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Pharmacological Characterization of Novel Ligands for CB1 and CB2 Cannabinoid Receptors

Kyriaki Thermos[1], Maria Papazoglou[1], Katerina Antoniou[2], Niki Mastrodimou[1], George Panagis[3], Styliani Vlachou[3], Eleni Renieri[1], Victoria Nahmias[4], Aristotelis Menisiou[4], Marianthi Gianni[4], M.P. Kondylis[5], Zeta Daifoti-Papadopoulou[6], Demetris Papahatjis[4], Christina Spyraki[6]

[1]Laboratory of Pharmacology, Department of Basic Sciences, Faculty of Medicine, University of Crete, Heraklion, 71110, Crete, Greece; [2]Department of Pharmacology, Medical School, University of Ioannina, 45110, Ioannina, Greece; [3]Laboratory of Behavioral Neuroscience, Department of Psychology, University of Crete, Rethymnon, 74100, Crete, Greece; [4]Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 11635, Athens, [5]Bristol-Myers Squibb, 14671, Athens, GR, [6]Department of Pharmacology, Medical School, University of Athens, 11527, Athens, Greece

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INTRODUCTION

Novel derivatives of Δ^8-tetrahydrocannabinol were synthesized and evaluated for CB1/CB2 receptor affinity and activity.

METHODS

Radioligand binding studies were performed using [^{3}H]CPP 55,940 as the radioligand, cortical membranes for CB1 receptor measurements and membranes from cells expressing the hCB2. [^{35}S]GTPgS binding assays were employed to examine the activity of the ligands. Twelve new agents (DPGs) were tested.

RESULTS

Six ligands (DPG 3, 4, 101, 102, 201 and 203) displayed low nanomolar affinities, three ligands (DPG 6, 7, 104) displayed intermediate affinities and three ligands (DPG 5,103,105) had no affinity for the CB1 receptor. Nine of the ligands tested (DPG 3, 4, 5, 7, 101, 102, 104, 201, 203) displayed high affinity, two (DPG 6 and 103) intermediate activity and one (DPG 105) low affinity for the hCB2 receptors. DPG4 [Ki (nM) 0.26 CB1; 0.12 CB2] and DPG5 [Ki (nM) 470 CB1; 3.54 CB2) were chosen for further activity studies. DPG4 increased basal [^{35}S]GTPgS binding [EC_{50} $1.65x10^{-6}$M], DPG5 had no effect and WIN55,212-2 displayed an EC50 value of $1.29x10^{-6}$ M. DPG4 and DPG5 increased GTPgS activity in hCB2(Sf9cells) membranes [EC50 $2.0x10^{-4}$ M and $1.0x10^{-4}$ M, respectively], WIN55,212-2 displayed an EC50 value of $3.0x10^{-4}$ M. Behavioral paradigms support the agonist nature of DPG-4 for the CB1 receptor.

CONCLUSIONS

These studies support the synthesis of novel cannabinoid ligands with high affinity, agonist activity and selectivity for CB1 and CB2 cannabinoid receptors. Studies are in progress to elucidate fully the pharmacological profile of the other novel ligands with the hope that selective CB1 and CB2 agents will be discovered with agonist, partial agonist or antagonist function and with promising therapeutic value.

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