
Preface

Marijuana has remained one of the most widely used and abused drugs in the world. Research on the biological basis of the effects of marijuana, and therefore its usefulness as medicine, may have been hampered by several decades of irrational prejudice and also by the lack of specific molecular tools and technology. But the discovery of specific genes coding for cannabinoid receptors (CBRs) that are activated by smoking marijuana, and that the human body and brain makes its own marijuana-like substances called endocannabinoids that also activate CBRs, has transformed marijuana–cannabinoid research into mainstream science. An overwhelming body of scientific evidence now indicates the existence of an elaborate, and previously unknown but ubiquitous, endocannabinoid physiological control system (EPCS) whose fundamental role in human development, health, and disease is unfolding. This system appears to exert a powerful modulatory action on retrograde signaling associated with cannabinoid inhibition of synaptic transmission. The promiscuous action and distribution of CBRs in most biological systems provides the EPCS limitless signaling capabilities of crosstalk within, and possibly between, receptor families that may explain the numerous behavioral effects associated with smoking marijuana. Advances in marijuana–cannabinoid research have already resolved the issue that marijuana use can be addicting in vulnerable individuals and that a missense in human fatty acid amide hydrolase, which inactivates endocannabinoids (anandamide) and related lipids, is associated with drug and alcohol dependence problems. These and other remarkable advances in understanding the biological actions of marijuana and cannabinoids have provided a much richer than previously appreciated cannabinoid genomics and raised a number of critical issues on the molecular mechanisms of cannabinoid-induced behavioral and biochemical alterations. Although these advances have enhanced our understanding of the molecular mechanisms associated with the behavioral effects of marijuana use, the molecular identity of other cannabinoid receptor subtypes and transporters (if any), along with the growing number of endocannabinoids, will allow specific therapeutic targeting of different components of the EPCS in health and disease.

The major focus of marijuana–cannabinoid research is to develop better understanding of the seemingly limitless signaling capabilities and endless complexity of the EPCS in the human body and brain with the expectation that new knowledge will contribute to elucidating this naturally occurring regulatory mechanism in health and disease. The primary goal of *Marijuana and*

Cannabinoid Research: Methods and Protocols is to provide experimental protocols for scientists interested in marijuana–cannabinoid research from genes to behavior. Although the effects of marijuana use and its medicinal applications may be influenced by multiple genetic factors, the role of environmental factors in the behavioral and psychological effects should not be overlooked, although these may be difficult to replicate in animal models. Nevertheless, animal models are widely used to study the physiological and behavioral correlates of human disorders. Of course, where applicable, humans have been used to study the biochemical, physiological, and behavioral effects of marijuana–cannabinoids as documented here.

The methods and protocols found useful in marijuana research are described here by experts using their specialized techniques to resolve issues from genes to behavior: the molecular neurobiology methods we present outline analysis of the structure, polymorphisms, molecular genomic, and expression studies of the CB1r gene and haplotypes, and the association with polysubstance abuse. Other chapters describe methods to study the role of CBrs in immune function, to localize cannabinoid receptors in different systems, to study morphometric cytoskeletal components of neuronal and astroglial cells after cannabinoid treatment, to visualize cannabinoid effects using brain slice imaging and electrophysiological approaches, to assay anandamide hydrolysis and transport in synaptosomes, to conduct CBr and stimulated [^{35}S]GTP γ S binding to membrane homogenates or intact cultured cells, to assay cannabinoids using the mouse-isolated vas deferens, to design and synthesize cannabinoids and endocannabinoids, and to study in vitro and in vivo effects of cannabinoids in animals including humans. It is difficult to include all the relevant techniques and expanding interests in the recent explosion of new knowledge in marijuana–cannabinoid research. A number of the methodologies described here will find application far beyond marijuana–cannabinoid research and may be extended to studying mental and neurological disorders, especially because the EPCS is intricately involved in almost all the biological processes of the human body and brain. We embrace with euphoria and excitement the current explosion of new information from marijuana–cannabinoid research in the hope that it will unravel the specific mechanisms of marijuana–cannabinoid actions, which are of potentially central importance in biology and therapeutics. *Marijuana and Cannabinoid Research: Methods and Protocols* should whet our appetites for further groundbreaking research that will lead to deeper understanding of these interesting genes, their variants, and roles in the vulnerability to addictions and other disturbances caused by deficiencies in the endocannabinoid physiological control system.

Emmanuel S. Onaivi



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