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Roger G. Pertwee *Editor*

Endocannabinoids

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For Teresa

Preface

The Endocannabinoid System: A Look Back and Ahead

The major neurotransmitter systems were discovered many decades ago. It is strange that the endocannabinoid system—certainly one of major physiological importance—remained unknown until the early 1990s. This was due, in part at least, to the lack of research on the plant cannabinoids, made difficult by legal constraints. Indeed, many of the major plant cannabinoids were not isolated, and their structures were not elucidated until the 1960s. Later, their chemistry, metabolism, biochemistry, and pharmacology were extensively investigated. However, the mechanism of action of Δ^9-tetrahydrocannabinol (THC), the major psychoactive constituent, remained elusive for nearly 20 years. It was originally believed that it acts nonspecifically on neural membranes. Gradually, pharmacological and chemical data surfaced, which were inconsistent with the nonspecificity of THC action. Indeed, in the late 1980s and early 1990s, two specific cannabinoid receptors, CB_1 and CB_2, were identified. Stimulation of CB_1 leads to the well-known marijuana effects; CB_2 is apparently part of a major, new protective system. Two endogenous cannabinoids (endocannabinoids), anandamide and 2-AG, were isolated in the 1990s. Anandamide is arachidonoyl ethanolamide and 2-AG is the arachidonoyl ester of glycerol. Thereafter, enzymes involved in their biosynthesis and metabolism were found. Many thousands of papers on this novel system have been published [see Di Marzo et al. (2015), Maccarrone et al. (2014), and Mechoulam et al. (2014), for recent reviews on the endocannabinoid system]. However, we are still far away from fully understanding this system, or, indeed, plant cannabinoids. Thus, although there are thousands of publications on THC and many hundreds on cannabidiol (CBD), the rest of the plant cannabinoids have barely been investigated. And neither anandamide nor 2-AG has ever been administered to humans. By comparison, insulin was administered to humans almost immediately after its discovery in the 1920s and became a medicine within months. Are we missing something?

Several additional endogenous fatty acid ethanol amides, in which the fatty acid moiety is not derived from arachidonic acid as in anandamide, but from other fatty acids, have been found to bind to the endocannabinoid receptors. Are they relevant to endocannabinoid activity? There are also some chemically related endogenous fatty acid–amino acid amides, which lower brain trauma damage, but do not bind to cannabinoid receptors. However, their activity can be blocked by CB_1 or CB_2 antagonists and they do not act on CB_2 knockout mice. Is the endocannabinoid system actually much more complex than was first thought?

Recently, two synthetic cannabinoid enantiomers were both reported to be CB_2 agonists; however, an inverse relationship was found between binding affinity and biological potency, which was cannabinoid-based (Smoum et al. 2015). A molecular-modeling analysis suggested that these enantiomers have two different binding conformations within the CB_2 receptor, with one of them possibly responsible for the affinity difference. Hence, different cannabinoid ligands may have different orientations relative to the same binding site. Thus, cannabinoid orientation-targeted ligands, at least for the CB_2 receptor, may have promising potential for the pharmacological activation of distinct processes. Is this a general phenomenon?

Many patients claim that plant extracts work better than pure THC in many disease states. It is widely believed that *Cannabis sativa* extracts differ in their activity from *Cannabis indica* extracts, regardless of the level of THC. And, in spite of the wide use of various medicinal cannabis products, which are mixtures of cannabinoids and other plant constituents, pure THC has remained a minor drug. Is this due to modification of THC actions via "entourage effects"? CBD is well known to modify THC activity in human users. Do additional plant cannabinoids and terpene constituents also affect THC activity?

Over the last few years, several research groups have noted that both THC and CBD, as well as anandamide, cause epigenetic modifications by methylation, leading to distinct therapeutic effects. Does epigenetics play a major role in the functioning of the endocannabinoid system? If it does, then cannabinoids may affect the bases of at least some diseases rather than their symptoms—a major difference from the activity of many drugs used today.

There have been very few clinical trials with THC or with CBD or with cannabis extracts containing fixed ratios of the major constituents. Such trials on small numbers of patients have shown very positive results in epilepsy, post-trauma, Parkinson's disease, Crohn's disease, and a few other disorders. Somewhat larger clinical trials on schizophrenia and graft-versus-host-disease (GVHD) have led to statistically significant therapeutic effects. But, where are the clinical trials in various cancer diseases where anecdotal evidence points to possible therapeutic effects?

We have made major advances in understanding the chemistry, biochemistry, and pharmacological effects of the plant cannabinoids and the endocannabinoids. The present book provides an outstanding summary of a wide variety of important endocannabinoid findings that will help generate novel ideas for future research.

Thus, I have no doubt that further research with endocannabinoids will throw additional light on the actions of these compounds. However, I believe that the most important future steps in the endocannabinoid area are to advance cannabinoid-based clinical trials in many disease states where strong anecdotal evidence already exists.

Jerusalem, Israel Raphael Mechoulam

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Contents

Endocannabinoids and Their Pharmacological Actions

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Contents

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Abstract

The endocannabinoid system consists of G protein-coupled cannabinoid CB_1 and CB_2 receptors, of endogenous compounds known as endocannabinoids that can target these receptors, of enzymes that catalyse endocannabinoid biosynthesis and metabolism, and of processes responsible for the cellular uptake of some endocannabinoids. This review presents in vitro evidence that most or all of the following 13 compounds are probably orthosteric endocannabinoids since they have all been detected in mammalian tissues in one or more investigation, and all been found to bind to cannabinoid receptors, probably to an orthosteric site: anandamide, 2-arachidonoylglycerol, noladin ether, dihomo-γ-linolenoylethanolamide, virodhamine, oleamide, docosahexaenoylethanolamide, eicosapentaenoylethanolamide, sphingosine, docosatetraenoylethanolamide, *N*-arachidonoyldopamine, *N*-oleoyldopamine and haemopressin. In addition, this review describes in vitro findings that suggest that the first eight of these compounds can activate CB_1 and sometimes also CB_2 receptors and that another two of these compounds are CB_1 receptor antagonists (sphingosine) or antagonists/inverse agonists (haemopressin). Evidence for the existence of at least three allosteric endocannabinoids is also presented. These endogenous compounds appear to target allosteric sites on cannabinoid receptors in vitro, either as negative allosteric modulators of the CB_1 receptor (pepcan-12 and pregnenolone) or as positive allosteric modulators of this receptor (lipoxin A_4) or of the CB_2 receptor (pepcan-12). Also discussed are current in vitro data that indicate the extent to which some established or putative orthosteric endocannabinoids seem to target non-cannabinoid receptors and ion channels, particularly at concentrations at which they have been found to interact with CB_1 or CB_2 receptors.

Keywords

2-Arachidonoylglycerol • Anandamide • Cannabinoid receptors • Dihomo-γ-linolenoylethanolamide • Docosahexaenoylethanolamide • Docosatetraenoylethanolamide • Eicosapentaenoylethanolamide • Endocannabinoid pharmacology • Haemopressin • Lipoxin A_4 • *N*-arachidonoyldopamine • Noladin ether • *N*-oleoyldopamine • Oleamide • Pepcan-12 • Pregnenolone • Sphingosine • Virodhamine

Abbreviations

5-HT	5-hydroxytryptamine
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CHO	Chinese hamster ovary
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate