Cannabinoids as Therapeutics
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Cannabinoid targets for pain therapeutics

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Introduction

Historical accounts and anecdotal reports show that among the most common medicinal uses of cannabis is pain relief [1]. Such accounts date back to the ancient Chinese physician Hoa-Gho thousands of years ago for surgical anesthesia, and to ancient Israel in 315–392 AD, likely for the control of pain in child birth [2]. The use of cannabis as medicine was so popular that there were at least 28 pharmaceutical preparations available in the United States prior to the passing of the Marijuana Tax Act in 1937 [3], which thwarted the legal use and development of cannabis-based medicine.

The isolation, structural elucidation and chemical synthesis of the active ingredient in marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), by Gaoni and Mechoulam [4] was a monumental step which revealed the molecular basis for the behavioral and physiological influences of cannabis reported throughout history. The subsequent recognition and cloning of specific cannabinoid CB_1 and CB_2 receptors (CB_1R and CB_2R) in the nervous system and the periphery [5–7] led to the realization of the likely importance of a cannabinoid neuromodulatory system in the body. More recently, the identification of several endogenous cannabinoids, beginning with anandamide [8], expanded the ever-more complex story of regulation of various physiological functions by the cannabinoid system.

Knowledge of the molecular components of the endocannabinoid system [9] allowed the development of pharmacological agents that target them [10]. Pharmacological agonists and antagonists have been synthesized for the cannabinoid CB_1R and CB_2R. The discovery of endogenous cannabinoids and studies of their biosynthetic and degradatory pathways also yielded molecular targets for perturbing the endocannabinoid system. Inhibitors of fatty acid amide hydrolase (FAAH), the enzyme that degrades several of the endogenous cannabinoids and inhibitors of the anandamide transporter, have been developed. These agents are useful research tools for studying the effects of cannabinoids on pain as well as potential therapeutic drugs. This review focuses on studies that evaluate the behavioral and physiological consequences of modulating the above-mentioned targets, as these are promising avenues for