Physical Exercise Increases Glucose Uptake in Skeletal Muscle of Obese Mice Through Rho-Kinase Metabolism

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PURPOSE: Obesity promotes several metabolic disorders, including insulin resistance (IR). It is known that physical exercise is an important non-pharmacological agent in the prevention and treatment of IR and consequently reducing the incidence of T2DM. Rho-kinase (Rock) has been postulated as an important protein that acts directly on the phosphorylation of IRS-1, collaborating up to 50% of glucose uptake in skeletal muscle tissue. Therefore, the aim of this study was to evaluate if physical exercise modulates Rock activity and whether the increase of glucose uptake by muscle tissue of obese and insulin resistant mice after physical exercise also occurs due to Rock metabolism.

METHODS: Twenty-four Swiss mice (4 weeks old) were divided into 3 groups (8 animals / group): Sedentary Control (C) sedentary animals fed with control diet, Sedentary Obese (SO) sedentary animals fed with HFD and Trained Obese (TO) animals fed with HFD and submitted to the training protocol. Protocol training was carried out for 1h / day, 5 days / week during 8 weeks and it was performed at the intensity of 60% of maximum power, which was determined at the beginning of the experiment. During the last experimental week the insulin tolerance test (ITT) and glucose tolerance test (GTT) were performed. Twenty four hours after the last exercise session the animals were euthanized and the muscle was harvested for subsequent analysis.

RESULTS: It was seen that in obesity condition there was a decrease of Rock activity in muscle tissue. This finding was, in part, due to the increase of RhoE, molecule that inhibits Rock activity and decrease of RhoA, molecule that increases Rock activity, which culminated in a lower activity of Rock and consequently lower phosphorylation of IRS-1/Akt pathway and thus lower glucose uptake, which collaborated with insulin resistance in obese. However, after physical exercise, obese mice showed their state of Rock metabolism reversed. It was found increase of RhoA and Rock levels and reduced level of RhoE.

CONCLUSION: Physical exercise can contribute to glucose homeostasis through Rock metabolism for obese mice. Thus, these results reveal a new mechanism by which physical exercise collaborates on glucose uptake in skeletal muscle of obese and insulin resistant animals without the use of insulin.

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Maternal Obesity Programs Offspring Muscle Mitochondrial Function: Response to Postweaning Diet

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A high-fat (HF) diet induces metabolic disease while initially increasing muscle mitochondrial content: a putative compensatory response to increased reactive oxygen species (ROS). Maternal obesity exacerbates the metabolic syndrome phenotype in offspring weaned to a HF diet, but little is known about the effects of maternal obesity on mitochondrial function.

PURPOSE: To determine whether maternal obesity influences the mitochondrial function in offspring weaned to a HF diet.

METHODS: Female mice were fed a control (CON, 10% kcal) or HF (45% kcal) diet to induce maternal obesity prior to mating. Diets were maintained throughout pregnancy and lactation. Male offspring (n=30) were weaned to HF or CON diet creating 4 groups (CON/CON, CON/HF, HF/CON, HF/HF). At 12 months body composition (DEXA) and mitochondrial function in permeabilized gastrocnemius bundles (high-resolution respirometry) was determined.

RESULTS: Newborns and adult offspring of obese dams were heavier than CON. Percent lean body mass was lower in offspring of obese mice, and those weaned to a HF diet (71±2, 52±2, 60±2, 50±1% in the 4 groups respectively; effect of maternal obesity: p<0.05). Flux control ratio for ADP+PC was also greater in HF diet (p<0.05). Flux control ratio for ADP+PC was also greater in HF diet (p<0.05). Flux control ratio for ADP+PC was also greater in HF diet (p<0.05). OXPHOS capacity tended to be lower in offspring of obese dams (64±16, 82±21 vs. 56±16, 72±12 pmol/s/mg, effect of maternal obesity p<0.02) and was accompanied by a greater LEAK respiration (5.7±3.1, 7.5±2.1 vs. 8.0±2.3, 8.7±3.8 pmol/s/mg, effect of maternal obesity p=0.06).

CONCLUSIONS: Greater LEAK in offspring of obese dams indicates pathologically dyscoupled respiration, perhaps consequent to increased ROS. Despite this, muscle oxidative capacity tended to be lower in the muscles of offspring of obese dams. Maternal obesity may contribute to HF-diet associated metabolic disease by ameliorating the compensatory increase in muscle mitochondrial content and function.

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Influence of Dietary Omega-3 Fatty Acids on Mitochondrial Biology in Skeletal Muscle of Older Humans

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PURPOSE: Aging is associated with reduced mitochondrial abundance and oxidative capacity in skeletal muscle. There are also intrinsic mitochondrial abnormalities with aging such as lower energetic efficiency and increased emission of reactive oxygen species (ROS). This so-called "mitochondrial dysfunction" is one of several factors that contribute to impaired physical function with age. We previously reported that dietary omega-3 fatty acids (n3-PUFAs) increase the expression of genes that regulate mitochondrial biogenesis and enhance mitochondrial capacity in muscle of old mice. We conducted a human intervention study to determine if the beneficial effects of n3-PUFAs on mitochondrial function were evident in aging humans.

METHODS: 12 older (67-83 yrs) adults were studied at baseline and after 4 months of n3-PUFA supplementation (4g/day). 12 young adults (19-34 yrs) were studied as a comparison group at baseline. Vastus lateralis muscle biopsies were collected in the postabsorptive state. High-resolution respirometry was used to evaluate the oxidative capacity and coupling of isolated mitochondria. Hydrogen peroxide emission was measured by spectrofluorometry. Muscle gene expression profiles were evaluated by RNA sequencing.

RESULTS: Older adults exhibited significantly lower oxidative capacity using substrates specific to carbohydrate oxidation (young: 6.60±0.70 pmol/s/ug, old: 4.67±0.47 pmol/s/ug, p=0.032) and lipid oxidation (young: 1.42±0.14 pmol/s/ug, old: 0.94±0.12 pmol/s/ug, p=0.016). Oxidative capacity was unchanged following n3-PUFA supplementation for carbohydrate substrates (3.99±0.38 pmol/s/ug) or lipid substrates (0.89±0.11 pmol/s/ug). However, mitochondrial ROS emission was significantly reduced following n3-PUFA supplementation in older adults (baseline: 671±78 pmol/s, follow-up: 530±62 pmol/s, p<0.001). None of the 764 mitochondrial-related genes measured by RNA sequencing were induced by n3-PUFAs in older adults.

CONCLUSIONS: Unlike aged mice, older humans do not exhibit any evidence of mitochondrial biogenesis or improvements to mitochondrial oxidative capacity in skeletal muscle in response to dietary n-3 FAs. However, n3-PUFAs may hold promise for reducing skeletal muscle oxidative stress by reducing mitochondrial ROS production.