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Analgesics can affect the sensitivity of temozolomide to glioma chemotherapy through gap junction

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Abstract

This study investigated the effect of frequently used analgesics in cancer pain management (flurbiprofen (FLU), tramadol (TRA), and morphine (MOR)) and a novel α2-adrenergic agonist (dexmedetomidine, DEX) on temozolomide (TMZ) sensitivity in glioma cells. Cell counting kit-8 and colony-formation assays were performed to analyze the viability of U87 and SHG-44 cell lines. A high and low cell density of colony method, pharmacological methods, and connexin43 mimetic peptide GAP27 were used to manipulate the function of gap junctions; "Parachute" dye coupling and western blot were employed to determine junctional channel transfer ability and connexin expression. The results showed that DEX (in the concentration range of 0.1 to 5.0 ng/ml) and TRA (in the concentration range of 1.0 to 10.0 μg/ml) reduced the TMZ cytotoxicity in a concentration-dependent manner but was only observed with high cell density (having formed gap junction). The cell viability percentage was 71.3 to 86.8% when DEX was applied at 5.0 ng/ml, while tramadol showed 69.6 to 83.7% viability at 5.0 μg/ml in U87 cells. Similarly, 5.0 ng/ml of DEX resulted in 62.6 to 80.5%, and 5.0 μg/ml TRA showed 63.5 to 77.3% viability in SHG-44 cells. Further investigating the impact of analgesics on gap junctions, only DEX and TRA were found to decrease channel dye transfer through connexin phosphorylation and ERK pathway, while no such effect was observed for FLU and MOR. Analgesics that can affect junctional communication may compromise the effectiveness of TMZ when used simultaneously.

Keywords: Analgesic; Cytotoxicity; Gap junction; Glioma; Temozolomide.