FENS Regional Meeting

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ДНС SNS Друштво за неуронауке Србије Serbian Neuroscience Society

National Neuroscience Society of Romania

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Abstract Book

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NANO SYMPOSIUM III

SYNERGISTIC ANTIGLIOMA ACTION OF LYSOSOMAL MEMBRANE PERMEABILIZATION AND GLYCOLYSIS INHIBITION

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During malignant transformation cells acquire changes in metabolism, signaling pathways as well as organelle content. The preferential use of aerobic glycolysis (Warburg effect), along with the increased number and volume of lysosomes can be viewed as glioma cells' Achilles heels. In the present study, we aimed to examine the *in vitro* antiglioma effects of combining lysosomal membrane permeabilization (LMP)-inducing agent N-dodecylimidazole (NDI) with glycolytic inhibitor 2-deoxy-D-glucose (2DG). NDI-triggered LMP and 2DG-mediated glycolysis block synergistically induced rapid ATP depletion, mitochondrial damage, and reactive oxygen species (ROS) production causing necrotic cell death of U251 glioma cells, but not primary astrocytes. Lysosomal cathepsin inhibitor E64 and antioxidant α-tocopherol partially prevented NDI/2DG-induced glioma cell death, thus implying the involvement of LMP and oxidative stress in the observed cytotoxicity. Likewise, LMP-inducing agent chloroquine showed synergistic cytotoxic effect with 2DG. Similarly, glucose deprivation as well as other glycolytic inhibitors, iodoacetate and sodium fluoride, synergistically cooperated with NDI, further corroborating that the observed antiglioma effect of the NDI/2DG combined treatment was indeed based on LMP and glycolysis block. Based on these results, we concluded that NDI-triggered LMP caused initial mitochondrial damage, which was further increased by 2DG causing the lack of glycolytic ATP required to maintain mitochondrial health. This created a positive feedback loop of mitochondrial dysfunction, ATP loss, and ROS production, culminating in necrosis. Therefore, the combination of glycolysis inhibitors and LMP-inducing agents seems promising antiglioma strategy.