THE ENDOGENOUS CANNABINOID SYSTEM: FROM MOLECULES TO THERAPEUTIC APPLICATION

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After decades of attempts to isolate the active principle of *Cannabis*, in 1964 Gaoni and Mechoulam described the major psychoactive component of the plant: (-)-Δ^9-tetrahydrocannabinol (THC). Discovering the targets of THC took about 30 years more, since it was not until the 90s when the two cannabinoid receptors known to date, CB_1 and CB_2, were cloned. Then, a search began to identify their naturally occurring ligands. To date, four main endocannabinoids [1] have been isolated: anandamide (AEA), 2-arachidonoylglycerol (2-AG), 2-arachidonyl glyceryl ether and virodhamine. A major step was the discovery that the two best characterized endocannabinoids, AEA and 2-AG, were involved in key signaling pathways acting as endogenous immune, neuro and endocrine modulators [1]. This discovery was translated into an intense search for the elucidation of their synthesis and degradation pathways [2]. Regarding the biosynthesis, only very recently three enzymes have been characterized, a *N*-acylphosphatidylethanolamine-selective phospholipase D (NAPE-PLD) and two *sn*-1-selective-diacylglycerol lipases (DAGL-α and DAGL-β). The inactivation is a two-step procedure in which the endocannabinoid is first transported inside the cell by a facilitated mechanism, and subsequently degraded by fatty acid amidohydrolase (FAAH, for AEA) or by monoacylglycerol lipase (MAGL, for 2-AG). To date, it is widely accepted that the endogenous cannabinoid system (ECS) is constituted by two cannabinoid receptors, their endogenous ligands, as well as the enzymes responsible for their biosynthesis and degradation.

This lecture will attempt to review, from a medicinal chemistry perspective, both the classical and novel methodologies that target the different proteins of the ECS, as well as the actual and the potential therapeutic applications of these approaches. Agonists and antagonists of CB_1 and CB_2 receptors have been developed to establish the involvement of the ECS in many central and peripheral physiological processes. Examples of these agents in current clinical trials will be discussed. The process by which anandamide is transported has been a topic of much interest and advances have been made in the synthesis of compounds [2] that specifically inhibit anandamide transport [2,3]. The recent role [4,5] of these agents in excitotoxic processes and neurodegenerative diseases, such as Huntington´s chorea and multiple sclerosis, will be explored. Pharmacological studies, in combination with novel functional proteomic methods, have generated the first selective FAAH inhibitors inducing analgesic and anxiolytic effects [6]. With regard to the enzymes MAGL, NAPE-PLD, DAGL-α and DAGL-β, there are no available inhibitors and innovative approaches are required for the development of selective inhibitors in order to probe their potential pharmacological and therapeutic benefits.

Continued investigations of each of the targets regulating the ECS should greatly enrich our understanding of the physiological and pathological functions of this system and offer new therapeutic strategies for the treatment of diseases that still lack adequate medical therapies.

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