Cannabinoids as Therapeutics
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Potential use of cannabimimetics in the treatment of cancer

Luciano De Petrocellis[1], Maurizio Bifulco[2], Alessia Ligresti[3] and Vincenzo Di Marzo[3]

[1] *Istituto di Cibernetica "Eduardo Caianiello", Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, Comprensorio Olivetti, Fabbricato 70, 80078 Pozzuoli (Napoli), Italy*
[2] *Istituto di Endocrinologia ed Oncologia Sperimentale, Consiglio Nazionale delle Ricerche, and Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno, via Ponte Don Melillo, 84084 Fisciano (SA), Italy*
[3] *Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, Comprensorio Olivetti, Fabbricato 70, 80078 Pozzuoli (Napoli), Italy*

Introduction

The medicinal use of *Cannabis sativa* preparations has a millennial history [1] and is currently being critically re-evaluated [2]. The hemp plant *Cannabis sativa* produces about 66 compounds known as cannabinoids, and the exact chemical structure of the major psychotropic principal, (–)-Δ^9-tetrahydrocannabinol (Δ^9-THC) [3], was only identified in 1964, after decades of attempts and failures. Δ^9-THC is highly hydrophobic and was initially thought to work by interacting directly with biomembranes. A few pharmaceutical items, such as Marinol® and Dronabinol®, both based on Δ^9-THC, and Cesamet®, which instead is based on a synthetic Δ^9-THC analog, nabilone, have been prescribed in the USA as anti-emetics and appetite-stimulants to cancer or AIDS patients even before the molecular mode of action of Δ^9-THC was revealed [4]. It took the development of more-potent and enantiomerically pure Δ^9-THC analogs to understand that psychotropic cannabinoids act via specific sites of action to produce their typical effects. The long-standing issue of the mechanism of action of Δ^9-THC was solved with the discovery of cannabinoid receptors [5], and then of the *endocannabinoids*, endogenous agonists at cannabinoid receptors [6]. Two such receptor types have been cloned and characterized in mammalian tissues; they are coupled to $G_{i/o}$ proteins, through which they inhibit the adenylate cyclases, stimulate mitogen-activated protein kinases, and modulate the activity of Ca^{2+} and K^+ channels to transduce the binding of agonists into biological responses (see [7] for a review). CB_1 receptors are expressed in several brain regions, with very high concentrations in the basal ganglia, hippocampus, cerebellum and cortex, and mediate the typical psychotropic effects of *Cannabis*, marijuana and Δ^9-THC. Lower, albeit functionally active, amounts of CB_1 receptors are also found in peripheral neurons and various extra-neural sites