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Glioblastoma weak metabolic points as a target for new drugs with high potential for Blood Brain Barrier penetration.

Glioblastomas are the most aggressive and practically incurable brain neoplasms for which treatment options are very limited. The main obstacle preventing development of more effective glioblastoma therapies is the Blood Brain Barrier (BBB), which prevents the majority of anticancer drugs from penetrating intracranial tumor tissue at therapeutically relevant concentrations. Our new anti-glioblastoma therapeutic approach is based on the previously reported anti-glioblastoma activity of a common lipid-lowering drug fenofibrate (FF). FF kills glioblastoma cells by direct interaction of unprocessed form of FF (ester) with mitochondrial membranes. This interaction leads to the severe inhibition of mitochondrial respiration which in consequence triggers depletion of intracellular ATP followed by extensive glioblastoma cell death. However, FF does not cross the BBB and its anti-glioblastoma effects can be attenuated by the elevated glucose content (4.5g/L). Therefore, we have designed and synthesized over 200 new metabolic compounds based on the FF skeletal structure, benzyl-phenoxy-acetamide (BPA). Two of the compounds, three of the compounds, PP1, PP21 and PP23, have physicochemical parameters that indicate high potential for improved BBB penetration. We have also confirmed that the compounds can effectively cross the triple coculture BBB model membranes. Similar to FF, the compounds block mitochondrial respiration, which is followed by an immediate increase of glycolysis. In consequence, glucose is quickly depleted leading to a severe decline of intracellular ATP, activation of AMPK, activation of autophagy, and ultimately, glioblastoma cell death. To improve anti-glioblastoma effects in a high glucose environment, we have tested multiple glycolysis inhibitors, and demonstrated that lonidamine and gnetin H (resveratrol trimer), synergize with PP1- and PP21-induced cytotoxicity in both low and high glucose media. In summary, we have developed a new class of metabolic compounds with improved BBB penetration that can effectively eliminate glioblastoma cells and synergize with the selected glycolysis inhibitors.