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organisms/100 g BW and then fasted. Rats were studied immediately following a swim to exhaustion at 72 h postinoculation and onset of fast. Results indicate that training did not alter disease-related mortality or alleviate the infection-induced decrement in performance. Metabolically, training only blunted the effects of acute exercise, but did not change the infection-induced alteration. Trained rats were less susceptible to the exercise stress, while their performance capacity was more sensitive to the debilitating effects of the infection than untrained rats.

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Exercise-induced changes in metabolic responses to infection
in trained rats

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Running Title: EXERCISE AND INFECTION IN TRAINED RATS

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Send request for reprints to Dr. Crawford.

Abstract

Previous studies have demonstrated that swimming performance was reduced during bacterial infection. Studies were performed to determine whether endurance training alters performance related energy metabolism during Streptococcus pneumoniae infection in trained and untrained rats. Trained rats swam a 5-day/week for 4 weeks. Swim periods were increased daily by 10-min increments from an initial 10 min to 2 h in the second week, and continued for the 2 remaining weeks. Rats were inoculated with 10^2 live or heat-killed organisms/100 g BW and then fasted. Rats were studied immediately following a swim to exhaustion at 72 h postinoculation and onset of fast. Results indicate that training did not alter disease-related mortality or alleviate the infection-induced decrement in performance. Metabolically, training only blunted the effects of acute exercise, but did not change the infection-induced alteration. Trained rats were less susceptible to the exercise stress, while their performance capacity was more sensitive to the debilitating effects of the infection than untrained rats.

Key Words: Swimming; endurance; training; performance capacity; exercise; infection; energy metabolism; oxygen consumption; glycogen; glucose; free fatty acids; ketone bodies; insulin; glucagon.

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ENDURANCE TRAINING increases maximum performance capacity by improving metabolic and cardiovascular functions (9, 13, 17, 29). Scheuer (29) and others (4) have hypothesized that training may afford protection against the debilitating effects of certain disorders. Literature is sparse in providing proof that conditioning has a protective effect, but indirect evidence favors this conclusion. These results cannot be extrapolated to diseases in general because bacterial infections have not been studied in the trained host.

Preliminary studies (5, 6, 10) have established a rat model for investigating the impact of acute exercise during bacterial infections. Using untrained rats, it was found that the combined stresses apparently increased disease-related mortality and reduced performance capacity. However, repeated sessions of exercise during the acute phase of the infection limited this reduction substantially and indicated that daily exercise evoked a training response even during the stress of infection (6, 10). Further studies are needed to clarify this phenomenon and determine if physiological-biochemical or psychological mechanisms are responsible.

Metabolically, pneumococcal infection has been shown to cause depletion of glycogen stores, hyperglycemia, hypolipidemia, inhibition of ketone body accumulation and increased circulating plasma insulin and glucagon in the fasted rats (3, 24, 33). Swimming superimposed on infection and associated anorexia exaggerated these aberrations (6).

Repeated swim sessions have resulted in a number of long term adjustments in energy substrate levels in the resting rats and in its response to acute exercise. This training appeared to induce adaptations in two ways; by an increased storage of energy substrates and

by an increased ability to utilize available fuels during strenuous exercise (29). Using trained rats, investigators have suggested there is a large increase in the oxidative metabolism and cardiovascular adjustments (29), thus causing lower blood lactate values (9), slower rates of muscle and hepatic glycogen depletion (13), free fatty acid (FFA) and ketone body oxidation (1, 34) with diminished hormonal responses (13, 16) to acute exercise in trained rats.

The purpose of this study was to determine if physical training was beneficial or detrimental to the rat by altering disease-related mortality, swimming performance, and energy substrate utilization during Streptococcus pneumoniae infection.

MATERIALS AND METHODS

Animals. Male, Fisher-Dunning rats (F-344/Mai f, Microbiological Associates, Walkersville, MD) weighing initially 175-200 g were utilized in these studies. Rats were maintained on a commercial diet (Wayne Lab-Blox, Allied Mills, Inc., Chicago, IL) until the beginning of the experiment. Animals were housed 5 rats/cage in rooms maintained on 0600-1800 h light cycle at $23 \pm 1^\circ\text{C}$ with food and water ad libitum. All rats were acclimatized for at least 7 days prior to experimentation. Rats were randomly divided into four treatment groups (30 rats/group) designated as untrained-fasted-noninfected, untrained-fasted-infected, trained-fasted-noninfected and trained-fasted-infected animals.

Training program. Rats were subjected to a 4 week endurance training program which consisted of swimming for specified periods in steel barrels filled with tap water to a depth of 55 cm and maintained between 33 and 35°C. On the first day of training, the rats were individually introduced to the swimming task with a 5 min swim. Only

10% of the rats tested were unable to swim during this initial test and were not used in these studies. Daily exercise periods following this introductory swim were administered by placing 5 rats together in one barrel. This procedure was used to insure vigorous activity and to discourage effortless floating which is sometimes observed. Weights were not attached to the exercising rats in this study. The first session of group swimming was 10 mins in duration. Subsequent daily swim periods were increased 10 mins per day until 120-mins was reached on the second week. Thereafter, trained rats swam once a day, 5 days per week between 0800-1200 h. All training exercise was closely monitored by an experienced technician to avoid accidental drownings.

Infection model. Ninety-six hours after completion of the endurance exercise program, both untrained and trained rats were inoculated subcutaneously (sc in the groin pouch) with 10^2 virulent colony forming units (CFU) of S. pneumoniae, type I, strain A5 per 100 g BW. Noninfected-trained and -untrained rats were injected with an equal number of heat-killed organisms. Following inoculation with bacteria all rats were fasted and allowed to rest until required to perform an exercise test.

Since trained rats consume less food than sedentary controls it was necessary to pair-feed sedentary rats to the food intake of their trained counterparts. To accomplish this, the food consumption of trained rats was monitored for a 2 day period on the second week of the training program and amount of food was adjusted to this value for untrained groups.

Exercise test. Pair weighed trained- and untrained-infected and noninfected rats (15 per group) were forced to swim continuously to the point of exhaustion. Exhaustion was taken as 10 sec below the water surface, at which point the rats were immediately removed from the barrel by the attending technician. The duration of exercise was timed for each

rat tested. Unloaded rats were studied at 24, 48, and 72 h postinoculation, immediately following exercise, and always between 0800-1200 h in order to eliminate circadian variations. Results will only be presented for the 72 h time point for simplicity, since these illustrate the most dramatic effects of the combined stresses on metabolic responses.

Exercise intensity. The strenuousness or intensity of an exercise session was monitored by a closed circuit procedure similar to a previously described system (22, 23). Mean O_2 uptake was obtained for wet rats (N=4) in a separate study using the same treatment groups as outlined above. Each rat served as its own control. Measurements were recorded prior to and again immediately following swim to exhaustion for noninfected rats and infected animals. The chamber (Volume 4.7 L) provided quick equilibration and measurements made for 15 min immediately postexercise using a 1-liter Collins spirometer. Air flow was regulated at a rate of 4.35 ± 0.04 L/ min (STPD) via a calibrated Collins vacuum motor blower. A Lab-Crest flowmeter measured the air flow through the pump. Calculations were adjusted to take water vapor pressure and body temperature differences of wet rats (23, 26).

Blood and tissue samples. Samples were acquired from each rat and treated individually. Blood samples were acquired from halothane anesthetized rats by thoractomy, incision of vena cave and collected in heparinized pipettes. Blood (8 ml) was obtained from sedentary rats and in exercise tested groups within 2 min after completion of the endurance test swim. Blood was placed in 15 ml polypropylene tubes; a 500- μ l aliquot was withdrawn and deproteinized separately in 500- μ l of 10% trichloroacetic acid to prevent lactate degradation; and a 1-ml aliquot was delivered to 5-ml polypropylene tubes containing 50 μ l aprotinin (Trasylol, FBA Pharmaceutical, New York, 10,000 kallikrein inactivator units/ml) to

prevent proteolysis of glucagon. The remaining heparinized blood samples were centrifuged, and the plasma was stored at -20°C until analysis.

Tissue samples (approximately 1 g) from heart, liver and gastrocnemius muscle were quickly excised (within 1 min of anesthesia) and placed in pre-weighed glass test tubes containing 30% potassium hydroxide (KOH) at 90°C . Tubes were heated to 100°C for 2 h to dissolve tissue for glycogen assay. The viscera and skin were removed, carcass weighed, cut into small pieces, ground in Waring blender containing warm 30% KOH. Resulting suspensions were placed in beakers which were placed in boiling water for 2 h. A 4-ml aliquot of the solution was assayed for glycogen content (31).

Analytic procedures. Previously published procedures were utilized for the determination of glycogen (15) as modified by Sobocinski (30), plasma glucose (12), FFA (8), ketone bodies (21) and plasma zinc (27). The plasma levels of insulin and glucagon were measured by method and insulin:glucagon molar ratio calculated using a published procedure (23). Whole blood lactate was analyzed by a semi-automated fluorimetric method (18).

Statistical analysis. Data were analyzed by unpaired two-way analysis of variance (ANOVA). A P value of < 0.01 was considered significant under the null hypothesis between trained vs. untrained and infected vs. noninfected rats. Data are presented as a mean $\pm$ SEM for at least 15 rats per group.

RESULTS

Infection. The progress of the infection was followed by alteration in plasma zinc concentrations and rectal temperature as previously described (24, 33). Rectal temperature were obtained immediately prior to bout of

exercise. Marked depression in plasma zinc (Fig. 1) and fever were noted at 24 h postinoculation and remained altered throughout the 72 h study. Both trained and untrained rats inoculated with viable S. pneumoniae responded similarly. Mortality of 48% were observed in trained- and untrained-infected rats at 72 h time point.

Swimming performance. The influence of a 72 h fast and infection on endurance of trained and untrained rats are presented in Table 1. The mean maximum performance capacity of swim task adaptable Fisher-Dunning rats has been found to be 300 ± 15 min (5). Prolonged fasting reduced the work maximum 45% in the untrained- and only 8% in the trained-noninfected animals. These percentages are further increased by sepsis. Endurance was decreased 76% from fasted -noninfected untrained times, if pneumococcal infection was present in these rats. Prior training improved this infection-induced decrement by 41%, but data indicates that the infection had more of a detrimental effect on the trained rats' performance.

Oxygen consumption. Table 2 summarized the effects of a swim to exhaustion during an acute febrile infection in trained vs. untrained rats. Basal rates of VO_2 has been reported in between 14-20 ml/kg·min⁻¹ in fed healthy rats (20). Previous studies (6) have demonstrated that fasting reduced mean O_2 consumption, while infection initially increase O_2 uptake giving way to lowered uptake. Strenuous swimming exercise elevated oxidative processes (20). Data (Table 2) indicates that mean VO_2 was relatively unaltered when untrained-infected rats were compared to their trained counterparts following exhaustion. The average VO_2 max of a separate 10 healthy fed rats showed a slight increase from 76.3 ± 2.8 to 81.0 ± 3.4 ml/kg·min⁻¹ (representing a 6% increase) as a result of this 4 week training program. The same animals were used for pre- and

post training O_2 uptake studies following a 20 swim. The VO_2 max was not obtained for the different treatment groups for logistical reasons.

Blood lactate. Fasting levels of blood lactate have been previously published at 4.2 ± 0.6 umoles/ml in untrained resting rats (6). Results (Fig. 2) demonstrated that conditioning diminished the exercise-induced elevation in noninfected animals. Although the trend was similar, less difference was evident during sepsis between the untrained and trained rats.

Plasma glucose. Circulating glucose has been shown to remain relatively constant at 122 ± 6.3 mg/dl in both fasted-noninfected and infected sedentary rats, while swimming caused a slight increase in these values (6). Training significantly ($P < 0.01$) lowered plasma glucose (Fig. 2) response in noninfected rats, while having little or no effect on fasted-infected-trained rats. Sepsis did reduce plasma glucose values in both trained- and untrained-infected animals following exercise.

Tissue glycogen. Figure 3 summarizes the effects of simultaneous infection and exercise on glycogen stores of trained and untrained rats. Studies (6, 9) have demonstrated that fasting increased cardiac glycogen depleted of hepatic glycogen and slightly depleted muscle glycogen. Pneumococcal infection inhibited fasting-induced heart glycogen accumulation, but did not accelerate fasting glycogen loss of the liver and skeletal muscles, while exercise reduced tissue glycogen stores to the same extent in both fasted-infected and noninfected rats (6). In this study training limited the exercise induced hepatic and skeletal muscle glycogen depletion in fasted-noninfected-trained rats and to a lesser degree in infected-trained animals. Chronic exercise not only reduced glycogen utilization during acute exercise, but also increased

resting levels of these glycogen reserves (data not shown). While fasting and exercise resulted in a 95% increase (from fed-exercised levels of 3.2 ± 0.8 mg/g) in fasted-noninfected-untrained rats, training limited this increase. Infection appears to have markedly reduced heart glycogen in fasted-infected-trained rats, while their untrained controls showed less of an infection-induced effect.

Plasma free fatty acids and ketone bodies. Fasting elevated plasma FFA and ketones, while infection superimposed on fasting reduced it in sedentary rats (24). Swimming amplified fasting ketosis and diminished infection ketonemia and markedly decreased plasma FFA values in fasted-infected rats (6).

Concentrations of plasma free fatty acids (Fig. 4) were significantly ($P < 0.01$) elevated in fasted-noninfected-trained rats compared to their untrained controls following swimming exercise. Simultaneous infection and acute exercise reduced plasma FFA concentrations in fasted-infected-untrained rats as previously shown (6) and to a lesser extent in fasted-infected-trained rats. Training increased plasma ketone body response in fasted-noninfected rats. However, infection inhibited this fasting ketonemia and caused a significant reduction in both fasted-infected-untrained and -trained values.

Plasma insulin and glucagon. Previous investigations (24) have indicated that fasting decreased plasma insulin, while glucagon remained unaltered. Infection in the fasted rat caused a progressive increase in both insulin and glucagon concentrations, while simultaneous exercise during sepsis abated the infection-induced elevation of both hormones (6). Endurance training diminished the insulin response (Fig. 5) to fasting and exercise in fasted-noninfected-trained rats when compared to their untrained controls. Sepsis elevated plasma insulin 43% in fasted-infected-

untrained and 29% in -trained rats from their respective control levels; thus, chronic exercise limited the insulin response to the combined stresses of infection and exercise. Conditioning also reduced the simultaneous effect of fasting and exercise of plasma glucagon in noninfected trained rats. The pneumococcal infection caused hypergluconemia in fasted-infected-untrained rats, but training abated this increase.

The insulin to glucagon molar ratio (I/G) was 0.58 ± 0.08 for fasted-noninfected-untrained rats and conditioning lower these non-infected values to 0.46 ± 0.06 . With bacterial infection, the I/G ratio increased in both fasted-infected-trained and -untrained rats to the same extent (0.61 ± 0.08 and 0.64 ± 0.03 , respectively).

DISCUSSION

Endurance training did not alter disease-related mortality of rats infected with S. pneumoniae. Since physical conditioning has been implicated in host resistance to certain debilitating disorders (29, 4), it would appear that a 4 week swim training regimen was insufficient to protect the rat against a lethal bacterial challenge. Preliminary studies in this laboratory using another disease model, Francisella tularensis (Schu-4 strain) in Sprague Dawley rats training for 8 weeks by a motor-driven wheel-running exercise apparatus have shown similar results. Conditioning did not modify mortality to this lethal challenge. Further studies are needed to clarify the endpoint at which a well conditioned animal is able to withstand the initial insult of bacterial infection or determine if training in general is of any benefit to the host during infectious insult, onset and recuperative stages of the disease processes.

This present study indicates that training did not alleviate the infection-induced decrement in swimming performance capacity noted previously (6, 10). Results can be interrupted in two ways as regards

conditioning and endurance during sepsis: 1) conditioning only limited the reduction in physical work capacity caused by infection; and more probably 2) infection had a greater effect on trained rats' endurance. With these hypotheses in mind, the first question that might be asked is whether one can legitimately compare untrained- to trained-infected rats, since these two groups were not exercised for the same duration.

To adequately answer this question, a number of metabolic parameters were measured as physiological evidence of training effects and relative indices of acute exercise intensity. The parameters were oxygen consumption, blood lactate, plasma glucose, FFA and ketone concentrations, tissue glycogen stores and gluco-regulatory hormones.

The 4 week training regimen only slightly increased maximal aerobic capacity in fed-trained rats, while mean oxygen consumption was essentially the same in the infected-untrained and -trained rats at the same submaximal work load. This observation is similar to results obtained in human training studies (28). Since aerobic capacity is thought by many investigators to be the most fundamental physiological factor determining work capacity (9, 20, 29), one could postulate that even though O_2 uptake was similar between trained- and untrained-infected rats, other adaptative mechanisms such as increased energy substrate stores or more efficient fuel utilization may provide the impetus for the septic-trained animals' ability to swim an average of 20 mins longer than their untrained counterparts.

In these metabolic investigations, all of the rats were studied immediately following an exhaustive swim test, thus all were at the same relative physiological state of exhaustion. The duration of swim and relative exercise intensity were variables.

Exercise intensity and metabolic responses to acute exercise in noninfected-untrained rats were similar to previously established criterion (9, 20). Infected-untrained rats exhibited more of an effect to the strenuous exercise than noninfected rats. Swimming did not alter the direction of the infection-induced changes, but did alter the magnitude of metabolic responses (6). Oxygen consumption, blood lactate and muscle glycogen results would indicate that infected-untrained rats can not be stressed to the same degree as noninfected-untrained rats. Exercise intensity was lower in these septic animals (6) as was observed in this investigation.

The present study also demonstrates that trained rats were less susceptible to the exercise stress as indicated by lowered blood lactate, limited swimming-induced muscle glycogen depletion, elevated free fatty acids and ketones with concomitant diminished plasma insulin and glucagon levels following acute exercise. These responses have been previously reported as adaptative metabolic responses to training (9, 1, 13, 17, 29). Exercise intensity was similar in both trained-infected and -noninfected rats as measured by VO_2 , blood lactate and muscle glycogen levels. In this study, the pneumococcal infection had little or no effect on the trained animals' response to swimming intensity.

The finding that performance capacity of trained rats was more sensitive to the debilitating influence of infection is surprising, since other studies (6, 10) have suggested an improved performance in response to daily swimming during the course of febrile infection. Psychogenic reactions may be a plausible explanation for this temporary improvement. But what causes the disproportionate infection-induced reduction in trained rats? In acute infectious disease skeletal muscle protein degradation accelerates to provide amino acid substrate for

hepatic gluconeogenesis, while muscle protein synthesis decreased (32). This combination of metabolic events result in reduced muscle mass and impaired muscle function (32). There are reports in humans that the activities of oxidative and glycolytic enzymes of skeletal muscle, which correlated with the capacity to perform exercise (19), may become transiently depressed as a result of infection (2). Recent studies (11) have suggested that bacterial infections of different etiologies cause a decrease in the activities of oxidative as well as glycolytic enzymes of skeletal muscle, and a simultaneous activation of several lysosomal enzymes. These investigators postulated that the catabolic responses of infection and the anabolic responses of training exercise may be independently mediated in muscle (11). A common factor between the two processes is the activation of a large number of acid hydrolases leading to exaggerated muscle protein degradation when the two stresses are combined. Further studies are needed to measure skeletal muscle breakdown, circulating amino acids and ammonia as a possible explanation of the trained rats sensitivity to infection.

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TABLE 1. Effect of a 72 h fast and S. pneumoniae infection on swimming endurance capacity of trained and untrained rats

Group	Mean Time to Exhaustion (min) $\pm$ SEM	
	Trained	Untrained
Fasted-noninfected	277.8 $\pm$ 12.8*	165.3 $\pm$ 16.1
Fasted-infected	57.5 $\pm$ 5.7*	34.2 $\pm$ 9.9

* $\underline{P} < 0.01$ trained vs. untrained.

TABLE 2. Influence of simultaneous swimming and infection on oxygen consumption in trained and untrained rats at 72 h postinoculation and onset of fast

Group	Oxygen Uptake (ml/Kg·min ⁻¹)	
	Trained	Untrained
Fasted-noninfected	37.8 $\pm$ 1.6*	58.3 $\pm$ 2.1
Fasted-infected	36.7 $\pm$ 0.9	40.6 $\pm$ 1.7

Values are means $\pm$ SEM for infected rats measured following a swim to exhaustion. * $\underline{P} < 0.01$ trained vs. untrained.

Figure Legends

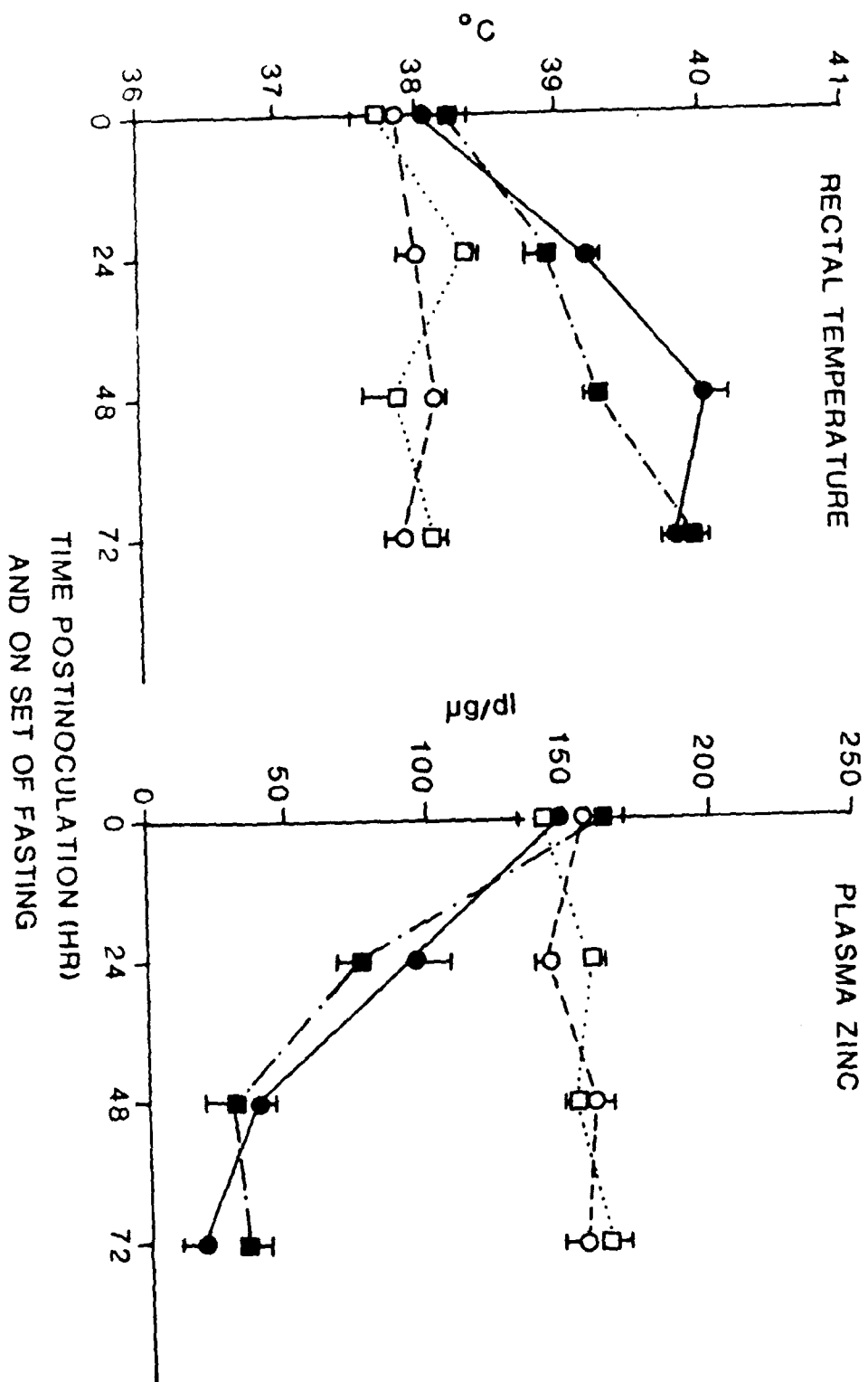
FIG. 1. Effect of pneumococci infection on rectal temperature and plasma zinc concentrations following swim to exhaustion of fasted-noninfected and infected-trained and -untrained rats at various times postinoculation. Closed symbols denote (●—●) infected-trained and (■—■) infected-untrained. Open symbols denote (○—○) fasted noninfected-trained and (□·····□) untrained. Each point represents means $\pm$ SEM of 15 rats per group. $^{\dagger}\underline{P} < 0.01$ fasted-infected versus fasted-noninfected and $^{*}\underline{P} < 0.01$ trained versus untrained animals.

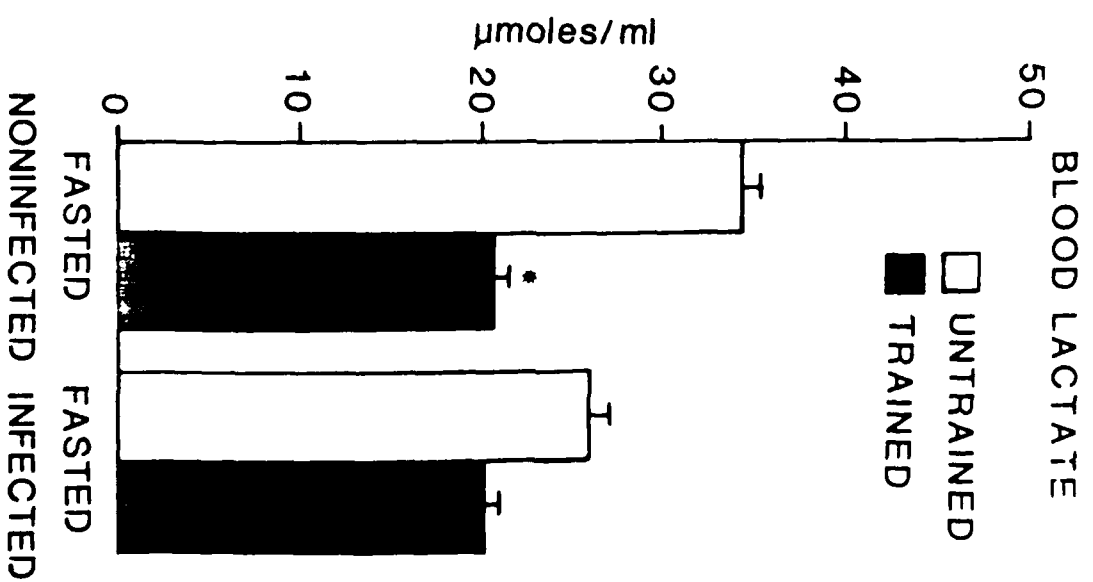
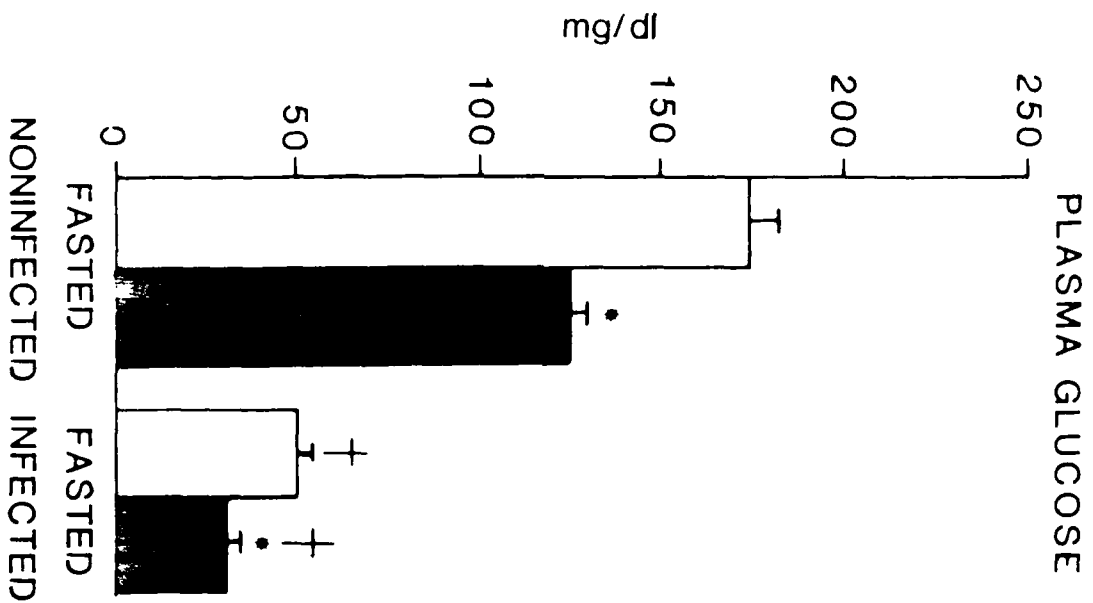
FIG. 2. Influence of swimming exercise on whole blood lactate and plasma glucose concentrations in noninfected and infected-trained and -untrained rats.

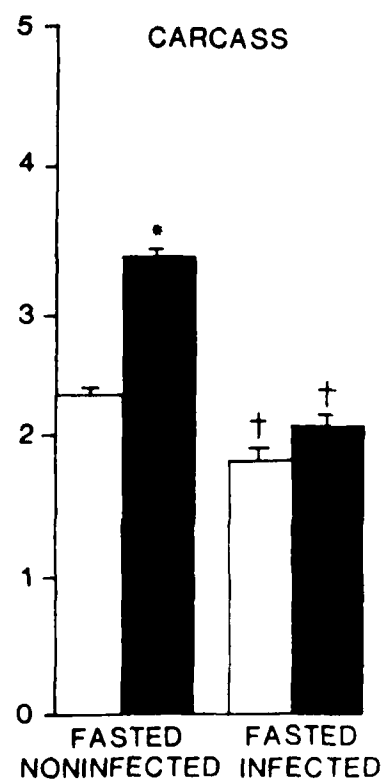
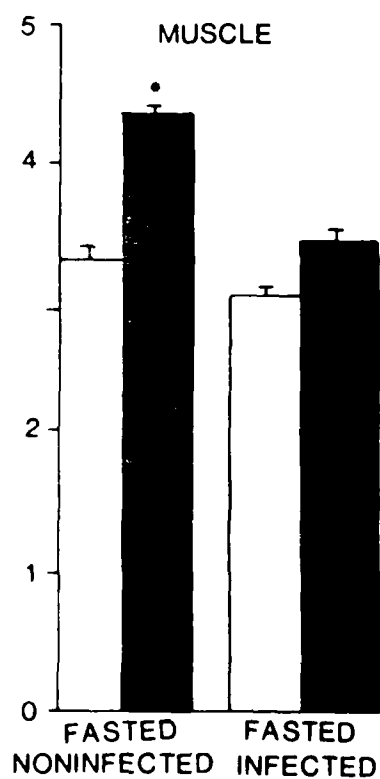
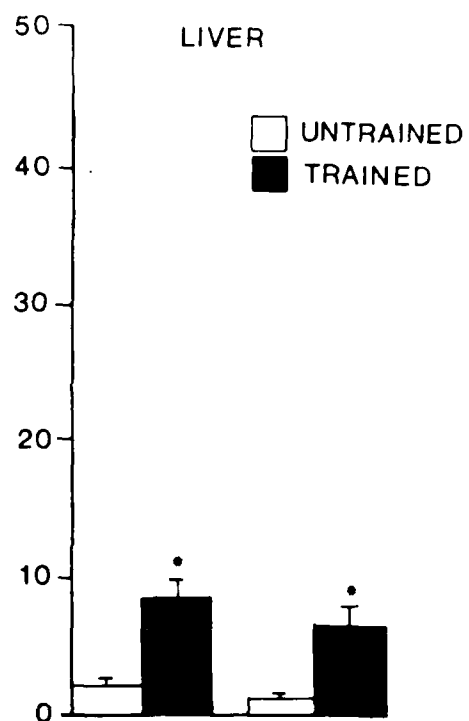
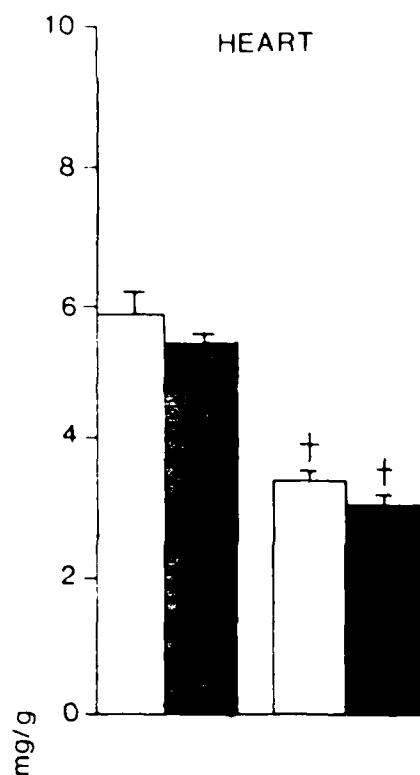
FIG. 3. Concentration of control and infected cardiac, liver, gastrocnemius muscle and carcass glycogen following exercise in trained and untrained rats. Each bar represents the mean $\pm$ SEM of 15 rats per group. $^{\dagger}\underline{P} < 0.01$ for fasted-infected versus fasted-noninfected and $^{*}\underline{P} < 0.01$ trained versus untrained animals.

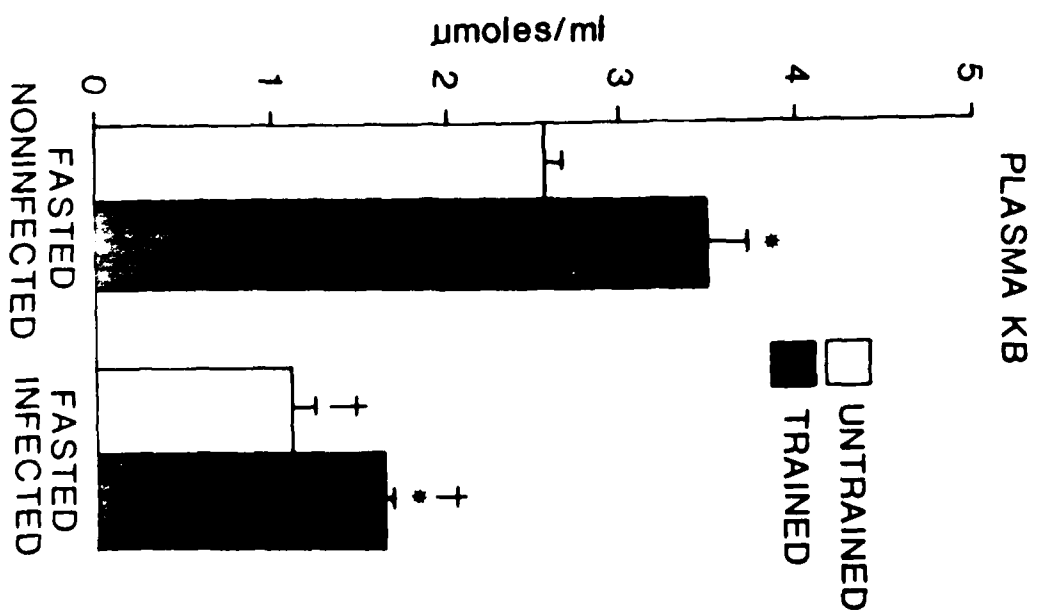
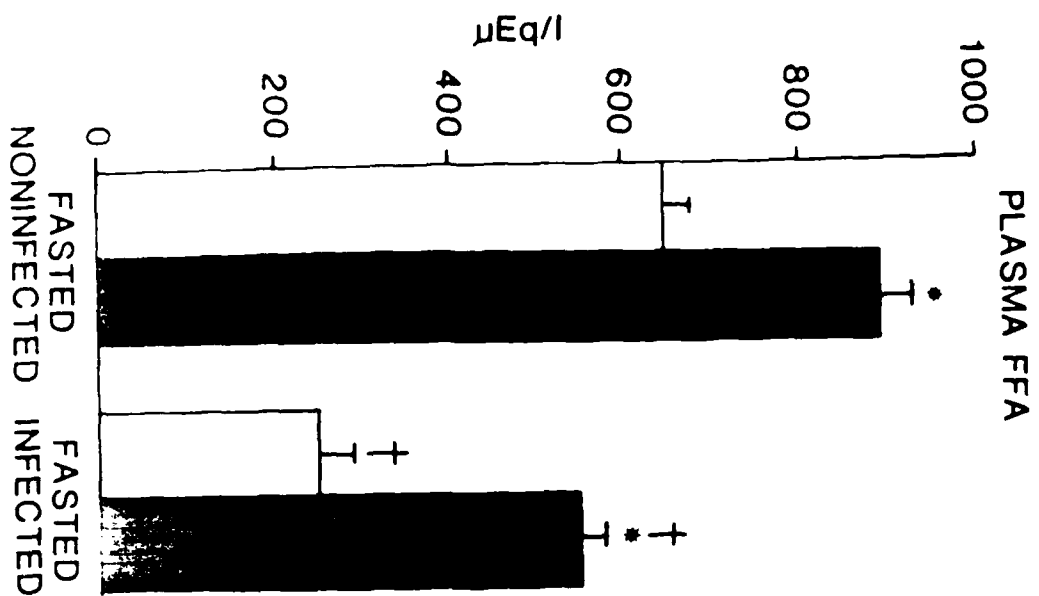
FIG. 4. Effect of pneumococci infection and swim to exhaustion on plasma FFA and KB concentration in trained and untrained rats.

FIG. 5. Hormone concentrations following exercise in noninfected and infected-trained and untrained animals.

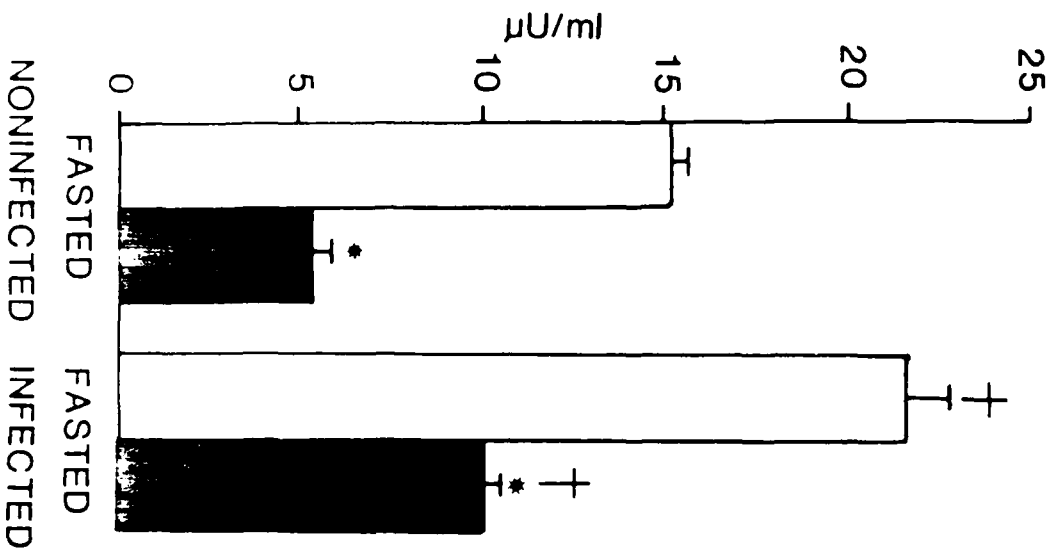








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