Immunomodulatory properties in multiple sclerosis patients of new quinoline- and 1,8 naphthyridine-3-carboxamide derivatives as CB2 receptor agonists

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The efficacy of cannabinoids in the symptomatic treatment of neurodegenerative diseases is widely documented; however their use is limited by psychoactivity mainly ascribed to the cannabinoid CB1 receptor. Due to the relevant role the immune/inflammatory system plays in the MS symptoms, emerging findings support as alternative strategy the application of immune-modulating CB2 receptor agonists in this disease. In this study, we describe the synthesis of quinoline (CF6), and 1,8-naphthyridine (LV8) derivatives as new CB2 receptor agonists, with high CB2 receptor affinity and selectivity. Moreover, the effects of these compounds on peripheral blood mononuclear cells isolated from both healthy donors and MS patient were evaluated. Agonist properties of CF6 and LV8 were determined by [35S]GTPγS binding assay. The anti-proliferative effects of both compounds on human lymphocytes were assessed by 3H-thymidine incorporation assay. Cell viability was analyzed by trypan blue staining; cell activation and migration by flow cytometry and transwell migration assay respectively; protein expression by western blot. CF6 and LV8 behaved as a full agonist and a partial agonist at the CB2 receptor, respectively. In lymphocytes from healthy donors, both compounds inhibited cell proliferation, the effect of LV8 was dose-dependent and partially mediated by the CB2 receptor. Both compounds reduced cell viability, activation, migration and down-regulated the expression of phosphorylated proteins, NF-κB, IKKα/β, IκBα, Akt, Erk and the enzyme Cox2. Results obtained with LV8, were reproduced in lymphocytes from MS patients, however the inhibition of cell viability and activation was more pronounced in patient derived cells than in controls.