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PROTECTIVE ROLE OF PALMITOLEATE AGAINST ZIKA VIRUS-INDUCED APOPTOSIS AND ENDOPLASMIC RETICULUM STRESS IN SHSY-5Y CELLS

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Background/Hypothesis: Zika virus (ZIKV) is a single-stranded positive RNA flavivirus and its infection during pregnancy leads to fetal complications like microcephaly and congenital Zika syndrome. ZIKV crosses the fetal blood-brain barrier and causes severe neuronal cell apoptosis and damage. Currently, there is no FDA approved vaccines or antivirals for the ZIKV. Further, it is crucial to develop an antiviral which is safe during pregnancy to avoid potential fetal damage. Considering these complications and possible re-emergence of ZIKV, a dietary nutritional approach to attenuate ZIKV infection will be a best choice. Our previous study showed that Palmitoleate (PO) which is an omega-7 monounsaturated fatty acid can protect ZIKV-induced apoptosis and ER stress in the trophoblast cells. In the present study, we investigated PO's protective role in neuroblastoma cells (SHSY-5Y).

Methods and Results: SHSY5Y cells were infected with 0.1 - 1 MOI of rMRV and PRV ZIKV strains for an hour using infection media and followed by PO treatment (100 µM and 200 µM) for different post-infection time points. Apoptosis was characterized by DAPI staining, caspase 3/7 activity, and immunoblot analysis. Activation of ER stress markers and viral envelope levels was investigated using qPCR and immunoblot. Further, a plaque assay was used to determine the infectious viral titer. The results showed that ZIKV infection in SHSY-5Y cells resulted in caspase-dependent apoptosis. An increase in cleaved-PARP, cleaved caspase-3, Bim, and PUMA, whereas a decrease in the anti-apoptotic markers such as Mcl-1, Bcl-1, and Bcl-xL was evidenced. Further, activation of three arms of ER stress namely IRE1, PERK, and ATF6 was observed. PO treatment has drastically decreased ZIKV-induced apoptosis by decreasing the apoptotic nuclei percentage, caspase 3/7 activity, and cleaved PARP protein expression. Further, PO significantly decreased sustained ER stress by preventing the phosphorylation of IRE1, eIF2a, and cleavage of ATF6. Importantly, PO treatment decreased the XBP1 splicing and CHOP expressions. PO treatment had significantly decreased the viral envelop levels; especially decrease in the infectious viral levels was observed. Although PO showed significant protection against ZIKV infection in SHSY-5Y cells the exact mechanism of protection must be investigated.

In conclusion, our findings show that PO treatment protects ZIKV-induced apoptosis and ER stress in SHSY-5Y cells.

Keywords: Zika virus, apoptosis, ER stress, palmitoleate