15P15

The beneficial effects of medium-chain fatty acids on metabolism and oxidative stress

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Dietary intake of long-chain fatty acids (LCFA, C>16) plays a causative role in insulin resistance and risk of diabetes. Whereas LCFA promote lipid accumulation and have detrimental effects on metabolic health, diets rich in medium-chain fatty acids (MCFA; C8–C14) have been associated with increased oxidative metabolism and reduced adiposity, with little effect on insulin action *in vivo*. The molecular mechanisms underlying these differences are poorly understood. To shed light into this question, we have treated L6 myotubes with specific MCFA (capric acid, 10:0 and lauric acid, 12:0) and LCFA (palmitic acid, 16:0 and oleic acid, 18:1) and determined the effect of fatty acid treatment on metabolic parameters including triglyceride accumulation and insulin-stimulated glycogen synthesis as a measure of insulin sensitivity. A potential mechanism linking lipid accumulation and insulin resistance is increased oxidative stress within the insulin-sensitive tissue. Therefore, these studies were extended by measuring reactive oxygen species (ROS) production and oxidative damage in muscle cells treated with different fatty acids.

Incubation of myotubes with LCFA led to lipid accumulation (+90% with palmitic acid vs. control BSA-treated cells, $p<0.01$), impaired glycogen synthesis (−40%, $p<0.05$) and decreased succinate dehydrogenase activity (−40–55% vs. control, $p<0.05$), however these deleterious effects were not observed in the MCFA-treated myotubes. Furthermore, ROS generation (both superoxide and hydrogen peroxide), measured using HPLC and spectrophotometry, was not significantly altered with MCFA, but was significantly greater in the LCFA-treated cells (+500% vs. control, $p<0.001$), suggesting that MCFA might prevent the induction of oxidative stress. Increased oxidative stress with LCFA, but not MCFA, was confirmed by measuring a marker of lipoxidative damage, lipid hydroperoxides, which were increased by LCFA (+40% vs. control, $p<0.01$), but remained unchanged in the MCFA-treated cells.

These results show that treatment of muscle cells with MCFA does not produce the detrimental metabolic effects observed when cells are exposed to LCFA. A potential mechanism is the differential effects observed in ROS production and oxidative damage in the MCFA- and LCFA-treated L6 myotubes.

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15P16

Obesity generates metabolic alterations in the myocardium leading to changes in mitochondrial membrane permeability

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Obesity is a chronic disease of multifactorial origin, characterized by an excessive accumulation of fat that generates multiple metabolic disorders leading to cardiovascular diseases (concentric cardiac hypertrophy, hypertension, atherosclerosis and heat failure), diabetes mellitus type 2, among others. High lipid accumulation has been found in the heart of obese rats and humans[1], and in addition it has been described that the apoptotic signaling pathway is active in hearts from obese patients[2]. Apoptotic cell death involves several mechanisms; one of them is the mitochondrial permeability transition (MPT), phenomenon that is activated by ionic deregulation and high production of reactive oxygen species (ROS). In this work we have evaluated the mechanism by which the MPT apoptotic pathway is activated in hearts from obese rats (mOb).

The results show that mitochondria from mOb were 2.5 and 3 times more susceptible to MPT than mitochondria from Lean rats (mLean) when the respiratory chain was supplemented with Glutamate–Malate (GM) or Glutamate–Succinate (GS). However, this effect was not observed in the presence of Succinate-rotenone, as substrate. In all experimental conditions, cyclosporine A (CSA) protected the mitochondria, therefore, suggesting that the main mechanism involved in the MPT is the high ROS production. Since the NADH dehydrogenase is one of the enzymes that generate ROS, and, under conditions of GS, the succinate dehydrogenase generates even more ROS[3], we analyzed the oxidative stress, finding higher production of H_2O_2 in mOb than in mLean, mainly when the substrate was GS. On the other hand, when the MPT was induced with carboxiatractyloside (CAT), an inhibitor of the adenine nucleotide translocase (ANT), the susceptibility to MPT was higher in mOb than mLean, using GM as substrate and in the presence of CAT 1.5 μM, and even more susceptible in the presence of GS and CAT 0.4 μM. Probably because ROS is higher in mOb, and they may induce conformational changes in mitochondrial proteins, increasing the binding of CAT and accelerating the MPT. Finally, mitochondrial integrity was evaluated by measuring respiration, and the results show that the respiratory control and oxygen consumption in state 3 was lower in mOb; the effect was observed only in the presence of GM. These results suggest that ATP synthesis might be impaired due to decreased membrane potential in mOb and contributes to MPT sensitivity. Conclusion: The mOb has a higher sensibility to MPT than mLean and the principal mechanism involved is the ROS production.

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15P17

Anti-mitochondrial therapy in human breast multi-cellular spheroids

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During growth of solid tumors, gradients of oxygen and nutrients develop inducing specific metabolic changes in the proliferative and quiescent cellular layers. An integral analysis of proteomics, metabolomics, kinetomics and fluxomics revealed that both enrich-proliferative (PRL) and -quiescent (QS) cellular layers of mature