According to the research field of scientists, either β-cell, peripheral insulin sensitivity, adipose tissue and related complex signalling environment is believed to be central in the pathology of type-II diabetes. Nevertheless and because of our interest in liver energy metabolism, we incline to consider liver insulin sensitivity and mitochondrial oxidative-phosphorylation relationship to be crucial. In a model of perfused rat liver cells, we have shown that metabolic consequences of uncoupling oxidative phosphorylation depend on the nature of respiratory substrate [1,2]. A progressive decline in respiration, following a transient burst was observed in the presence of carbohydrate or ethanol (cytosolic NADH suppliers) associated with Δp collapse and ATP-to-ADP ratio fall. By contrast, in the presence of octanoate or proline (matricial $FADH_2$ suppliers), a large and sustained increased in respiration was observed while the effect on Δp and ATP/ADP was minimized. This indicates that mitochondrial membrane potential plays a role in determining the nature of oxidized substrate, depending on the pathway of reducing equivalent supply to the chain, i.e. potential-dependent (malate–aspartate shuttle) or independent (quinone pool). Interestingly, it was recently shown that *in vivo* DNP administration to rats exposed to high-fat diet abolished their metabolic abnormalities [3]. We investigated hepatocytes and mitochondrion energy metabolism in rats exposed high-fat diet. We report that the steps involved in β-oxidation pathway were enhanced while the actual rate of mitochondrial oxidation was inhibited. This was accompanied by a higher mitochondrial redox state as well as membrane potential, assessed in situ in intact cells. In addition, a higher rate of reactive oxygen species production was observed with fatty acids as respiratory chain substrates but not with other respiratory-chain substrates. This led us to propose that increased matricial redox state and mitochondrial membrane potential in "insulin-resistant state" leads to decrease β-oxidation. Hence, modulating mitochondrial membrane potential might be attractive to lessen metabolic effects of liver insulin resistance and may represent a valuable therapeutic target because of its capacity to regulate the hierarchy of oxidized substrates.

References

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9P.12 Tetradecylthioacetic acid influences mitochondrial metabolism and enhances insulin-sensitivity of C2C12 myotubes

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Insulin resistance is a pre-diabetic state preceding diabetes type 2 development. In muscle cells it manifests as an impaired insulin-stimulated glucose uptake due to improper signal transduction from insulin receptor and eventually affected translocation of glucose transporter GLUT-4 into the plasma membrane. It is accepted, that inefficient response to insulin results from abnormally high lipid deposits in muscle cells. Therefore stimulation of fatty acids oxidation might improve insulin sensitivity. This can be achieved by stimulation of mitochondrial oxidative metabolism and/or enhancement of mitochondrial biogenesis. Tetradecylthioacetic acid (TTA) was shown to exert antylipidemic and antiglycemic effect in rats *in vivo*. Its activity was referred to stimulation of fatty acid oxidation probably due to activation of PPARs (Berge RK *et al.*, 2002, *J. Lipid Res.* **43**: 742–750). The aim of our study was to explain biochemical mechanism of TTA action in C2C12 myotubes. We found, that TTA applied at a concentration of 10 μM and 20 μM for 72 h slightly increases oxygen consumption but it doesn't affect ATP level and ROS production. In addition, it doesn't influence total mitochondrial mass measured with NAO probe, but it affects the relative amount of respiratory chain complexes protein. C2C12 myotubes exposed to TTA exhibit increased UCP2 protein content. Moreover, these changes correlate with TTA-evoked enhancement of protein kinase B (Akt kinase) phosphorylation in response to insulin. In conclusion, TTA slightly affects energy cell metabolism and mitochondrial biogenesis. These changes do not compromise cell viability but positively influence the insulin sensitivity of C2C12 myotubes.

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