PRAVASTATIN INCREASES MITOCHONDRIAL PERMEABILITY TRANSITION AND H$_2$O$_2$ PRODUCTION IN THE LIVER OF HYPERCHOLESTEROLEMIC MICE

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Statins are drugs widely used in the treatment of hypercholesterolemia to inhibit cholesterol synthesis and lower plasma LDL-cholesterol levels. However, liver adverse effects are reported including enzymes abnormalities and mitochondrial dysfunction, namely higher susceptibility to mitochondria membrane permeability transition (MPT). The aim of the present study was to clarify mechanisms underlying hepatotoxicity caused by pravastatin in LDL receptor knockout mice (LDLr$^{-/-}$). Oxygen consumption, mitochondrial permeability transition (MPT, measured as cyclosporine dependent calcium retention capacity), H$_2$O$_2$ production rate (Amplex Red®) and antioxidant enzymes activities were evaluated in liver mitochondria isolated from LDLr$^{-/-}$ mice treated during 60 or 90 days with therapeutic doses (40 mg/kg) of pravastatin. We observed no significant differences in isolated mitochondria respiratory parameters after both periods of treatments. Regarding increased susceptibility to MPT, we observed significant differences among mitochondria, as follows: 60 days = LDLr$^{-/-}$ Pravastatin (P) > LDLr$^{-/-}$ Control (C) (12%) and 90 days = P > C (33%). The production of H$_2$O$_2$ by liver mitochondria followed the same MPT pattern: 60 days = P > C (10%) and 90 days = P > C (28%). Interestingly, pravastatin increased glucose-6-phosphate dehydrogenase activity (59%), the key enzyme that supplies reducing equivalents as NADPH to cells. No alterations in the antioxidant enzymes activities were observed, including superoxide dismutase, glutathione reductase and peroxidase as well as catalase after 90 days of treatment. No enzymatic alterations were observed after 60 days of treatment. Taken together, these results indicate a higher susceptibility to MPT induced by Ca$^{2+}$ and higher production of H$_2$O$_2$ in LDLr$^{-/-}$ mice treated with pravastatin. These alterations are more prominent as the time of pravastatin treatment increases.

Keywords: Pravastatin, Liver, Mitochondria permeability transition (MPT).

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