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BIOLOGY OF GLIOBLASTOMA: POSSIBLE PHARMACO THERAPEUTICAL APPLICATIONS

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Among adult tumors, glioblastoma multiforme is known typically to be both one of the most invasive neoplasms and one of the most recurring as far as the Central Nervous System (CNS) is concerned. Moreover, survival in patients with glioblastoma is limited to one year (Cancer lett, 142:11, 1999). The possible therapeutic use of marijuana's active principles, the cannabinoids, is currently being debated. Recently there has been renewed interest in the use of such substances as anticancer drugs due to the synthesis of agonists and antagonists with high therapeutical potential and limited psychoactivity (Biochemical Pharmacol, 62: 755, 2001). Recent studies demonstrated *in vivo* efficacy of THC and WIN-55,212-2 (a potent synthetic cannabinoid) when administered intratumorally to rats harboring intracranial C6 gliomas (Nature Med, 6: 3,2000). Although the numerous studies on cannabinoids and their effects on glioma both *in vivo* and *in vitro* there are few data in literature, on the effects of such substances on human tumors.

Our preliminary data show: the presence at mRNA level of both subtypes of cannabinoid receptors (CB1 and CB2) in the human glioblastoma cell line A172 (CB2 is usually absent from untransformed brain), inhibition of cell proliferation mediated by WIN (which is an agonist of both CB receptors); such antiproliferative effect is not mediated by CB1 receptors since SR141716A (a potent agonist of CB1 receptors) does not abrogate WIN effect. We also show that the concentration of Win that induces antiproliferative effects on A172 causes ERK1/2 phosphorylation (usually induced by proliferative events) and an increase in iNOS protein levels at 24 and 48 hours of treatment. We aim at elucidating the signal transduction mechanisms involved in WIN inhibition of A172 proliferation *in vitro* and at comparing such results with the analysis of the expression of genes such as CB1 and CB2 in tissue sections of glioblastoma with the intention of constituting a new experimental model for the study of the therapy of this type of tumors.

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