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Mitochondria-Targeted Plastoquinone Derivative SkQ_1 Decreases Ischemia–Reperfusion Injury during Liver Hypothermic Storage for Transplantation

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Abstract—The ability of the mitochondria-targeted plastoquinone derivative 10-(6′-plastoquinonyl)decyl triphenylphosphonium (SkQ_1) to decrease ischemia–reperfusion injury in isolated liver during hypothermic storage (HS) was studied. Rat liver was stored for 24 h at 4°C without or in the presence of 1 μM SkQ_1 with following reperfusion for 60 min at 37°C. The presence in the storage medium of SkQ_1 significantly decreased spontaneous production of reactive oxygen species and intensity of lipid peroxidation in the liver during HS and reperfusion. The GSH level after HS in solution with SkQ_1 was reliably higher, but reperfusion leveled this effect. At all stages of experiment the presence of SkQ_1 did not prevent the decrease of antioxidant enzyme activities such as catalase, GSH peroxidase, GSH reductase, and glucose-6-phosphate dehydrogenase. The addition of SkQ_1 to the storage medium improved energetic function of the liver, as was revealed in increased respiratory control index of mitochondria and ATP level. SkQ_1 exhibited positive effect on the liver secretory function and morphology after HS as revealed in enhanced bile flow rate during reperfusion and partial recovery of organ architectonics and state of liver sinusoids and hepatocytes. The data point to promising application of mitochondria-targeted antioxidants for correction of the ischemia–reperfusion injury of isolated liver during long-term cold storage before transplantation.

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Key words: mitochondria-targeted antioxidant, SkQ_1, ischemia–reperfusion injury, hypothermic storage of isolated liver, free radical processes, respiratory activity of mitochondria

Ischemia–reperfusion injury and procedures for their amelioration are important problems of contemporary medicine and biology. In particular, such injuries are responsible for low adaptability of organs such as liver after transplantation. The procedure of liver preparation in most cases includes hypothermic storage (HS) accompanied by the cold-induced ischemia, while after transplantation, during return of the organ to normal temperature and resumption of circulation, its re-oxygenation takes place.

The search for efficient components of preservation solutions facilitating prolonged safe storage of isolated organs is a main direction of investigations in transplantation.

It is known that in conditions of cold ischemia, functioning of the mitochondrial respiratory chain, tricarboxylic acid cycle, and oxidative phosphorylation is disturbed, which results in inhibition of ATP synthesis [1]. The result of respiratory chain disturbance is the single-electron reduction of some oxygen in "parasitic" reactions with formation of reactive oxygen species (ROS) – O_2^-, H_2O_2, and $HO^\cdot$. The intensity of this process depends on the potential on the internal mitochondrial membrane [2, 3]. The hypothesis of "mild uncoupling" [4] was based on these data, according to which the decrease of "excessive" membrane potential should decrease ROS production. We have supposed, in turn, that the use of oxidative phosphorylation uncoupler 2,4-dinitrophenol (DNP) as a component of solution for HS will make it possible to lower oxidative injury of liver. In fact, this approach allowed us to decrease the level of accumulation of lipid peroxidation (LPO) products in liver, to prevent inhibition of antioxidant enzyme activities, and to improve the morpho-func-

Abbreviations: DHR 123, dihydrorhodamine 123; DNP, 2,4-dinitrophenol; G6PDH, glucose-6-phosphate dehydrogenase; HS, hypothermic storage; LPO, lipid peroxidation; MDA, malonic dialdehyde; NR, normothermic reperfusion; RCI, respiratory control index; ROS, reactive oxygen species; SkQ_1, 10-(6′-plastoquinonyl)decyl triphenylphosphonium; TBA, thiobarbituric acid.

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