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Metabolic Effects of Exercise

I. Effect of Exercise on Serum Lipids and Lipogenesis in Rats[1,2] (38600)

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The metabolic effects of exercise are not well understood. There are controversial reports in the literature on the effect of exercise on body weight and food intake of rats (1–4) as well as on serum lipids of rats and men (5–8). Perhaps these contradictory reports stem from the dissimilarities of the experimental conditions employed by different investigators: degree, type and duration of exercise, age of the animals, type of diet, etc. However, there are relatively few reports on the metabolic effects of voluntary exercise in rats.

The present study was undertaken as part of a program aimed to explore the biochemical basis of the effects induced by exercise. Here are reported the effects of measured voluntary exercise on body weight, adrenal size, serum lipid levels and enzymes related to lipogenesis of rats achieving different levels of exercise.

Materials and Methods. Young adult male Fisher rats were used in these experiments. In each experiment the exercising group was matched by body weight with the sedentary group. Each rat in the exercise group was housed individually in a rodent activity cage allowing voluntary exercise whereas each sedentary rat was housed in a shoe-box type cage. The amount of exercise in the activity cages was recorded as the number of revolutions of the 14″ diameter revolving drum to which the rats were given free access. Both control and exercising rats were fed Purina rat chow and water *ad libitum*. Food consumption and body weight were measured weekly during the experimental periods. At the termination of the study, exercised and control rats were decapitated after an overnight fast. Blood was collected and the following organs dissected: liver, heart, adrenals and epididymal fat pad. Each organ was blotted with paper, weighed on a torsion balance and processed for the different assays or otherwise immediately frozen.

Serum lipids were extracted with isopropanol (1:20 v/v). This extract was used to measure total cholesterol and triglycerides (9) by techniques developed in our laboratory and previously reported. Glucose-6-phosphate dehydrogenase (G-6-PD) (EC 1.1.1.49) was measured in the 16000 *g* supernatant fraction of liver homogenates (20% in 0.5 *M* KCl) according to the procedure of Rudack, Chisholm and Holten (11) using a spectrophotometer with a recorder attached, enabling changes in optical density with time to be recorded automatically. α-Glycerophosphate dehydrogenase (α-GPD) activity was determined in both hepatic and adipose tissue homogenates (0.5% in cold Ringer solution). Mitochondrial preparations of hepatic homogenates were obtained after centrifugation. In hepatic and epididymal tissue preparations both soluble (EC 1.1.1.8) and insoluble (EC 1.1.2.1) forms of α-GPD were measured by the methods of Fried et al (12) and Young and Pace (13). Protein was measured by the biuret reaction (10) and enzyme specific activities expressed as units of enzyme per mg of protein.

All experiments were statistically designed as complete randomized designs and differences between treatment means were determined by Student's *t* test.

Results. Three consecutive and similar experiments were carried out on three differ-

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TABLE I. EFFECT OF EXERCISE ON BODY WEIGHT, FOOD INTAKE AND GROWTH EFFICIENCY.

Group	Revolutions	Body weight			Food intake	Weight gain[c] (average)
		Initial	Final	Gain		
		g	g	g		
Experiment I						
Exercise (5)[a]	29667 ± 890[b]	138 ± 30	286 ± 18	148 ± 32	1256 ± 56*	11.9
Control (5)	—	133 ± 30	284 ± 42	151 ± 21	1075 ± 112	14.0
Experiment II						
Exercise (6)	40074 ± 1210	242 ± 17	321 ± 11**	78 ± 17**	1593 ± 425**	5.2
Control (6)	—	241 ± 16	340 ± 20	99 ± 13	1178 ± 127	8.5
Experiment III						
Exercise (10)	172225 ± 12346	154 ± 8	287 ± 15**	133 ± 16**	1280 ± 117*	10.4
Control (10)	—	153 ± 8	303 ± 21	150 ± 22	1174 ± 72	12.8

[a] In parenthesis, number of animals.

[b] Mean and standard deviation. Statistically different from control. * ($P < 0.05$); ** ($P < 0.01$).

[c] $\frac{\text{Total body weight gain (g)}}{\text{Total food intake (g)}} \times 100.$

ent shipments of the same strain of rats. Although not by design the rats will be considered as having done light activity in experiment I, moderate activity in experiment II and heavy activity in experiment III. When the amount of exercise is expressed as miles run per day, the rats ran 0.30, 0.70, and 1.75 miles per day in experiment I, II, and III respectively.

The effect of exercise on body weight, food intake and weight gain is shown in Table I. The final body weights of rats doing light exercise (experiment I) did not differ from their control group but rats doing moderate (experiment II) and heavy exercise (experiment III) had lower final body weights than their controls. Food intake was greater in the exercised rats than in their sedentary controls in all three experiments. Weight gain efficiency seemed to be dependent upon initial body weight but did show a trend of being lower in the exercised rats as compared with their respective controls at each level of exercise.

Table II summarizes the organ weights and serum lipid values obtained at the end of the experiments. The adrenal glands were larger in rats doing moderate (exp. II) and heavy exercise (exp. III) but not in those doing light exercise (exp. I). Interestingly enough, right adrenals seemed to be consistently smaller than left adrenals in both exercise and sedentary rats. There were no differences observed in the weight of the hearts when comparing exercise to control rats. Differences in the liver weight were significant only in experiment II, the liver weight of the sedentary rats being larger than the liver weight of the exercise rats. It should be noted that the rats in this group had higher initial weights than the rats in experiment I and III. Liver weight was the only parameter that was inconsistent with the patterns observed in the other parameters which were affected by the increasing level of exercise between experiments. No significant differences were observed in serum cholesterol between the control and exercise groups. Highly significant differences were observed in serum triglycerides with the values of the exercise rats being consistently lower than those of the sedentary group.

The activity of two enzymes related to lipogenesis were measured. Glucose-6-phosphate dehydrogenase activity was measured in all experiments. No differences were observed in the activity of this enzyme except for the rats in experiment III (Table II). In experiment III, the heavy exercise group had lower values of glucose-6-phosphate dehydrogenase than the controls. The effect of exercise on the activity of α-glycerophosphate dehydrogenase (αGPD) in both liver and epididymal adipose tissue is shown in Table III. The activity of α-GPD

TABLE II. EFFECT OF EXERCISE ON ORGAN WEIGHTS, SERUM LIPIDS AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE.

	Experiment I		Experiment II		Experiment III	
	Control	Exercise	Control	Exercise	Control	Exercise
Adrenal						
Right (mg)	16.2±2.8[b]	17.7±1.7	19.1±1.6	21.8±3.5	18.0±2.1	20.3±2.1*
Left (mg)	16.6±1.9	17.8±1.5	19.8±0.4	24.5±2.4**	20.4±2.4	22.7±1.5*
Heart (g)	0.99±0.12	1.08±0.11	0.82±0.05	0.85±0.06	1.28±0.6	1.29±0.4
Liver (g)	11.8±4.3	10.1±1.0	9.8±0.9	8.8±0.7*	7.7±0.9	7.6±0.5
Serum cholesterol (mg%)	94±10	91±12	68±5	67±6	78±12	71±4
Serum triglycerides (mg%)	118±6	87±16**	88±20	59±14**	100±32	55±11**
G-6-PD[a]	6.6±13	6.3±1.0	5.1±2.2	3.6±1.3	2.4±0.8	1.5±0.6*

[a] Glucose-6-phosphate dehydrogenase activity expressed as change in OD/min/mg of protein.

[b] Mean and standard deviation. Statistically different from control. * ($P < 0.05$); ** ($P < 0.01$).

in epididymal fat was higher in the exercise group than in the sedentary group. This occurred in the mitochondrial and cytoplasm fractions as well as in the total fraction. There were no differences obtained between exercise and control groups for liver α-GPD.

Discussion. Our data support Mayer's contention (14) that there are critical levels of activity for normal control and regulation of appetite. The data shown in Fig. 1 were obtained by taking the weight gain and food consumption of those rats doing the specified amount of exercise shown. The values for the sedentary rats are placed at zero revolutions. Values from experiment I and III only were used since the age and initial body weights of these groups were similar. As shown in Fig. 1, below a certain level of physical activity (150,000 revolutions) an increase in physical activity results in a decrease in both food consumed and weight gained. However, above this level of physical exercise, an increase in exercise resulted in an increase in food consumption and an increase in weight gained.

Although exercising rats showed smaller growth efficiency than the controls, there is no way under the conditions of our experiments to separate the energy required for weight gain from that required for exercise. However, weight gain efficiency appeared to be related to the initial weight of the animals. This could be explained on the basis that the heavier animals had already passed the most rapid stage for protein deposition and perhaps they were depositing more fat. Increase in heart weight of exercising rats has been reported by other investigators (15) and is characterized by increased myocardial mass (16). The absolute liver size was slightly larger in sedentary animals, but significant only in exp. II, confirming the observations of Montoye *et al.* (17). However, there are also reports showing that forced exercise can produce increased liver size (18). Larger adrenals have been reported in rats forced to exercise, while no such enlargement was observed in animals participating in spontaneous rather than forced exercise (17) (19). This dis-

TABLE III. EFFECT OF EXERCISE ON α-GLYCEROPHOSPHATE DEHYDROGENASE.[a]

Enzyme	Experiment III	
	Control	Exercise
Epididymal fat		
Total	1.4 ± 0.9[b]	6.0 ± 4.2*
Mitochondrial	0.48 ± 0.22	1.99 ± 0.65*
Cytoplasmic	0.46 ± 0.75	4.03 ± 3.81*
Liver		
Mitochondrial	0.34 ± 0.10	0.34 ± 0.10
Cytoplasmic	0.98 ± 0.22	1.02 ± 0.06

[a] Enzyme activity is expressed as mg formazan produced per min/mg protein.

[b] Mean and standard deviation. Statistically different from control. * ($P < 0.01$).

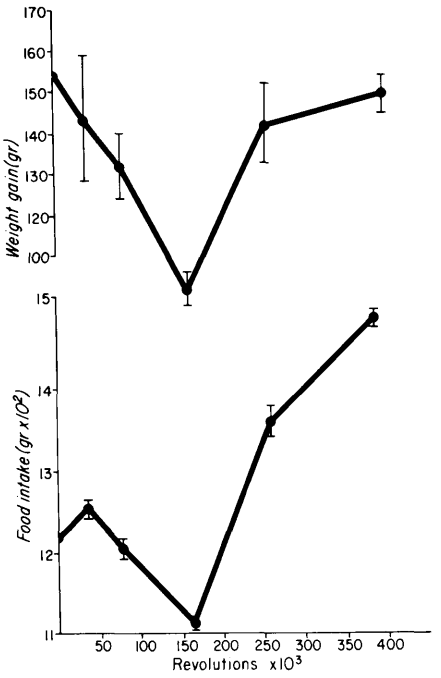

FIG. 1. Changes in body weight gain and voluntary food intake with degree of exercise (no. of revolutions) in rats from experiment I and III. Each point represents the mean food intake and body weight of animals from both experiments at each level of exercise.

crepancy would suggest that the stress associated with forced exercise was the cause of the enlarged adrenals. In our studies significantly larger adrenals were observed in the voluntarily exercised rats in experiments II and III and thus can be attributed to increased level of activity. Similar observations have been reported by Ring *et al.* (3), and apparently the adrenal cortex rather than the medulla is the region enlarged (20). It is not known if the observed adrenal morphological changes induced by exercise are accompanied by qualitative or quantitative adrenocortical functional changes. In human volunteers we have noted qualitative and quantitative changes in the urinary excretion of 17-ketosteroids after 6 wk of exercise.

Contradictory results have been reported regarding the effect of exercise on serum lipids of rats, (5–7). We found that no statistical difference was observed in serum cholesterol in the exercising animals. Significantly lower levels of triglycerides were observed after exercise in these experiments and there is general agreement that a decrease in triglycerides is the most consistent effect of exercise on serum lipids (21–23). These findings in the rat of decreased serum triglycerides and no significant changes in serum cholesterol after exercise may be in agreement with our observations in humans (24) that after a period of exercise there is reduction in the serum concentration of β and pre-β-lipoproteins with a concomitant increase in the α-lipoproteins. The net effect of these changes in serum lipoproteins will result in significantly reduced serum triglyceride levels and small or no change in total serum cholesterol.

The exact mechanism by which exercise produces these changes in serum lipids and lipoproteins remains unknown. Exercise could affect synthesis or removal of serum lipids either directly, or indirectly through its effect on certain tissues or organs. It has been suggested that exercise will mobilize preferentially unsaturated fatty acids from adipose tissue and thus promote the transport and metabolism of cholesterol from liver and serum (2) with an increase in bile acid and steroid excretion (2). Other investigators have postulated that the effect of exercise on serum cholesterol is mediated through the effect of exercise on thyroid function (25–27).

Our observations of decreased activity of hepatic G-6-PD and increased activity of α-GPD in experiment III after exercise adds to our understanding of the metabolic changes occurring during exercise. On one hand, exercise by reducing the activity of G-6-PD may modify lipid synthesis by reducing the supply of NADPH required for fatty acid and cholesterol synthesis (28) (29). Similar effects of exercise on G-6-PD have been reported by other investigators (30) (31). On the other hand, an increase in the activity of α-glycerophosphate dehydrogenase could increase the oxidation of α-glycerophosphate which is an obligatory acyl acceptor for the synthesis of triglycerides, resulting in a net decrease in this lipid fraction. Similar effects of exercise on G-6-PD and α-GPD activities have been

observed in experiments aimed at the study of the residual effect of exercise and will be presented in the accompanying paper. These changes in enzymes related to lipogenesis could suggest an effect of exercise on lipogenesis, but do not provide direct evidence for it. Further studies are needed, measuring lipogenesis directly, in order to validate such suggestion.

How exercise affects those two key enzymes related to lipid metabolism still remains to be established. The activity of the enzyme α-GPD is known to be affected by thyroid hormone (32) (33) and thus exercise could influence this enzyme through its effect on thyroid activity. With regard to G-6-PD, exercise could affect the activity of this enzyme through an effect on adrenals which are found to be enlarged with exercise. We have shown a potent inhibitory effect of the activity of hepatic G-6-PD by certain steroids (34) whose urinary excretion was markedly increased after exercise. Experiments are in progress in our laboratory to elucidate the role of thyroid and adrenocortical hormones in the metabolic effects induced by exercise.

The results presented here also suggest that the level of activity is important in detecting the metabolic effects of exercise. For example the activity of G-6-PD was significantly decreased only in the group of rats achieving heavy exercise (exp. III), while the effect of exercise on adrenal size was apparent at both moderate (exp. II) and heavy (exp. III) levels of exercise. The most dramatic effect of exercise on serum lipids, the reduction of serum triglyceride concentration, shows an increased effectiveness with increased levels of exercise: 26% reduction at light, 32% at moderate and 45% at heavier levels of exercise. These findings suggest specific levels of exercise to achieve specific metabolic effects.

Summary. To evaluate the metabolic effects of exercise, three groups of exercised male rats were compared to their sedentary controls at the end of 10 wk of voluntary exercise in rodent activity cages. Exercised rats consumed more food than sedentary rats but had greater weight gain only at the higher levels of activity. Exercised rats had significantly lower serum triglycerides and higher values of adipose tissue α-glycerophosphate dehydrogenase activity. At higher levels of physical activity, the exercised rats exhibited larger adrenal glands and lower values of hepatic glucose-6-phosphate dehydrogenase. It is concluded that specific levels of voluntary exercise are needed to achieve specific metabolic effects.

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