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Aerobic exercise during pregnancy reverts maternal insulin resistance in rats

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ABSTRACT

Aerobic exercise during pregnancy reverts maternal insulin resistance in rats. *Med. Sci. Sports Exerc.,* Vol. 30, No. 10, pp. 1510-1514, 1998.

Purpose and Methods: To determine whether pregnancy modifies the effect of aerobic exercise on insulin responsiveness, female rats were mated or kept nonpregnant and exercised or not on a treadmill (10° slope, 20 $m \cdot min^{-1}$) 5 $d \cdot wk^{-1}$ during a 20-min period that was increased progressively up to 70 min on the 19th d. On day 20, a hyperinsulinemic euglycemic clamp was performed with 0.8 IU $insulin \cdot h^{-1} \cdot kg^{-1}$ under conscious conditions.

Results: Food intake and body weight, circulating lactic acid, glucose, and insulin as well as fetal body weight and number were unaffected by the exercise protocol. The rate of glucose infusion required to maintain basal glucose levels during the clamp was similar in exercised and nonexercised virgin rats and significantly lower in pregnant than in virgin nonexercised rats. However, in exercised pregnant rats the glucose infusion rate was almost as high as in the exercised virgin rats.

Conclusions: The results show that although our aerobic exercise protocol does not affect insulin responsiveness in nonpregnant rats, it completely reverts the insulin resistance present in late pregnant rats.

Glucose tolerance during late gestation remains within normal nonpregnant limits (2,6) despite the increased insulin secretion rate in response to glucose (18,20,28).

This indicates a state of insulin resistance. Decreased insulin sensitivity has been well documented in late pregnancy in both women (4,26) and rats (18,20), with the skeletal muscle as the primary site of insulin resistance during gestation (17,23).

In contrast to gestational insulin resistance, exercise in the nonpregnant state increases insulin sensitivity (14) and improves glucose tolerance in both humans (27) and rats (15); the skeletal muscle is also the site of this enhanced insulin action (24). The insulin resistant condition predisposes the pregnant mother to the development of gestational diabetes, the most common medical complication of pregnancy. Although exercise has been recommended to improve carbohydrate tolerance during diabetic pregnancy (3,16), it remains controversial because little empirical evidence exists so both the benefits and risks can only be hypothesized (12). Acute exercise in trained pregnant rats has been shown to increase glucose uptake in maternal skeletal muscle (19), and, although it has recently been reported that a short exercise bout in pregnant women did not to modify glucose kinetics as compared with the nonpregnant state (7), moderate exercise has been shown to be a useful treatment option for gestational diabetic women and has even been proposed to preclude the need for insulin (16). Although these and other reports support the notion that exercise during pregnancy enhances insulin responsiveness, this has not been previously investigated in a direct manner, to our knowledge. The present study is therefore addressed to investigating insulin responsiveness in late-pregnant and virgin rats subjected to an aerobic exercise protocol, using the euglycemic hyperinsulinemic clamp technique. Because anesthesia can cause different metabolic perturbations in pregnant and nonpregnant rats (32), the technique has been adapted for use in conscious animals.

METHODS

Animals. Female Wistar rats bred in our laboratory were used. Housing was at 22-24°C with light from 08:00 to 20:00 with free access to water and chow pellets (diet A04 from Panlab, S.L., Barcelona). Rats were selected at random for each group when weighing 160-180 g, and half were mated; gestation was timed by the appearance of spermatozoids in vaginal smears; the remaining rats were kept virgin and studied in parallel. Animals were housed in individual cages and the exercise protocol was begun the same day as day 0 of gestation. Food intake was measured by weighing the pellets daily. The experimental protocol was approved by the Animal Research Committee of the Universities of both Alcalá de Henares and San Pablo-CEU, and accorded with the policy statements of the American College of Sports and Medicine as well as the European Union.

Exercise protocol. The rats were exercised during the dark cycle, because rats are nocturnal animals and most physically active at night. The exercise protocol consisted of a treadmill run, for 5 $d \cdot wk^{-1}$, at a speed of 20 $m \cdot min^{-1}$ on a 10° slope for a period of 20 min, that was progressively increased each day so as to attain 70 min on the 19th day. On this day, and just after the treadmill exercise, the trained pregnant and virgin rats and the control virgin and pregnant rats (those that were not subjected to the exercise protocol were kept without food and water while the other animals were exercised) were anesthetized with an intraperitoneal injection of 0.1 $mL \cdot 100\ g^{-1}$ of a ketamine cocktail [(in $mg \cdot mL^{-1}$) 50 ketamine, 5 diazepam, and 1 atropine; 5:4:1, vol/vol/vol]. A Silastic catheter (Dow Corning, 0.02-inch ID, 0.037-inch OD) was tunneled under the back skin and introduced 3 cm into the right jugular vein. This catheter was exteriorized on the back of the rat and filled with 0.9% NaCl solution until use.

Blood lactic acid concentrations during exercise were analyzed with a commercial kit (Boehringer Mannheim) in rats from the exercise group that was not subjected to the catheter surgery. The blood for this analysis was collected from the tail tip at

different times during the treadmill exercise on day 0, 6, 15, and 20 of the experiments. At day 20 of the experiment, exercised and nonexercised rats were decapitated and trunk blood collected in heparinized, chilled tubes. After weighing the conceptus, fetuses were weighed and decapitated, and their blood was collected as indicated above. Blood from all the fetuses from the same dam was pooled and processed in parallel to that of adults. Plasma was separated by centrifugation at 1500 × *g* for 15 min at 4°C and kept frozen at -20°C until analysis; glucose was determined with a commercial kit (Boehringer-Mannheim) and insulin (13) with a specific radioimmunoassay for rats (Incstar Corporation, U.S.).

Euglycemic clamp studies. The amount of infused glucose required to maintain euglycemia in conscious rats receiving an insulin infusion at a constant rate was determined on day 20, approximately 24 h after both the surgical procedure and the last treadmill run (day 19 of experiment) (23). Animals were studied 2-3 h after starting the light cycle, when they were in the postabsorptive state. Briefly, the catheter placed at the jugular vein was connected to a two-way interconnector that received the flux from two different pumps (Precidor infusion pump type 5003, Infors HT). Human insulin (Actrapid monocomponent, Novo) was infused by means of one of the pumps at a constant rate of 16 $\mu L \cdot min^{-1}$ (0.8 $IU \cdot h^{-1} \cdot kg^{-1}$). Blood glucose concentration was maintained constant at basal levels by infusing glucose (20%) at variable rates, through the other pump. Blood samples (5 µL) were collected from the tip of the tail every 5 min, starting just before the beginning of insulin infusion, and the glucose concentration was measured with a Reflolux II analyzer (BM-Test-Glycemie 20-800 R, Boehringer Mannheim). A steady-state glucose infusion was achieved within 30 min after the clamp was begun; from then on, some additional blood samples (200 µL) were collected to determine the steady-state insulin concentration as above.

Statistics. Results are expressed as means ± SE of the mean. Statistical analyses were performed using a one-way ANOVA (ANOVA) from the IBM Graph Pad Instat, and Student's *t*-test was used to compare two groups. Significance was set at the $P < 0.05$ level, and Newman-Keuls multiple test post hoc analysis was performed on significant ANOVA results.

RESULTS

As shown in Table 1, net body weight (free of conceptus) and mean daily food intake during the last week of the experiment were higher in pregnant than in virgin rats, and the exercise protocol did not affect these variables. Neither total conceptus or mean fetal weights nor the number of fetuses per litter were affected by exercise (Table 1). Plasma lactic acid levels were measured in sedentary nonexercised (control) virgin rats (day 0) and on day 6, 12, 15, and 20 of gestation and in the exercised rats just before and at every 15 min during the exercise protocol on the same days as above, being day 6, 12, 15, and 20 of the experiment. As shown in Table 2, except for a significant increase in plasma lactic acid levels on day 20 of gestation in nonexercised control rats when compared with any of the other groups, there were no significant differences among the remaining groups. Values registered before beginning exercise were the same as those found at the different times of exercise.

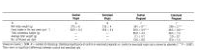

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TABLE 1. Effect of treadmill exercise on body weight and food intake in virgin and 20-d pregnant rats.

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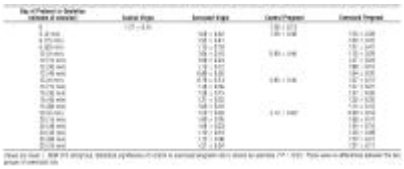

TABLE 2. Effect of treadmill exercise on plasma lactic acid levels in virgin and pregnant rats.

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Blood glucose and plasma insulin levels at 0 and 60 min of the hyperinsulinemic euglycemic clamp with 0.8 IU insulin·h^{-1}·kg^{-1} are shown in Table 3. Basal (time 0) blood glucose concentration was significantly lower in control pregnant than in control virgin rats. Exercise slightly enhanced blood glucose levels in the two groups, and although this effect was not significant in either of the groups, average values appeared now similar in pregnant and virgin exercised rats. Blood glucose concentrations were clamped at lower levels in pregnant than in virgin rats, and no difference was found in either group between those that were exercised and their respective controls. Basal plasma insulin levels were much higher in control pregnant rats than in virgins, and although these levels were slightly lower in the corresponding exercised groups, the difference between the values in pregnant and virgin rats remained significant (Table 3). Plasma insulin levels greatly increased in the four groups during the first 60 min of the clamp, and although values in pregnant rats always remained slightly higher than in virgin rats, the difference between the two groups was only significant in the control rats.

TABLE 3. Effect of treadmill exercise on blood glucose and plasma insulin before (time 0) or after 60 min of the hyperinsulinemic euglycemic clamp in virgin and 20-d pregnant rats.

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As shown in Figure 1, the rate of glucose infusion needed to maintain the blood glucose concentrations at the basal levels was always much lower in pregnant control than in virgin control rats. Whereas the exercise protocol slightly increased the rate of the glucose infusion value in virgin rats, this value greatly enhanced in the pregnant rats, which attained a value similar to those detected in both nonexercised and exercised virgin rats. The rate of glucose infusion remained constant during the last 45-60 min of the clamp, and its value (R) can be corrected by (i) total body weight to find the glucose disposal rate in the steady state (M), (ii)

by the conceptus-free body weight (M'), or (iii) by the ratio of the increase in glucose utilization measured during the clamp ([DELTA]R) and the blood glucose concentration (G) times the increase in plasma insulin ([DELTA]I) and the body weight (body wt), to give the insulin sensitivity index [(S_{ip}) = [DELTA]R/G × [DELTA]I × body wt], as previously proposed (23). All these indexes for insulin responsiveness are shown in Table 4. Values for all the indexes studied were found to be significantly lower in the pregnant nonexercised rats than in the virgin nonexercised rats. Whereas none of these indexes differed significantly in the virgin exercised rats from those found in nonexercised virgin rats, the values were significantly higher in pregnant exercised rats than in the pregnant controls and were similar to those found in virgin control rats.

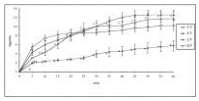

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Figure 1-Effect of pregnancy and exercise on the rate of glucose infusion during the hyperinsulinemic euglycemic clamp in rats. Values are mean ± SEM of 6-8 rats/group. CV = control nonexercised virgins; EV = exercised virgins; CP = control nonexercised pregnant rats; EP = exercised pregnants. Significant statistical differences are shown by the letters: a = $P < 0.01$ and b = $P < 0.001$ for pregnant vs virgin controls; c = $P < 0.01$ and d = $P < 0.001$ for exercised vs control pregnant; e = $P < 0.01$, exercised pregnant vs control virgin.

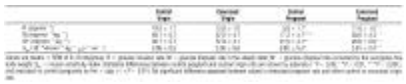

TABLE 4. Effect of treadmill exercise on insulin sensitivity indexes in virgin and 20-d pregnant rats.

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DISCUSSION

The present study confirms the insulin resistant condition of the late pregnant rat by applying a hyperinsulinemic euglycemic clamp in the conscious rat. This condition was shown to be completely reverted after moderate aerobic exercise, because insulin responsiveness did not differ between exercised late pregnant rats and virgin rats whether exercised or not. The present study also found that our exercise protocol affects neither fetal growth in pregnant rats nor insulin responsiveness in virgin rats.

Previous studies in exercised rats have also found a differential metabolic effect between pregnant and nonpregnant rats, with higher responsiveness in the pregnant animals (19,30), and our study is the first to report an exercise protocol that can completely revert insulin resistance in pregnant rats, without affecting insulin responsiveness in virgin rats at all. The difference with previous studies is that the protocol used here is aerobic, as indicated by the unchanged blood lactate levels during the study. Nevertheless, there was a specific increase in blood lactate levels in nonexercised pregnant rats on day 20, as compared with the same rats in

earlier stages of gestation and to unexercised virgin rats, but this is not surprising given the lactic acid produced by the placenta and the fetus (5,21), which can be released into the maternal or fetal bloodstreams and would contribute to an increase in maternal lactic acid levels. Interestingly, present results on the specific increase in lactic acid levels in the sedentary pregnant group as compared with the trained pregnant and both sedentary and trained virgin rats agrees with a similar finding reported by Mottola et al. (19), despite the substantial differences between our exercise protocols. The fact that the increase in blood lactate levels does not appear in the exercised pregnant rat may be a consequence of the enhanced use of lactate as a gluconeogenic substrate. Although not studied in the pregnant rat, conditions of moderate exercise are normally associated to enhanced gluconeogenic activity (1,31); lactic acid is a gluconeogenic substrate, and its conversion into glucose is enhanced with exercise (22). Direct experiments would be needed to test this explanation for the absence of increased blood lactate in exercised pregnant rats.

The fact that our exercised virgin rats did not show any change in insulin sensitivity as compared with controls contrasts with the enhanced insulin responsiveness found in virgin rats subjected to other exercise protocols (9,25). However, there is evidence that moderate exercise does not modify insulin responsiveness in nonpregnant rats (10). This lack of effect seen in the insulin responsiveness of our exercised virgin rats contrasts with the clear effect found in pregnant rats after the same exercise protocol. This different effect is not surprising because pregnancy induces many changes in the mother, and these can modify her response to exercise. As reviewed by Gorski (11), besides the obvious body weight and biomechanical differences, there are extensive endocrine, metabolic, and physiological adaptations inherent to pregnancy that may justify a different response to exercise in nonpregnant individuals.

A differential response between pregnant and virgin rats to stimulus that modifies insulin sensitivity has been reported recently in rats subjected to a prolonged glucose infusion: the infusion decreases insulin responsiveness in virgin rats but reverts insulin resistance in late-pregnant rats (23). The mechanism that rules these differential responses between late pregnant and nonpregnant rats to the same stimulus on insulin sensitivity is unknown, but the subject deserves attention. Additional studies of these conditions would allow us to obtain a better understanding of the mechanisms underlying the insulin resistance normally present during late gestation and maybe even determined which metabolic changes normally taking place at this gestational stage are caused by the reduced insulin sensitivity.

Although maternal exercise may negatively affect fetal metabolism, growth, and even viability (8,30), the present results show that an aerobic exercise protocol that is intense enough to revert maternal insulin resistance in rats does not affect fetal weight or litter size. In pregnant women, moderate exercise has also been shown to not affect birth weight or other maternal and infant outcomes adversely (29), and despite interspecies differences, our findings support the notion, already derived from clinical studies in gestational diabetic women (3,16), that controlled exercise protocols may reduce the diabetogenic tendencies normally present in pregnancy and may even be prescribed to pregnant diabetic women to reduce their need for insulin.

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Key Words: MATERNAL EXERCISE; HYPERINSULINEMIC EUGLYCEMIC CLAMP; INSULIN SENSITIVITY; GLUCOSE; FETAL BODY WEIGHT; RATS