ABSTRACT

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A hypothetical proposal to employ meperidine and tamoxifen in treatment of glioblastoma. Role of P-glycoprotein, ceramide and metabolic pathways.

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Meperidine (pethidine) is a μ-opioid receptor (MOR) agonist widely used in the treatment of cancer pain. While MOR agonists in experimental models have demonstrated both pro- and antitumorigenic properties, meperidine has unique features which may be predominantly anticancer in nature. Meperidine both inhibits NMDA (N-methyl-D-Aspartate) receptors, which are involved in the progression of glioblastoma, and blocks NADH:Ubiquinone Oxidoreductase, which may hinder mitochondrial respiration. In the developing embryonic neural tissue, meperidine reduces cell proliferation around the neural tube and lowers the expression of the B RE (brain and reproductive organ-expressed). This is notable given that the B RE gene is implicated in cancer chemoresistance and gliomagenesis. Further, meperidine inhibits P-glycoprotein, which is involved in cancer multidrug resistance and the degradation of the sphingolipid backbone, ceramide. By enhancing the pro-autophagic and pro-apoptotic ceramide levels in cancer cells, meperidine stimulates cell death and reverses multidrug resistance. Tamoxifen, a safe medication employed in the treatment of breast cancer, directly blocks P-glycoprotein and boosts levels of ceramide both via inhibition of glycosylceramide synthase and ceramidase. Further, tamoxifen blocks NMDA-neurotoxicity and therefore it may act synergistically with meperidine in reducing glioblastoma progression associated with NMDA-activation. Finally, tamoxifen blocks glycolysis which may enhance the mitochondrial-blocking activity of meperidine to shut down energy metabolism of glioblastoma cells. Because of these properties, we believe that the combination of meperidine and tamoxifen merits study in cell culture and animal models to investigate a potential synergistic relationship in the treatment of glioblastoma.

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