

Research Article

Maternal Moderate Physical Training during Pregnancy Attenuates the Effects of a Low-Protein Diet on the Impaired Secretion of Insulin in Rats: Potential Role for Compensation of Insulin Resistance and Preventing Gestational Diabetes Mellitus

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The effects of pregestational and gestational low-to-moderate physical training on insulin secretion in undernourished mothers were evaluated. Virgin female Wistar rats were divided into four groups as follows: control (C, $n = 5$); trained (T, $n = 5$); low-protein diet (LP, $n = 5$); trained with a low-protein diet (T + LP, $n = 5$). Trained rats ran on a treadmill over a period of 4 weeks before mate (5 days week⁻¹ and 60 min day⁻¹, at 65% of VO_{2max}). At pregnancy, the intensity and duration of the exercise were reduced. Low-protein groups were provided with an 8% casein diet, and controls were provided with a 17% casein diet. At third day after delivery, mothers and pups were killed and islets were isolated by collagenase digestion of pancreas and incubated for a further 1 h with medium containing 5.6 or 16.7 mM glucose. T mothers showed increased insulin secretion by isolated islets incubated with 16.7 mM glucose, whereas LP group showed reduced secretion of insulin by isolated islets when compared with both C and LP + T groups. Physical training before and during pregnancy attenuated the effects of a low-protein diet on the secretion of insulin, suggesting a potential role for compensation of insulin resistance and preventing gestational *diabetes mellitus*.

1. Introduction

Pregnancy requires an increase in insulin secretion-induced glucose metabolism, in order to compensate for the insulin resistance at the end of gestation [1]. In pregnant rats, the threshold of glucose-stimulated insulin secretion begins to diverge from controls by day 10 and islet cell proliferation and insulin secretory profiles are inhibited by day 20 to avoid gestational diabetes [2]. Return to normal values of insulin secretion and inhibition of cell division is particularly important when the adequate nutrient intake is not provided

during pregnancy. For example, maternal low-protein diet (6% casein) causes a loss of glucose sensitivity and secretory capacity in pancreatic islets, which is probably the result of alterations to the coupling of stimuli with insulin secretion [3]. In fact, a maternal low-protein diet decreases insulin secretion and impairs glucose homeostasis, leading to gestational *diabetes mellitus* and increased risk of chronic diseases in later life [1, 4].

Recently, it has been recognized that an active maternal lifestyle, including regular to moderate physical activity, improves aerobic fitness and the maternal-fetal physiological

reserve by enhancing nutrient and oxygen availability to the fetus [5–7]. Maternal physical activity is associated with normalised body weight gain, enhanced cardiorespiratory, and improved oxidative capacity and insulin sensitivity of skeletal muscle [8]. These physiological benefits mainly occur according to the type and volume of the exercise, physical fitness of the mother, the time point in the pregnancy when the exercise is carried out and also the duration and intensity of the exercise [9, 10]. Physical exercise training has been associated with reduced risk of metabolic disease and enhances both cardiorespiratory and metabolic functions [11–14]. These effects are mainly due to improved oxidative capacity and insulin sensitivity of skeletal muscle, since reduced muscle dysfunction and insulin resistance have been associated to the development of several chronic diseases [15–20]. Exercise is considered moderate intensity when oxygen consumption is 50–70% of the maximal oxygen consumption ($VO_{2\max}$). In our previous study, we demonstrated in rats that a controlled moderate to low-intensity exercise before and during gestation (5 days week⁻¹, 60 min day⁻¹, 40%–70% of $VO_{2\max}$) increased the mothers' resting oxygen consumption [21]. In humans, the rate of placental bed blood flow increases, and more glucose and oxygen delivery to the placental site are observed in women submitted to a physical training [22].

The effects of maternal moderate physical training can be expected modifying glucose metabolism in pregnancy once regular physical activity in nonpregnant individual is known to improve peripheral insulin sensitivity, glucose tolerance, and may aid in preserving β -cell function [11]. Regular practice of moderate exercise has been associated with improved fitness, reduction of body weight, and increased muscle mitochondrial biogenesis and antioxidant defence [5, 23]. Our previous experimental data supports the idea that maternal physical training may protect mothers against perinatal undernutrition environment [21, 24]. Recently, we showed in rats that physical training was able to normalise the effects of a low-protein diet on fasting serum glucose at the second and third weeks of gestation [25]. This differential effect observed in previously active compared with undernourished dams may be related to reduced risk of gestational *diabetes mellitus*, since an exercise program may improve insulin sensitivity and fasting plasma glucose concentrations of women at risk for gestational *diabetes mellitus* [26].

Thus, the main goal of this study was to evaluate the impact of a moderate to low intensity protocol of physical training during gestation on the secretion of insulin whose mothers were undernourished. Our hypothesis is that maternal physical training-induced physiological adaptations during gestation attenuate the impact of a perinatal low-protein diet on the secretion of insulin. This is a topic of particular interest as a maternal lifestyle can be considered a therapeutic means of countering the effects of either maternal undernutrition or overnutrition.

2. Methods

Experimental protocol was approved by the Ethical Committee of the Biological Sciences Center, Federal University of

TABLE 1: Composition of the diets (control 17% and low protein 8%).

Ingredients	Amount for 1 Kg of diet	
	Low protein	Control
Casein	79.3 g	179.3 g
Vitamin mix*	10 g	10 g
Mineral mixture#	35 g	35 g
Cellulose	50 g	50 g
Bitartrato of choline	2.5 g	2.5 g
DL-methionine	3.0 g	3.0 g
Soya oil	70 mL	70 mL
Corn starch	750.2 g	650.2 g

Mineral mixture contained the following (mg/kg of diet): CaHPO₄, 17200; KCl, 4000; NaCl, 4000; MgO, 420; MgSO₄, 2000; Fe₂O₃, 120; FeSO₄·7H₂O, 200; trace elements, 400 (MnSO₄·H₂O, 98; CuSO₄·5H₂O, 20; ZnSO₄·7H₂O, 80; CoSO₄·7H₂O, 0.16; KI, 0.32; sufficient starch to bring to 40 g [per kg of diet]). *Vitamin mixture contained the following (mg/kg of diet): retinol, 12; cholecalciferol, 0.125; thiamine, 40; riboflavin, 30; pantothenic acid, 140; pyridoxine, 20; inositol, 300; cyanocobalamin, 0.1; menadione, 80; nicotinic acid, 200; choline, 2720; folic acid, 10; p-aminobenzoic acid, 100; biotin, 0.6.

Pernambuco, Brazil and followed the Guidelines for the Care and Use of Laboratory Animals [27].

2.1. Animals. Virgin female albino Wistar rats (*Rattus norvegicus*) aged 60 days and weighting 180 ± 11 g (mean \pm S.E.M.) were obtained from the Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, Brazil. Female rats were maintained at a room temperature of $22 \pm 1^\circ\text{C}$ and controlled light-dark cycle (dark 6:00 a.m.–6:00 p.m.). The standard laboratory chow for animals (52% carbohydrate, 21% protein, 4% lipids-Nuvelab CR1-Nuvital) and water were given *ad libitum*. Animals were randomly divided into two groups: untrained rats (NT, $n = 10$) and trained rats (T, $n = 10$). Trained rats were submitted to a training program of moderate running over a period of 4 weeks (5 days per week and 60 minutes per day) on a treadmill (Millennium Inbramed, Brazil) at a controlled intensity based on their $VO_{2\max}$. After a 4-week training period, the rats were mated (2 females for 1 male). The day on which spermatozoa were present in a vaginal smear was designated as the day of conception (day 0 of pregnancy). Pregnant rats were then transferred to individual cages. Half of rats of each group received either 17% casein diet or 8% casein (low-protein group, LP) isocaloric diet *ad libitum* (Table 1). Thus, two more groups were formed: untrained (C, $n = 5$), trained (T, $n = 5$), untrained with low-protein diet (LP, $n = 5$), and trained with low-protein diet (T + LP, $n = 5$). Mother's body weight was weekly determined throughout the experiment. On the time of delivery, the litter size and pup's birth weight were recorded. The litters of six pups represent the sample that was evaluated: control (C, $n = 5$); trained (T, $n = 5$); low-protein diet (LP, $n = 5$); trained with low-protein diet (T + LP, $n = 5$). The evaluation of body weight and gain of body weight of pups was recorded until the 3rd d of life with a Marte scale with 100 mg precision. Afterwards, mothers and pups were killed by decapitation.

2.2. Protocol of Physical Training. Considering that maternal physical exercise-induced changes depends on intensity, duration, and frequency of effort, our group standardized an experimental protocol of maternal physical training (based on blood lactate concentration and oxygen consumption) [21]. Briefly, rats ran on a treadmill during the four weeks prior to pregnancy (5 days week⁻¹ and 60 min day⁻¹, at 65%VO_{2max}). The protocol was divided into four progressive stages in each session: (i) warm-up (5 minutes); (ii) intermediary (20 minutes); (iii) training (30 minutes); (iv) cool-down (5 minutes) periods. The percentage of VO_{2max} during the sessions of training was kept around 55–65% [21]. During pregnancy, rats ran at a progressively lower intensity of effort (40%VO_{2max}, 5 days week⁻¹, and 20 min day⁻¹) until the 19th day of gestation [21].

2.3. Mother's Body Weight and Food Intake. Mother's body weight was daily recorded. Daily food consumption was determined by the difference between the amount of food provided at the onset of the dark cycle (06.00 hours) and the amount of food remaining 24 h later [28]. Body and food weights were recorded with a Marte Scale (AS-1000) with a 0.01-g accuracy.

2.4. Islet Isolation and Insulin Secretion. Islets were isolated from five fasting mothers in each group by collagenase digestion of pancreas followed by separation from pancreatic debris by centrifugation on Ficoll gradients as previously described [29]. Groups of five islets were initially incubated for 45 min at 37°C in Krebs-bicarbonate buffer containing 5.6 mM glucose and equilibrated with 95% O₂/5% CO₂, pH 7.4. The solution was then replaced with fresh Krebs-bicarbonate buffer and the islets were incubated for a further 1 h with medium containing 5.6 or 16.7 mM glucose. The incubation medium contained (in mM): NaCl 115, KCl 5, NaHCO₃ 24, CaCl₂ 2.56, MgCl₂ 1, and BSA 0.3% (w/v). The cumulative insulin release during 1 h was quantified by radioimmunoassay using rat insulin as standard.

2.5. Statistical Analyses. Values are presented as means ± S.E.M. For statistical analysis, data were analyzed by two-way repeated measures ANOVA, with mothers' diet and physical training as factors. Bonferroni's *post-hoc* test was used. Each litter of six pups was considered one sample, and statistical analyses were performed by using the mean values of each litter. Significance was set at $P < 0.05$. Data analysis was performed using the statistical program Graphpad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

Body weight was lower in trained rats during the third and fourth weeks pregestation (Figure 1(a)). LP mothers showed a reduction in the body weight when compared to C mothers during gestation ($P < 0.01$), whereas physical training had no effect in the body weight (Figure 1(a)).

The number of pups (litter size) born from mothers was similar among groups. Litter weight, birth weight, and body

weight in the first three days of life of pups from mothers submitted to a low-protein diet during gestation, trained or not, were lower when compared to control (Table 2).

Trained mothers showed an increase of insulin secretion by isolated islets incubated with stimulatory (16.7 mM) concentration of glucose (Figure 2). However, low-protein diet during gestation induced a reduction in the secretion of insulin by isolated islets when compared with both control and LP + T groups (Figure 2).

4. Discussion

Maternal exercise guidelines preconize that 30 min, at least, of moderate-intensity exercise a day on most, if not all, days of the week is satisfactory for health [8]. Following these recommendations, a controlled prospective studies have demonstrated that moderate pregestational exercise (approximately 50% to 70% of VO_{2max}) is useful to increase metabolic rate (reduction of body weight) and improve cardiorespiratory fitness and maternal-fetal physiological reserve [30]. In addition, previous study has demonstrated an improved cardiovascular function, limited gain of body weight, and reduced risk of gestational *diabetes mellitus* and hypertension [31]. In the present study, trained mothers demonstrated reduced body weight in the second and third weeks pregestation, but this normalized throughout gestation. Our results are in agreement with previous studies [21, 24]. It is well established that regular physical exercise increases lean body mass and induces a higher utilisation of fatty acids as fuel by skeletal muscles once the intensity of the exercise is maintained at 65–70% of VO_{2max} [32].

Maternal physical training and low-protein diet did not alter the amount of food intake as seen in previous studies [25, 33]. However, dams submitted to a low-protein diet showed a reduction in body weight in the last week of gestation and the first days postdelivery. Maternal protein restriction is associated with lower stores of maternal nutrients, and it has been found previously that an undernutrition-induced reduction of maternal gain of body weight is positively correlated with a low birth weight, an impaired offspring growth rate, and a loss of lean mass during development [34].

During pregnancy, there is an increase in basal hepatic glucose production, a progressive decrease in insulin sensitivity, and an associated 3.0–3.5-fold increase in insulin response in the last third of gestation [2]. Environmental stimulus as undernutrition can impair the normal hormonal/metabolic response during gestation. Herein we showed that maternal low-protein diet induced a reduction in the secretion of insulin. Our results are in accordance with previous studies where maternal low-protein (6% casein) diet induced impairment in the metabolism of glucose and secretion of insulin [1, 35, 36]. It has been suggested that the poor secretory response to glucose observed in islets from low-protein diet rats may be related to a defect in the ability of glucose to increase Ca²⁺ uptake and/or to reduce Ca²⁺ efflux from β -cells [36] and a reduced islet mass and/or insulin biosynthesis [3].

Given that previous studies have described an inverse relationship between maternal insulin and maternal insulin

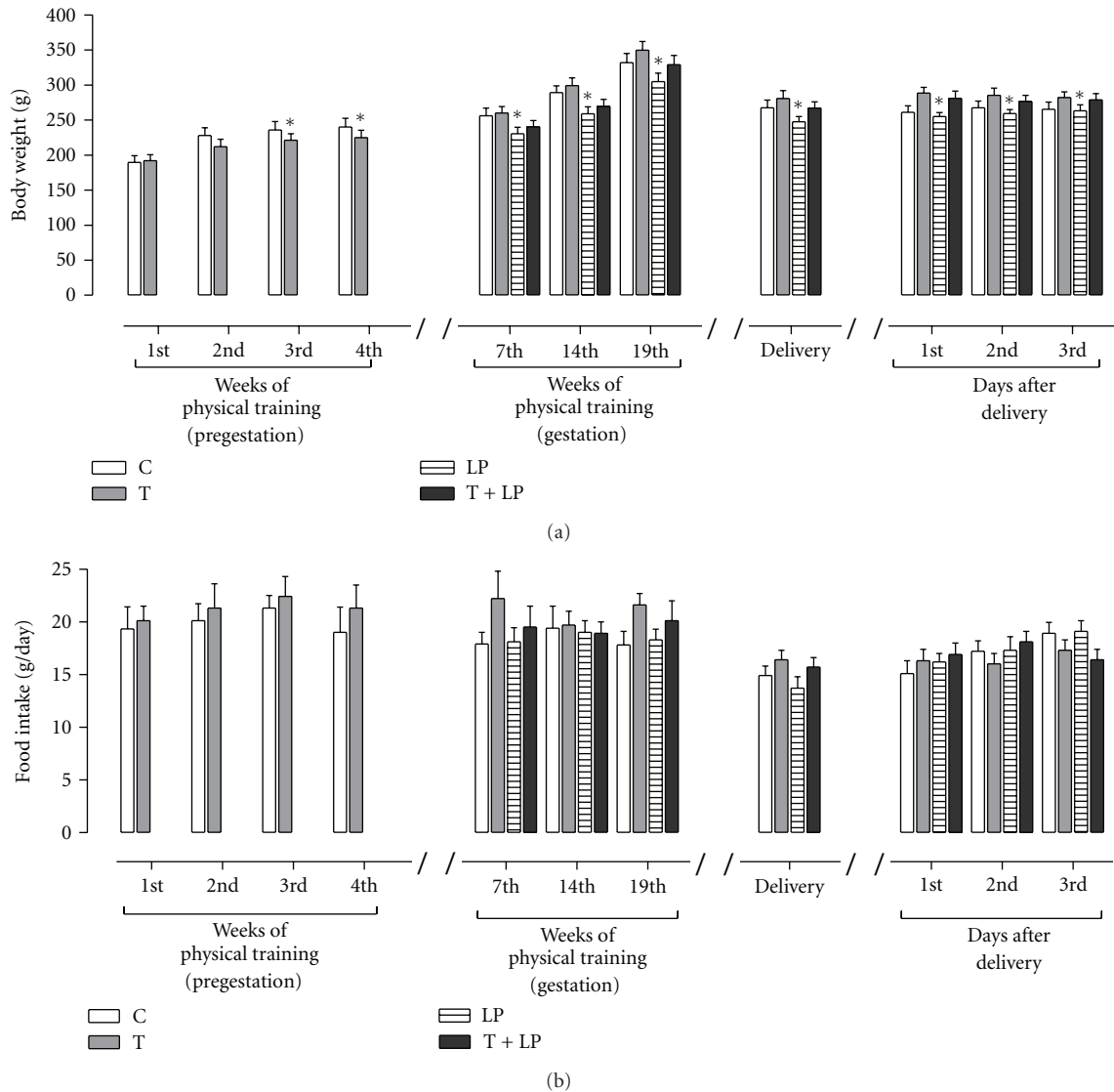


FIGURE 1: Body weight (a) and food intake (b) during pregestational and gestational physical training by control (C, $n = 5$), trained (T, $n = 5$), low-protein diet (LP, $n = 5$), and trained + low protein dams (T + LP, $n = 5$). The protocol of physical training was initiated four weeks before pregnancy (5 days per week, and 60 minutes per day). During gestation, duration and intensity of each session of physical exercise were progressively reduced and each group received either 17% casein diet (C and T) or 8% casein (low-protein group, LP and LP + T) isocaloric diet *ad libitum*. The values are presented as means \pm S.E.M. * $P < 0.05$ versus C group using two-way ANOVA and Bonferroni's *post-hoc* test.

sensitivity with fetal growth restriction, it is expected that the processes governing fetal growth will be also affected. Indeed, we and previous investigators have showed that pups from mothers submitted to a low-protein diet present a reduction in body weight at postnatal period [24, 37–39]. These changes may result from a reduction in nutrient delivery to the fetus, then it would result in lower fetal insulin concentrations and a decrease in fetal IGF-I and IGF-II that would downregulate fetus-placental growth [40].

Little is known about the effects of maternal physical activity on the secretion of insulin. Here, we demonstrated for the first time that a controlled protocol of physical training before and during gestation increased pancreatic islets glucose-stimulated insulin secretion. This effect was

particularly important once maternal protein-restriction has been shown to impair secretion of insulin leading to gestational diabetes as seen in previous study [1]. The underlying mechanism to the effects of maternal physical training on glucose-stimulated insulin secretion remains unknown but can be associated to increased pancreatic β -cell mass by upregulation of growth and survival pathways (AKT, ERK pathways) in pancreatic islets [41]. In addition, it can be resulted from the high peripheral glucose uptake by skeletal muscle in response to moderate physical training. Indeed, our previous study demonstrated that dams submitted to a low-protein diet (8% casein) during gestation present a higher fasting glycaemia than control (17% casein) while trained mothers remained with normal glycaemia [25]. Our

TABLE 2: Indicators of litter size, litter weight, and body weight at birth to 3rd d of life.

	Groups							
	Control		Trained		Low protein diet		Trained + low protein diet	
	Mean	S.E.M	Mean	S.E.M	Mean	S.E.M	Mean	S.E.M
Litter size	11.0	0.3	10	0.2	10	0.3	10	0.2
Litter weight (g)	66.9	0.9	65.2	0.9	55.7*	1.1	55.8*	0.9
Birth weight (g)	7.1	0.09	6.9	0.1	5.7*	0.1	5.9*	0.1
Body weight (g)								
1st d	7.9	0.1	7.1	0.08	5.9*	0.1	6.1*	0.2
2nd d	8.9	0.2	8.7	0.2	5.9*	0.03	5.9*	0.1
3rd d	9.4	0.1	9.7	0.1	6.1*	0.1	6.5*	0.2

During gestation, the dams were submitted to physical training (5 days per week, with a progressively reduction of duration and intensity) and fed a low-protein diet. The pups into each litter were evaluated at birth to 3rd d of life. The values are presented as mean and S.E.M.

* $P < 0.05$ versus C using two-way ANOVA and Bonferroni's *post-hoc* test.

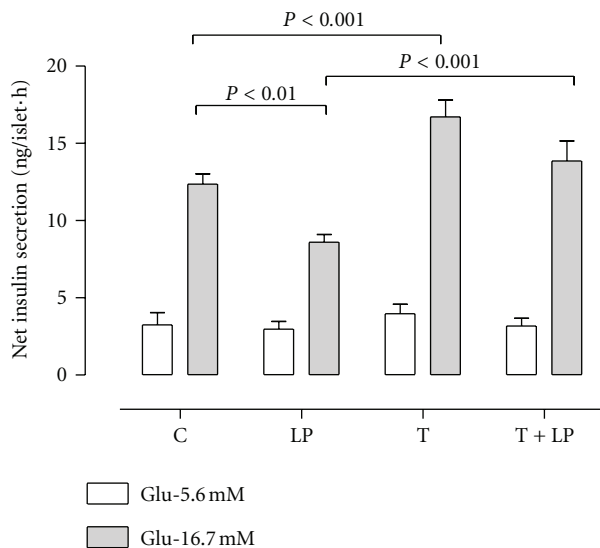


FIGURE 2: Glucose-induced insulin secretion in islets from rats submitted to a protocol of physical training four weeks before gestation and during gestation. During gestation, duration and intensity of each session of physical exercise were progressively reduced and each group received either 17% casein diet (C and T) or 8% casein (low-protein group, LP and LP + T) isocaloric diet *ad libitum*. Groups of five islets were initially incubated for 45 min at 37°C in Krebs-bicarbonate buffer containing 5.6 mM glucose. The solution was then replaced with fresh Krebs-bicarbonate buffer and islets were incubated for a further 1 h with medium containing 5.6 or 16.7 mM glucose. The values are presented as means \pm S.E.M. * $P < 0.05$ versus C group using two-way ANOVA and Bonferroni's *post-hoc* test.

data reinforce the impaired effects of a maternal low-protein diet on the pancreatic islets glucose-stimulated insulin secretion that is preventable by moderate physical training.

The present study demonstrated that a controlled protocol of physical training during gestation resulted in increased insulin secretion, and mothers fed a low-protein diet during gestation showed similar results. This differential effect

observed in the present study refers to dams which were previously trained when were contrasted with pregnancy and low-protein diet. These observations indicate that maternal physical exercise initiated in early pregnancy induces maternal adaptations and can be considered as a therapeutic mean of countering the effects of maternal undernutrition, which may provide a useful strategy since an exercise program may improve insulin sensitivity and fasting plasma glucose concentrations of women at risk for gestational diabetes [26].

Similarly to our results, previous study demonstrated that light-to-moderate physical activity during pregnancy is associated with reduced risk of abnormal glucose tolerance and hyperglycemia during pregnancy [42]. Rats submitted to 10 degrees slope treadmill for 5 days/week at 20 m/min, starting with a 20 min run and with a progressive daily increase of 5 min, throughout gestation showed a lower rise in blood glucose after an oral glucose load (2 g/kg body weight) than untrained pregnant rats [33]. In human, previous study has found that associations between the physical activity and insulin sensitivity and β -cell response do not appear to differ in pregnant versus nonpregnant women [43]. Further experiments are necessary to understand the mechanism underlying to those effects.

5. Conclusions

The present study showed that low-protein diet during gestation affects the secretion of insulin. In contrast, pregestational and gestational moderate physical training acts as an environmental stimulus by increasing insulin secretion and attenuating the effects of perinatal undernutrition in rats, suggesting a potential strategy for compensation of insulin resistance and preventing gestational *diabetes mellitus* during late pregnancy.

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