Effect of Nitric Oxide on Mitochondrial Function in HepG2 cells Infected by Dengue virus.

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Introduction: Dengue is an infectious disease that affects millions of people over the world. Dengue virus (DENV) can produce a subclinical infection, a mild self-limiting disease, dengue fever, or the life-threatening dengue hemorrhagic fever that can lead to shock and death. Experimental evidences suggest that the liver is an important site of virus replication and serious damage of this organ has been found in severe cases of DENV infection. It has been shown that the human hepatocyte cell line, HepG2 produces cytokines, lipid mediators, and nitric oxide (NO) upon infection, which may be involved in disease manifestations. The aim of the present work was to evaluate the effect of NO production on virus replication and mitochondria function in HepG2 cells.

Material and Methods: Cells were grown in appropriated medium and infected with DENV, M.O.I 1. DENV replication in HepG2 cells was evaluated by plaque assay and flow cytometry. NO production was investigated by intracellular NO quantification and inducible Nitric Oxide Synthase (iNOS) expression. Mitochondrial function was measured in intact cells using high-resolution respirometry (OROBOROS Oxygraph-2k).

Results and Discussion: The results showed an increase in NO production and in the expression iNOS and pro-apoptotic genes (BAX, Caspase-9) during the course of infection. Additionally, we demonstrated that infected cells present a significantly decrease in basal respiration and a 45% decrease in FCCP-induced maximum electron transport system capacity followed by apoptosis when compared to mock-infected cells. When the cells were treated with the NO inhibitor 1400w, these effects were abolished, suggesting NO involvement in mitochondrial alteration and apoptosis. Conclusions: We propose that NO modulates mitochondria bioenergetics and dysfunction in DENV-infected cells. These alterations precede the apoptosis observed. We believe that this study contribute to elucidate the molecular mechanisms underlying the role of NO in liver dysfunction caused by DENV.

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