This is in fair agreement with data reported in the literature.[33-35] EPI shows a slight but statistically nonsignificant response to fasting under baseline conditions. This agrees with the view that EPI may be regarded as a reflection of physiological or emotional stress, whereas NOR might be a reflection of sympathetic nervous activity.[34,36] During swimming, EPI and NOR were increased in comparison to the control experiment. EPI is known to increase blood glucose concentration.[37] It may act either directly by stimulation of hepatic glycogenolysis or indirectly through stimulation of glucagon secretion,[38] or by stimulating muscle glycogenolysis,[7,29,39] which saves blood glucose. NOR elicits lipolysis, leading to an increase in plasma FFA.[37]

*Adrenoceptor Blockade After Starvation*

As we have observed previously in fed rats,[1] adrenoceptor blockade in starved rats leads to a reduction in the exercise-induced increase in EE (Fig 5). In a former study in fed rats, we observed that the decrease in EE was accompanied by an increase in CHO-ox and a reduced exercise-induced increase in fat-ox.[1] However, in starved rats, no augmented increase in CHO-ox was observed either in the experiment with alpha-blockade or in the experiment with beta-blockade. The exercise-induced increase in CHO-ox in starved rats was slightly but not significantly reduced after blockade of either of the adrenoceptor types.

Beta-blockade in starved rats led to the same alterations in exercise-induced energy metabolism as observed after beta-blockade in fed rats, except for the reduced increase in CHO-ox.[1] However, exercise-induced changes in concentrations of circulating hormones and nutrients showed remarkable differences. Compared with beta-blockade in fed rats, beta-blockade in starved rats led to a lower blood glucose concentration during swimming, and glucose even declined to a level less than baseline. The low blood glucose concentration in starved beta-blocked rats was accompanied by a more pronounced increase in EPI than in fed beta-blocked rats (2,518 ± 801 *v* 670 ± 170 ng/L[1]). The decrease in FFA was less pronounced. These starvation-

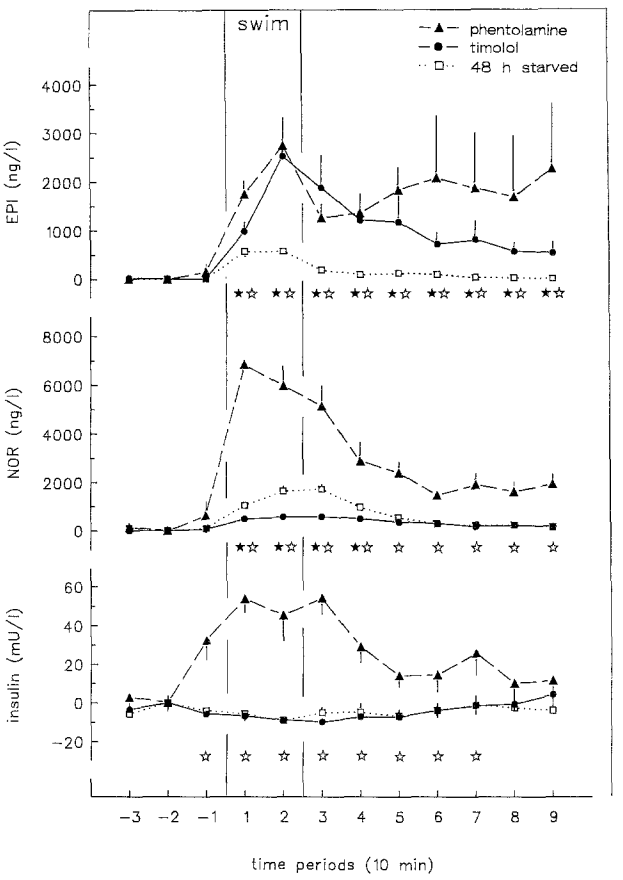


**Fig 7. Effect of intravenous administration of the α-adrenoceptor antagonist phentolamine (0.9 mg) and the β-adrenoceptor antagonist timolol (0.7 mg) on plasma EPI, NOR, and insulin in 48-hour–starved rats as compared with untreated 48-hour–starved rats. Data are expressed as in Fig 5.**

induced alterations support the idea that in fed rats during exercise after beta-blockade, hepatic glycogen is a major source of fuel, with lipolysis in white adipose tissue and muscle glycogenolysis then being diminished.[1,2] In fed control rats, hepatic glycogenolysis has been reported to be of minor importance for energy supply to the working muscle during exercise of less than 1 hour.[40,41]

The reduced availability of blood glucose after beta-blockade will induce the increased response in EPI, with glucose decreasing to less than the starvation-induced baseline (Figs 6 and 7). Despite the increased EPI concentration and the low blood glucose concentration, insulin did not decrease more than it did during exercise in starved control rats. In fed rats treated with a β-blocker, we found that during swimming insulin declined more than in the control experiment,[1] indicating that during exercise insulin release is stimulated by a β-adrenoceptor mechanism. The observation that insulin does not show an extra decline during exercise after β-exercise in starved rats raises the idea that during fasting insulin decreases to a level just high enough to ensure a necessary minimal glucose uptake by insulin-dependent tissue. The fact that plasma FFA increased from a minimal level in period 1 might indicate that a shortage of fuel was noted in either the periphery or central nervous system and that counterregulating mechanisms were activated. Underlying mechanisms for these starvation-induced effects of β-blockade might be found in altered adrenoceptor responses or in altered concentrations of glucagon and corticosteroids.[33,38]

Related to alpha-blockade in fed rats, alpha-blockade in starved rats led to almost the same alterations in concentrations of circulating nutrients and hormones.[1] NOR shows an exaggerated increase during swimming after alpha-blockade, due to blockade of prejunctional $\alpha_2$-adrenoceptors.[42,43] The increase in insulin after the first injection of the alpha-blocker phentolamine is in accordance with the view that even under baseline conditions the release of insulin is actively inhibited by α-adrenergic action on pancreatic β cells.[44,45] Alpha-blockade in starved rats did not lead to significant alterations in substrate utilization and EE as compared with alpha-blockade in fed rats. These results support the idea that the alpha-adrenoceptor blockade–induced decrease in EE is mainly the result of alterations in circulatory rather than nutritional parameters, as we described previously.[1]

In summary, starvation leads to considerable alterations in energy metabolism under baseline conditions. Exercise-induced metabolism appears not to be influenced by starvation, at least not during exercise at a level of 60% $V_{O_2}$max. In relation to exercise in fed rats, both EPI and NOR show an exaggerated increase during steady-state swimming. Adrenoceptor blockade in starved rats during steady-state exercise led to a reduction in CHO-ox as compared with exercise during adrenoceptor blockade in fed rats. This may mainly be caused by an insufficient availability of blood glucose. The shortage in blood glucose was most obvious after beta-adrenoceptor blockade. The results support the idea that alpha-adrenoceptor blockade–induced changes in energy metabolism are the result of a diminished oxygen supply, whereas in the case of beta-blockade, changes in energy metabolism are mainly the result of a decrease in energy substrate availability.

## ACKNOWLEDGMENT

The authors thank Gerrit Mook for critically reading the manuscript, Piet Schiphof for taking good care of the animals, Wilma Meeuwsen for analytical assistance, Rob Coppes (Department of Pharmacology and Therapeutics) for determination of catecholamine concentrations, and Marianne Brunsting for preparation of the figures.

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