DUALSTERIC ACTIVATION OF M2 MUSCARINIC ACETYLCHOLINE RECEPTORS INHIBITS CELL PROLIFERATION IN HUMAN GLIOBLASTOMA CELL LINES

Carlo Matera[1], Marco De Amici[1], Marta Quadri[1], Maria Di Bari[2], Ilaria Cristofaro[2], Ada M. Tata[2], Clelia Dallanoce[1]

1. *Department of Pharmaceutical Sciences, Medicinal Chemistry Section "Pietro Pratesi", University of Milan, Via L. Mangiagalli 25, Milan, Italy*
2. *Department of Biology and Biotechnologies "Charles Darwin", Research Center of Neurobiology "Daniel Bovet", Sapienza University of Rome, P.le A. Moro 5, Rome, Italy*

Muscarinic acetylcholine receptors (mAChRs) are expressed in several primary and metastatic tumours. ACh synthesized by the tumour cells can modulate cell proliferation by an autocrine mechanism which involves cholinergic receptors. Although a direct or indirect role of transduction pathways activated by cholinergic receptors has not yet been demonstrated, the inhibition of ACh synthesis as well as the release or use of cholinergic antagonists are able to counteract tumour cell growth and slow down the tumour progression in small cell lung carcinoma [1]. In mammary adenocarcinoma and melanoma cell lines, mAChRs can also modulate cell migration and angiogenesis, suggesting their involvement in the metastases formation [2]. The characterization of mAChR effects on more aggressive brain tumours is still poorly investigated. Glioblastomas are the most common brain tumours in humans. Recently, Tata et al. demonstrated that M2 receptor activation inhibits glioma cell growth and survival, suggesting that this receptor subtype may represent a new putative target for glioblastoma therapy [3,4]. Therefore, the identification of more selective ligands for M2 mAChRs may be of clinical significance. Here we report the results on the effects of the muscarinic orthosteric superagonist Iperoxo [5] and its related dualsteric agonists P-6-Iper and N-8-Iper [6]. Our data demonstrate that cell proliferation as well as cell survival of the U251 and U87 stable cell lines were unaffected by treatment with Iperoxo and P-6-Iper. Conversely, N-8-Iper decreased cell proliferation in a time and dose dependent manner. Similarly, N-8-Iper (100 μM) was also able to counteract cell proliferation in glioblastoma cancer stem cells (GB7) obtained from human biopsy. The antiproliferative effect shown by N-8-Iper was significantly counteracted by the selective M2 antagonist methoctramine (10^{-7} M), suggesting an actual contribution of the M2 selective activation.

References:

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