NADP-transhydrogenase Deficiency Causes the Mitochondrial Dysfunction Observed in Hypercholesterolemic Ldlr -/- Jackson mice.

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INTRODUCTION: Hypercholesterolemic Ldlr -/- Jackson mice is a valuable experimental model to study familiar atherosclerosis. It was recently discovered that this mice strain carry a homozygous NADP-transhydrogenase (NNT) mutation. Loss of NNT is presumed to cause oxidative stress due to a poor supply of mitochondrial NADPH. Here we investigated the mitochondrial redox status of three mice strains (LDLr-/-, C57BL6/J and C57BL6/Uni) in order to ascertain whether NADPH oxidation is caused by increased rates of cholesterol synthesis or by the deficiency in mitochondrial transhydrogenase activity.

MATERIAL AND METHODS: Liver mitochondria were isolated from LDLr -/- mice (deficient of both LDL receptor and NTT), C57BL6/J (deficient in NNT, only) and the wild type control mice C57BL6/Uni. NAD(P) redox status, respiration and mitochondrial permeability transition (MPT) were analysed.

RESULTS AND DISCUSSION: The results show that mitochondria isolated from either LDLr-/- or C57BL6/J mice cannot sustain a reduced state of pyridine nucleotides as compared to control when respiring on NADH-linked substrates. However, isocitrate addition brought NADP reduction of both mice to the control levels. Accordingly, LDLr-/- and C57BL6/J mice mitochondria presented higher susceptibility to MPT when compared to C57BL6/Uni. These results were supported by mitochondrial membrane potential dissipation followed by mitochondrial swelling sensitive to cyclosporin A.

CONCLUSIONS: The redox state of mitochondrial NADP in LDLr/- - and C57BL/6J mice is not correlated with increased cholesterol synthesis, but with deficiency in NNT. On the basis of these results we may conclude that deficiency in NNT explains the increased susceptibility to mitochondrial permeability transition in both LDLr/- - and C57BL/6J mice.

Keywords: Mitochondrial permeability transition (MPT), NADP-transhydrogenase (NNT), hypercholesterolemic mice (LDLr/- -), redox status.
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