Early exercise regimen improves insulin sensitivity in the intrauterine growth-restricted adult female rat offspring

Meena Garg, Manikkavasagar Thamotharan, Shilpa A. Oak, Gerald Pan, Duncan C. MacLaren, Lee PW, Devaskar SU. Early exercise regimen improves insulin sensitivity in the intrauterine growth-restricted adult female rat offspring. Am J Physiol Endocrinol Metab 296: E272–E281, 2009. First published November 11, 2008; doi:10.1152/ajpendo.90473.2008.—We examined the effect of early exercise training (Ex) on glucose kinetics, basal, and insulin-stimulated skeletal muscle (SKM) plasma membrane (PM) GLUT4 in pre- and/or postnatal nutrient-restricted adult rat offspring compared with sedentary (Sed) state. Pregestational control female (Ex CON vs. Sed CON) and offspring exposed to prenatal (Ex IUGR vs. Sed IUGR), postnatal (Ex PNGR vs. Sed PNGR), or pre- and postnatal (Ex IUGR + PNGR vs. Sed IUGR + PNGR) nutrient restriction were studied. The combined effect of exercise and pre/postnatal nutrition in the Ex IUGR demonstrated positive effects on basal and glucose-stimulated plasma insulin response (GSIR) with suppression of endogenous hepatic glucose production (HGP) compared with sedentary state. Ex PNGR was hyperglycemic after glucose challenge with no change in glucose-stimulated insulin production or HGP compared with sedentary state. Ex IUGR + PNGR remained glucose tolerant with unchanged glucose-stimulated insulin production but increased endogenous HGP compared with sedentary state. Basal SKM PM-associated GLUT4 was unchanged by exercise in all four groups. Whereas Ex PNGR and Ex IUGR + PNGR insulin responsiveness was similar to that of Ex CON, Ex IUGR remained nonresponsive to insulin. Early introduction of regular Ex in the pregestational female offspring had a positive effect on hepatic adaptation to GSIR and HGP in IUGR and IUGR + PNGR, with no effect in PNGR. Change in insulin responsiveness of SKM GLUT4 translocation was observed in exercised IUGR + PNGR and PNGR but not in exercised IUGR.

glucose tolerance test; metabolic programming; glucose transporter 4; insulin-responsive glucose transporter 4 translocation

RESEARCH DESIGN AND METHODS

Animals

Sprague-Dawley rats (Charles River Laboratories, Hollister, CA) were housed in individual cages, exposed to 12:12-h light-dark cycles at 21–23°C, and allowed ad libitum access to standard rat chow (composition carbohydrate 63.9%, fat 4.5%, and protein 14.5%). The National Institutes of Health guidelines were followed as approved by the Animal Research Committee of the University of California Los Angeles.

Maternal Nutrient Restriction Model

Pregnant rats received 50% of their daily food intake (11 g/day) beginning from day 11 through day 21 of gestation, which constitutes mid- to late gestation, compared with their control (CON) counter-
parts that received ad libitum access to rat chow (22 g/day). Both groups had ad libitum access to drinking water. At birth, the litter size was culled to six to ensure no interlitter nutritional variability. Postnatally, the cross-fostering of animals generated four experimental groups, as described previously by us (19). Briefly, the newborn pups born to ad libitum feeding CON mothers were reared either by mothers on seminutrient restriction from PN1–PN21 (PNGR) or by CON mothers (Fig. 1A). The intrauterine semi-nutrient-restricted progeny was fed either by CON mothers with ad libitum access to nutrients representing intrauterine nutrient restriction (IUGR) alone or by semi-nutrient-restricted mothers representing a combination of intrauterine and postnatal nutrient restriction (IUGR + PNGR) (Fig. 1A). After being weaned from the mother, all animals had ad libitum access to food and water.

**Moderate ET**

Postweaned animals in all four groups underwent daily supervised ET, whereas another set of postweaned animals in each group were maintained under sedentary conditions from PN21 to PN60 (~2 mo). The ET comprised of running on a motorized treadmill at a speed of 11 m/min for 15 min/day, spanning 5 days/wk and lasting for a total of 6 wk (Fig. 1B). This moderate exercise regimen was devised to accommodate the perinatally energy-restricted animal groups in our study.

**Surgical Catheter Placement**

The adult females were anesthetized using an anesthetic cocktail of ketamine HCl (50 mg/kg) and xylazine (4.5 mg/kg) by intraperitoneal injection (19). Jugular vein catheters were inserted aseptically and maintained patent with heparinized saline, as described previously (19). All animals were allowed full recovery from the surgical procedure prior to glucose tolerance tests (GTTs) being conducted.

**Intravenous GTT**

All tests were performed in the resting state 48–72 h after ET was completed following an overnight fast. The awake animals received 1 g/kg body wt of the 1:1 mixture of [2-2H]- and [6,6-2H2]glucose via the surgically placed jugular vein catheters. Blood (500 μl) was obtained at 0, 5, 15, 30, 60, and 120 min for assessment of glucose and insulin concentrations and isotopomer enrichment (19).

**Insulin Tolerance Test**

Awake adult females received 0.75 U/kg of human insulin via the jugular venous catheter, and blood was obtained at 0, 15, 30, and 60 min subsequently to measure glucose concentration (41).

**Plasma Assays**

Plasma was separated and aliquots stored for measurement of glucose by the glucose oxidase method (sensitivity = 0.1 mM; Sigma Diagnostics, St. Louis, MO). Insulin was quantified by enzyme-linked immunosorbent assays using rat standards and anti-rat insulin antibody (sensitivity: insulin = 0.2 ng/ml; Linco Research, St. Charles, MO). Homeostasis model of insulin resistance (HOMA-IR) was calculated on the basis of these measured values.

**Gas Chromatography-Mass Spectrometry Analysis**

Glucose was analyzed by modified gas chromatography-mass spectrometry method, as described previously (19, 43, 44). All isotopometric determinations were performed using a Hewlett-Packard gas chromatograph (model 6890) connected to a mass selective detector (model 5973A) (Hewlett-Packard, Palo Alto, CA). Electron impact ionization was used to characterize glucose positional isotopomers of [6,6-2H2]glucose at mass-to-charge ratio (m/z) of 187 for C3–C6 of [2-2H]glucose at m/z of 242 for C1–C4 fragments (19, 44).

**Analysis and Interpretation of Glucose Tolerance Test**

Mass isotopomer distribution was determined using the method of Lee et al. (27). Briefly, disappearance of the two isotopes [2-2H]- and [6,6-2H2]glucose was determined for the M1 label that represented [2-2H]glucose and the M2 label that represented the [6,6-2H2]glucose (19, 43, 44). The difference between disappearance rates of M1 and M2 was used as a measurement of futile cycling (i.e., glucose to glucose 6-phosphate and back) (19, 27).

**SKM AMPK Studies**

To validate our exercise regimen, SKM AMPK enzyme activity was initially measured after an acute 15-min bout of similar treadmill training in control animals and compared with their respective sedentary controls. To guard against detecting remnant effects from the last 15-min bout of acute exercise that can potentially contaminate the chronic effects of exercise lasting over 6 wk duration, we measured SKM total AMPK, phosphorylated AMPK (pAMPK) (32), and AMPK enzyme activity (28, 42) in all four exercise (Ex) groups 48–72 h after their last 15-min bout of exercise and compared them with their respective Sed groups.

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**Fig. 1.** A: study design demonstrating the control (CON) group and nutrient restriction achieved by cross-fostering postnatal rat pups. Nutrient-restricted mothers received 50% of daily nutrient intake from mid- to late pregnancy [embryonic days 11 (e11) to 21 (e21)] through lactation [postnatal days 1 (PN1) to 21 (PN21)]. B: experimental protocol for exercise (Ex) in 4 groups is shown. The CON and nutrient-restricted groups of animals either underwent supervised exercise or remained sedentary; (Sed) from PN day 21 to PN day 60 (d60) (2 mo). Ad lib, ad libitum; IUGR, intrauterine growth restricted; PNGR, postnatal growth restricted.
Western Blot Analysis

The animals were deeply anesthetized with inhalational isoflurane to maintain organ blood flow, and SKM was rapidly separated from all four Ex and Sed groups. To examine insulin action, skeletal muscle homogenates were prepared. PM and low-density microsomal (LDM) subfractions were isolated as described previously, and the homogenate, determined by marker enzyme enrichment. The homogenate, were isolated as described previously, and the relative purity was were prepared. PM and low-density microsomal (LDM) subfractions
were isolated. The Western Blot Analysis

AMPK Enzyme Activity

Five milligrams of skeletal muscle homogenate supernatants were incubated overnight at 4°C with protein A/G Sepharose beads pre-bound for 2 h at 4°C (32) at a 1:500 dilution to antibodies raised against total AMPK (containing α1 and α2 isoforms, H-300; Santa Cruz Biotechnology) or specifically against either nonconserved rat AMPKα1 peptide (amino acids 231–251) or rat AMPKα2 peptide (amino acids 351–366) (Cell Signaling Technology, Boston, MA) both collectively comprised of AMPKα1 and α2 isoforms. Protein bands were visualized by using the enhanced chemiluminescence method (Amersham Biosciences, Piscataway, NJ). The quantification of protein bands was performed by densitometry using the Scion Image software (32).

Skeletal Muscle GLUT4 Studies

To investigate the effect of exercise, skeletal muscle homogenates from all four Ex and Sed groups were employed. To examine insulin responsiveness of SKM GLUT4 translocation, 2-mo-old female animals from all four Ex groups received either vehicle or insulin (8 U/kg by intraperitoneal injection). After 20 min, the predetermined optimal time point hindlimb SKM was harvested, and subcellular fractions were prepared. PM and low-density microsomal (LDM) subfractions were isolated as described previously, and the relative purity was determined by marker enzyme enrichment. The affinity-purified rabbit anti-rat GLUT4 antibody (1:2,500 dilution) was used as the primary antibody (40, 41).
IUGR + PNGR groups (\(P < 0.001\), Holm-Sidak test), whereas brain weights increased in Ex CON, Ex IUGR, Ex PNGR, and Ex IUGR + PNGR groups vs. their Sed counterparts (\(P < 0.001\), Holm-Sidak test). Brown adipose tissue weight was no different, but abdominal white adipose tissue increased in Ex CON and Ex IUGR groups (\(P < 0.001\) and \(P < 0.001\), Holm-Sidak test; Table 1).

ET did not alter fasting plasma glucose concentration (Table 2); a significant decrease in fasting plasma insulin concentration was observed by exercise alone (\(F = 11.16, P < 0.002\)) and by pre/postnatal nutrition alone (\(F = 3.69, P < 0.001\), Holm-Sidak test; Table 1).

ET decreased HOMA-IR values significantly in Ex CON and Ex IUGR groups (\(P < 0.03\), Holm-Sidak test), supporting improved insulin sensitivity vs. their Sed counterparts (Table 2). The Ex

### Glucose tolerance test - Plasma glucose concentrations

![Graph A](image1)

### Glucose tolerance test - Plasma glucose AUC

![Graph B](image2)

### Glucose tolerance test - Plasma insulin concentrations

![Graph C](image3)

### Glucose tolerance test - Plasma insulin AUC

![Graph D](image4)

Fig. 2: A: plasma glucose concentration at 0, 5, 15, 30, 60, and 120 min after intravenous glucose challenge is shown in Ex and Sed states in individual graphs (graph 1, CON; graph 2, PNGR; graph 3, IUGR; graph 4, IUGR + PNGR). *\(P < 0.006\), **\(P < 0.02\), ***\(P < 0.05\), Ex vs. Sed counterpart. B: area under the curve (AUC) for plasma glucose concentration during glucose tolerance test (GTT) is shown for all groups. Two-way ANOVA revealed a significant effect of exercise alone (\(F = 0.491, P = 0.488\)) or pre/postnatal nutrition (\(F = 0.653, P = 0.586\)) alone. Holm-Sidak test showed *\(P < 0.04\), Ex CON vs. Sed CON; **\(P < 0.03\), Ex PNGR vs. Sed PNGR. C: plasma insulin concentration at 0, 5, 15, 30, 60, and 120 min after an intravenous glucose challenge is shown in Ex and Sed states in individual graphs (graph 1, CON; graph 2, PNGR; graph 3, IUGR; graph 4, IUGR + PNGR). The scale for plasma insulin is adjusted from 0 to 50 nmol/l to show the lower values in PNGR (graph 2) and IUGR + PNGR (graph 4). Holm-Sidak test showed a significant decrease at 5, 15, 30, 60, and 120 min in Ex CON and Ex IUGR compared with their respective Sed states; n = 6 for all study groups, except n = 5 each for Sed and Ex PNGR groups alone.
PNGR and Ex IUGR + PNGR groups remained unchanged from the sedentary insulin-sensitive state.

GTT and Glucose-Stimulated Insulin Release

An intravenous glucose challenge led to a lower peak plasma glucose concentration at 5 min in Ex CON (Holm-Sidak test, $P < 0.007$; Fig. 2A, graph 1) compared with that of Sed CON. The plasma glucose concentration was higher at 5 and 15 min in Ex PNGR (Holm-Sidak test, $P < 0.02$ and $P < 0.05$ respectively; Fig. 2A, graph 2) vs. Sed PNGR, but Ex IUGR (Fig. 2A, graph 3) was similar to Sed IUGR. The interactive effect of exercise $\times$ pre/postnatal nutrition resulted in a reduced glucose area under the curve (AUC) in Ex CON ($P < 0.04$ by Holm-Sidak test; Fig. 2B) but significantly increased AUC in Ex PNGR ($P < 0.03$ by Holm-Sidak test). Euglycemia during GTT was maintained by a significant lowering of the glucose-stimulated insulin release (GSIR) at 5, 15, and 30 min (Fig. 2C, graphs 1 and 3) and a lower insulin AUC ($P < 0.001$ by Holm-Sidak test; Fig. 2D) in Ex CON and Ex IUGR groups. These findings support improved insulin sensitivity. The GSIR in Sed PNGR and Sed IUGR + PNGR was decreased vs. Sed CON but did not change further after ET (Fig. 2C, graphs 2 and 4).

Insulin Tolerance Test Reflecting Insulin-Stimulated Glucose Uptake

The percent decrease in plasma glucose concentration from the zero time value was greater at 15 and 30 min in Ex PNGR, Ex IUGR, and Ex IUGR + PNGR groups and at 60 min in Ex IUGR and Ex IUGR + PNGR (Fig. 3A, graphs 1–4) vs. their Sed counterparts. This resulted in decreased percent glucose AUC in Ex IUGR and Ex IUGR + PNGR after ET ($P < 0.00001$ by Holm-Sidak test; Fig. 3B).

Glucose Metabolic Adaptations After a Glucose Challenge

Hepatic glucose production. ET resulted in greater suppression of endogenous hepatic glucose production (HGP) during the GTT in Ex CON and Ex IUGR at various time points (5, 15, 30, and 60 min) compared with that of Sed CON and Sed IUGR, respectively. Sixty minutes after the glucose challenge, HGP in Ex IUGR was suppressed to a greater extent than that observed in Ex CON, Ex PNGR, and Ex IUGR + PNGR ($P < 0.04$ by Holm-Sidak test). This translated into a greater suppression of HGP AUC in Ex CON and Ex IUGR ($P < 0.05$ by Holm-Sidak test; Fig. 4A). The HGP AUC in Ex PNGR did not change, whereas it increased by 11% in Ex IUGR + PNGR.
from their sedentary counterparts (Fig. 4A). These findings support improved insulin sensitivity only in the Ex IUGR vs. the Sed IUGR being similar in range to that achieved by the Ex CON vs. Sed CON.

Glucose clearance and hepatic glucose recycling. The resting glucose clearance rate was unchanged after ET (Fig. 4B). Hepatic glucose futile cycling (GFC) increased in Ex IUGR + PNGR compared with the nonexercised state, an adaptation geared toward meeting the glucose requirements. Hepatic glucose recycling in Ex CON, Ex PNGR, and Ex IUGR groups was similar to that of their respective sedentary group.

**SKM Studies**

**AMPK protein concentrations and enzyme activity.** The AMPKα1 and AMPKα2 activity was increased in Ex CON 15 min after an acute bout of exercise compared with Sed CON (P < 0.04 and P < 0.01, respectively; Fig. 5A). In contrast, when pAMPK and total AMPK protein concentrations were examined 48–72 h after cessation of the chronic exercise regimen, there was no statistical difference in all experimental groups between Sed and exercised rat SKM (Fig. 5B). Separate and combined AMPKα1 and -α2 enzyme activity in all exercised groups was also not significantly different from that of the sedentary counterparts (Fig. 5C).

**Total and subcellular GLUT4 protein distribution.** Examination of total GLUT4 protein revealed no differences between Ex and Sed states in all four experimental groups (Fig. 5D). We have previously reported increased SKM basal PM-associated GLUT4 concentrations in Sed IUGR and Sed IUGR + PNGR groups, which was unresponsive to exogenous insulin administration (41). After ET, the basal SKM PM- and LDM-associated GLUT4 protein concentrations in Ex IUGR, Ex PNGR, and Ex IUGR + PNGR groups were no different from each other, being similar to that of Ex CON (Fig. 5E). Insulin-responsive SKM GLUT4 translocation to PM from LDM was observed in Ex IUGR + PNGR (P < 0.05) and Ex PNGR (P < 0.05) groups, the former being more and the latter being less than that seen in Ex CON, but was absent in Ex IUGR (Fig. 5E). Similar to Ex CON, the attaining of insulin-responsive SKM GLUT4 protein translocation from LDM to PM over that not present in the previously reported sedentary counterpart (41) was observed only in the Ex IUGR + PNGR group that overshot the Ex CON group (P < 0.05).

**DISCUSSION**

**Effect of Exercise**

The positive effect of exercise on glucose kinetics, GSIR, and skeletal muscle PM GLUT4 association was observed in the CON group as anticipated. Most animal investigations link IUGR to adult-onset glucose intolerance and tissue-specific insulin resistance, lending credence to the Barker hypothesis (1, 2). The IUGR adult female develops gestational diabetes (7) and poses additional risk of transgenerational inheritance of the insulin-resistant phenotype (9, 39). Therefore, we focused the present study on the critical pregestational phase by initiating submaximal exercise training prior to the appearance of gestational diabetes with the onset of pregnancy (7). Exercise training in IUGR offspring improved insulin sensitivity by suppressing glucose-stimulated insulin production and hepatic glucose production. It also altered baseline skeletal muscle PM GLUT4 concentrations similar to that seen in Ex CON but did not further affect the insulin-responsive PM association of GLUT4.

Epidemiological human studies indicate that premature birth and catchup growth are associated with insulin resistance and higher susceptibility to adult chronic diseases (4, 33, 34). Further poor growth during infancy also predisposes toward glucose intolerance and type 2 diabetes mellitus (6). Contrary to our expectation in the pregestational PNGR group, early exercise training resulted in hyperglycemia with a 20% increase in glucose AUC without perturbations in basal glucose
or basal and GSIR compared with the sedentary counterpart and Ex CON. This was despite partial insulin responsiveness of skeletal muscle PM GLUT4 association. Inadequacy of basal energy stores (fat and glycerogen) and the superimposed increased metabolic demands of early exercise training may cause a shortfall in replenishing depleted stores. This in turn may cause a dependency on unsuppressed hepatic glucose production to meet the exercise-induced metabolic demands. The resultant hyperglycemia may have decreased hepatic glucose recycling.

Early implementation of exercise training in the Ex IUGR + PNGR group improved insulin sensitivity and maintained eu-glycemia due to the adaptive decrease in GSIR and increase in HGP, GFC, and insulin responsiveness of skeletal muscle PM GLUT4 association (41). Thus early exercise training in the pregestational state may prove protective when exposed to additional metabolic stress as encountered in a pregnant state.

These results indicate that the exercise-induced glucose metabolic adaptations are specifically tailored to the preexisting metabolic phenotype. Although these adaptations ameliorate hepatic insulin resistance in IUGR, they have no effect in PNGR. Thus, when considering exercise regimen in the prevention of T2DM, the lack of an effect in a preexisting PNGR phenotype is a distinct possibility.

Insulin Sensitivity

Benefits of acute exercise and endurance training in human and rat consist of lowered insulin concentrations, improved glucose tolerance, and insulin sensitivity. The latter is achieved by decreasing hepatic glucose production and enhancing skeletal muscle glucose utilization (8, 11, 14, 20, 21, 30). In the adult female IUGR offspring, we have previously observed increased GSIR and diminished HGP during GTT (19). Several studies demonstrate that modest weight loss and physical activity can reduce the risk of diabetes (16, 26, 31). Human studies show that moderate levels of endurance and resistance training protect adult males and females with impaired glucose tolerance from developing type 2 diabetes (26). Furthermore, regular exercise protects adult human males and females born with a low birth weight (16). Similar to these observations, our present results demonstrate beneficial effects of exercise training in the presence of preexisting conditions such as IUGR that are of high risk for adult-onset diabetes mellitus. T2DM is a progressive disease where the β-islets fail in the face of increasing insulin resistance, which in turn is linked to obesity and sedentary lifestyle (29). The acquisition of these pheno-
typic features can be prevented by regular exercise and physical activity (10, 15, 18, 23, 24, 45). Moderate exercise prior to overt symptoms may preserve pancreatic β-islet cell function and prevent the onset of chronic insulin resistance. Our present results demonstrated enhanced insulin-responsive glucose uptake during insulin tolerance test in all exercised nutrient-restricted groups (Ex IUGR, Ex PNGR, and Ex IUGR + PNGR) compared with their corresponding sedentary counterparts. These responses further support that moderate exercise training prior to developing glucose intolerance or obesity improved insulin sensitivity in the IUGR female offspring.

Fig. 5. A: skeletal muscle AMPKα1 and α2 isofrom-specific activities measured 15 min after acute Ex (n = 4) or in a Sed state (n = 3) and expressed as a percent of the sedentary CON state are shown in a subgroup of control animals. *P < 0.04, acute Ex vs. Sed CON; **P < 0.01, acute Ex vs. Sed CON. B: skeletal muscle pAMPK and total AMPK protein concentrations were no different between the Sed and Ex groups (n = 3 each for all groups). Representative Western blots are shown at top, and the densitometric quantification of pAMPKtotal AMPK expressed as a percent of Sed CON is shown as a bar graph. C: skeletal muscle AMPK (AMPKα1 and α2 isoforms) enzyme activity measured 48–72 h after the last bout of exercise training (n = 3–4 each for all groups) did not significantly change when compared with the Sed counterpart (n = 3–4 each for all groups). Representative Western blots are shown at top, and the densitometric quantification of pAMPKtotal AMPK expressed as a percent of Sed CON is shown as a bar graph. D: skeletal muscle total GLUT4 protein concentrations were no different between the Sed and Ex groups (n = 3 each for all groups). Representative Western blots of GLUT4 and vinculin (internal control) are shown at top, and the densitometric quantification of total GLUT4/vinculin expressed as a percent of Sed CON is shown as a bar graph. E: basal and insulin-responsive skeletal muscle GLUT4 distribution in plasma membrane (PM) and low-density microsomes (LDM) of Ex CON, Ex PNGR, Ex IUGR, and Ex IUGR + PNGR is shown; n = 3 each for PM and LDM in all experimental groups. Top: representative Western blots of GLUT4 in PM and LDM subfractions in the presence (+) and absence (−) of insulin administration in the 4 Ex groups (Ex CON, Ex PNGR, Ex IUGR, and Ex IUGR + PNGR). The densitometric quantification is expressed in arbitrary units as a bar graph. PM GLUT4 concentrations increased after insulin administration (+) vs. the corresponding basal state (−) in Ex CON, Ex PNGR, and Ex IUGR + PNGR (*P < 0.05) but not in Ex IUGR. PM GLUT4 concentrations in the Ex IUGR + PNGR were higher than Ex CON (#P < 0.05). Sed state results were reported previously (41) and not shown.
regarding the effect of exercise training on reversing preexisting perturbed skeletal muscle subcellular GLUT4 distribution (41). Six weeks of exercise training led to partial reversal in Ex IUGR by bringing basal PM GLUT4 concentration closer to that of Ex CON. Therefore, although this submaximal exercise training improved basal insulin sensitivity of skeletal muscle PM GLUT4 association in Ex IUGR, no further response to exogenous insulin administration was observed. Such disparity in the exercise-induced response of glucose homeostasis was previously described to depend on the severity of the preexisting metabolic perturbation. This includes an example of improved glucose tolerance in a mild state of diabetes (20), with no effect in the severe insulin-deficient state (21). Along similar lines, perhaps exogenous insulin in IUGR has no further effect on chronically exercised skeletal muscle PM GLUT4 concentrations while affecting that of IUGR + PNGR. An alternate explanation may be that, in the IUGR, exercise had a maximal impact with no further room for an added insulin effect. In contrast, the IUGR + PNGR group while exercised still retained some insulin sensitivity of the skeletal muscle GLUT4. At the same time, intertissue differences between the effects of exercise on liver vs. skeletal muscle within the same experimental group (IUGR or IUGR + PNGR) may relate to end-organ specificity and sensitivity. Whether a more intense exercise regimen than the one we employed would demonstrate insulin responsiveness of skeletal muscle PM GLUT4 association in Ex IUGR remains unknown. Since skeletal muscle GLUT4 expression in insulin-resistant obese Zucker rat parallels the intensity of the exercise regimen instituted (12), this is a possibility in the Ex IUGR as well. Total glucose clearance in Ex CON was similar to Ex IUGR, Ex PNGR, and Ex IUGR + PNGR. These observations support a previous report of unaltered skeletal muscle glucose uptake due to moderate exercise of endurance training in female rats (38).

Summary

Early exercise training in the nutrient-restricted offspring that positively regulates the growth potential impacts tissue-specific adaptations involved in nutritional programming of glucose kinetics. This occurs in a phenotype-specific manner, proving advantageous to the IUGR and IUGR + PNGR, but without affecting the PNGR adult female offspring.

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