HEP (2005) 168:147–185

The Biosynthesis, Fate and Pharmacological Properties of Endocannabinoids

V. Di Marzo[1] (✉) · L. De Petrocellis[2] · T. Bisogno[1]

[1]Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Via Campi Flegrei 34, Comprensorio Olivetti, Fabbricato 70, 80078 Pozzuoli (Napoli), Italy
vdimarzo@icmib.na.cnr.it

[2]Endocannabinoid Research Group, Istituto di Cibernetica, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, Comprensorio Olivetti, Fabbricato 70, 80078 Italy

Abstract The finding of endogenous ligands for cannabinoid receptors, the endocannabinoids, opened a new era in cannabinoid research. It meant that the biological role of cannabinoid signalling could be finally studied by investigating not only the pharmacological actions subsequent to stimulation of cannabinoid receptors by their agonists, but also how the activity of these receptors was regulated under physiological and pathological conditions by varying levels of the

endocannabinoids. This in turn meant that the enzymes catalysing endocannabinoid biosynthesis and inactivation had to be identified and characterized, and that selective inhibitors of these enzymes had to be developed to be used as (1) probes to confirm endocannabinoid involvement in health and disease, and (2) templates for the design of new therapeutic drugs. This chapter summarizes the progress achieved in this direction during the 12 years following the discovery of the first endocannabinoid.

Keywords Anandamide · 2-Arachidonoylglycerol · Cannabinoid · Enzyme · Inhibitors

1 Introduction

When the longstanding issue of the mechanism of action of (–)-Δ^9-tetrahydrocannabinol (THC) was solved with the finding of the cannabinoid receptors, studies aimed at finding endogenous ligands for these receptors could be started. These studies culminated in 1992 with the report of the discovery of the first of such ligands, *N*-arachidonoyl-ethanolamine (AEA), which was named anandamide from the Sanskrit word *ananda*, meaning "internal bliss" (Devane et al. 1992). In the following years, the finding of anandamide, which apart from binding to cannabinoid CB_1 (and later also CB_2) receptors could also functionally activate them, led to the revelation that there is a whole endogenous signalling system now known as the *endogenous cannabinoid system*. This comprises, apart from the cannabinoid receptors (Pertwee 1997), other endogenous ligands [named endocannabinoids by our group in 1995 (Di Marzo and Fontana 1995)] and the proteins for their synthesis and inactivation, as well as, possibly, other molecular targets for the endocannabinoids (see Pertwee 2004 for review). First came the finding that a well-known intermediate in phosphoglyceride metabolism, 2-arachidonoyl-glycerol (2-AG), was also able to activate both CB_1 and CB_2 receptors (Mechoulam et al. 1995; Sugiura et al. 1995). The end of the 1990s brought: (1) the finding of the biochemical pathways and the identification of the first enzymes for the formation and inactivation of AEA and 2-AG (Di Marzo et al. 1994; Cravatt et al. 1996; Bisogno et al. 1997b), a breakthrough that was very much facilitated by important similar studies carried out in the 1970s on other lipids belonging to the same families as the two endocannabinoids (Schmid et al. 1990 and Horrocks 1989 for reviews); and (2) the recognition that AEA was a rather promiscuous ligand for several membrane receptors and channels, particularly for vanilloid VR1 receptors (now classified as TRPV1 receptors) (Zygmunt et al. 1999), and as-yet-uncharacterized binding sites in the vascular endothelium (Jarai et al. 1999). Therefore, at the turn of the century it was clear that the endocannabinoid system was going to include new receptors, new ligands and new enzymes. This feeling was confirmed, among other things, by the characterization of: (1) more putative endocannabinoids, all derived from arachidonic acid, i.e. 2-arachidonyl-glyceryl ester (noladin, 2-AGE), *O*-arachidonoyl-ethanolamine (virodhamine, OAE) and *N*-arachidonoyl-dopamine (NADA) (Bisogno et al. 2000;