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Fatty acids, endocannabinoids and inflammation

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ABSTRACT

From their phylogenetic and pharmacological classification it might be inferred that cannabinoid receptors and their endogenous ligands constitute a rather specialised and biologically distinct signalling system. However, the opposite is true and accumulating data underline how much the endocannabinoid system is intertwined with other lipid and non-lipid signalling systems. Endocannabinoids per se have many structural congeners, and these molecules exist in dynamic equilibria with different other lipid-derived mediators, including eicosanoids and prostamides. With multiple crossroads and shared targets, this creates a versatile system involved in fine-tuning different physiological and metabolic processes, including inflammation. A key feature of this 'expanded' endocannabinoid system, or 'endocannabinoidome', is its subtle orchestration based on interactions between a relatively small number of receptors and multiple ligands with different but partly overlapping activities. Following an update on the role of the 'endocannabinoidome' in inflammatory processes, this review continues with possible targets for intervention at the level of receptors or enzymes involved in formation or breakdown of endocannabinoids and their congeners. Although its pleiotropic character poses scientific challenges, the 'expanded' endocannabinoid system offers several opportunities for prevention and therapy of chronic diseases. In this respect, successes are more likely to come from 'multiple-target' than from 'single-target' strategies.

1. Introduction

By definition, endocannabinoids constitute a relatively small group of fatty acid-derived endogenous ligands of the cannabinoid receptors CB_1 and CB_2 (Pertwee et al., 2011, 2010). These two G-protein coupled receptors (GPCRs) were cloned in the 1990s, after they were found to respond to (-)-trans-Δ9-tetrahydrocannabinol (THC) from the *Cannabis* plant (Matsuda et al., 1990; Munro et al., 1993). To date, 9 'true' endocannabinoids (Fig. 1) have been classified by the IUPHAR Receptor Nomenclature and Drug Classification system.

These are derived from long chain (C18 or longer) polyunsaturated fatty acids (LC-PUFAs) or oleic acid (C18:1) (Pertwee et al., 2011). The first two endocannabinoids discovered, anandamide (N-arachidonoylethanolamine; AEA), and 2-arachidonoylglycerol (2-AG) are still the most studied so far. The term 'endocannabinoid system' (ECS) in a strict sense refers to the two cannabinoid receptors CB_1 and CB_2, the 9 endocannabinoids per se, and a group of enzymes involved in their synthesis and breakdown (see Section 2.3). However, in contrast to what this classification might suggest, the ECS should not be considered a specific and distinct biological system. It has become increasingly clear how much the ECS is intertwined with other lipid- or non-lipid signalling pathways and connected to other regulatory networks. From a biochemical point of view, classical endocannabinoids can be seen as part of a large family of structurally related amides, esters and ethers of fatty acids, which are continuously formed and degraded in a dynamic equilibrium. The vast majority of these molecules are fatty (acid-) amides like AEA, although analogues of 2-AG including 2-oleoylglycerol and 2-linoleoylglycerol have been found as well (see Section 2.1). Members of these groups show broad and overlapping activity for molecular targets that go far beyond the classical cannabinoid receptors. Furthermore, 'true' endocannabinoids display 'promiscuous' behaviour by activating or blocking other receptors besides CB_1 or CB_2,with potencies that differ little from those with which they

Abbreviations: AA, arachidonic acid; 2-AG, 2-arachidonoylglycerol; ABHD6, alpha/beta-hydrolase domain 6; AEA, *N*-arachidonoylethanolamine (anandamide); CB (receptor), cannabinoid (receptor); CBD, cannabidiol; COX, cyclooxygenase; Δ9THC, Δ9-tetrahydrocannabinol; DAGL, diacylglycerol lipase; DHA, docosahexaenoic acid (22:6*n*-3); DHEA, *N*-docosahexaenoylethanolamine; ECS, Endocannabinoid system; FAAH, Fatty acid amide hydrolase; GPCR, G-protein coupled receptor; LOX, lipooxygenase; MAGL, monoacylglycerol lipase; NAAA, N-acyl ethanolamine-hydrolysing acid amidase; NADA, *N*-arachidonoyldopamine; NAEs, *N*-acylethanolamines; OEA, *N*-oleoylethanolamine; PEA, *N*-palmitoylethanolamine; PG-ester, prostaglandin-ester; PPAR, peroxisome proliferator-activated receptor; (LC-)PUFA, (long chain-) polyunsaturated fatty acid; THC, (-)-trans-Δ9-tetrahydrocannabinol; THCV, Δ9-tetrahydrocannabivarin; TRP (receptor), transient receptor potential (receptor); TRVP1, transient receptor potential channel type V1

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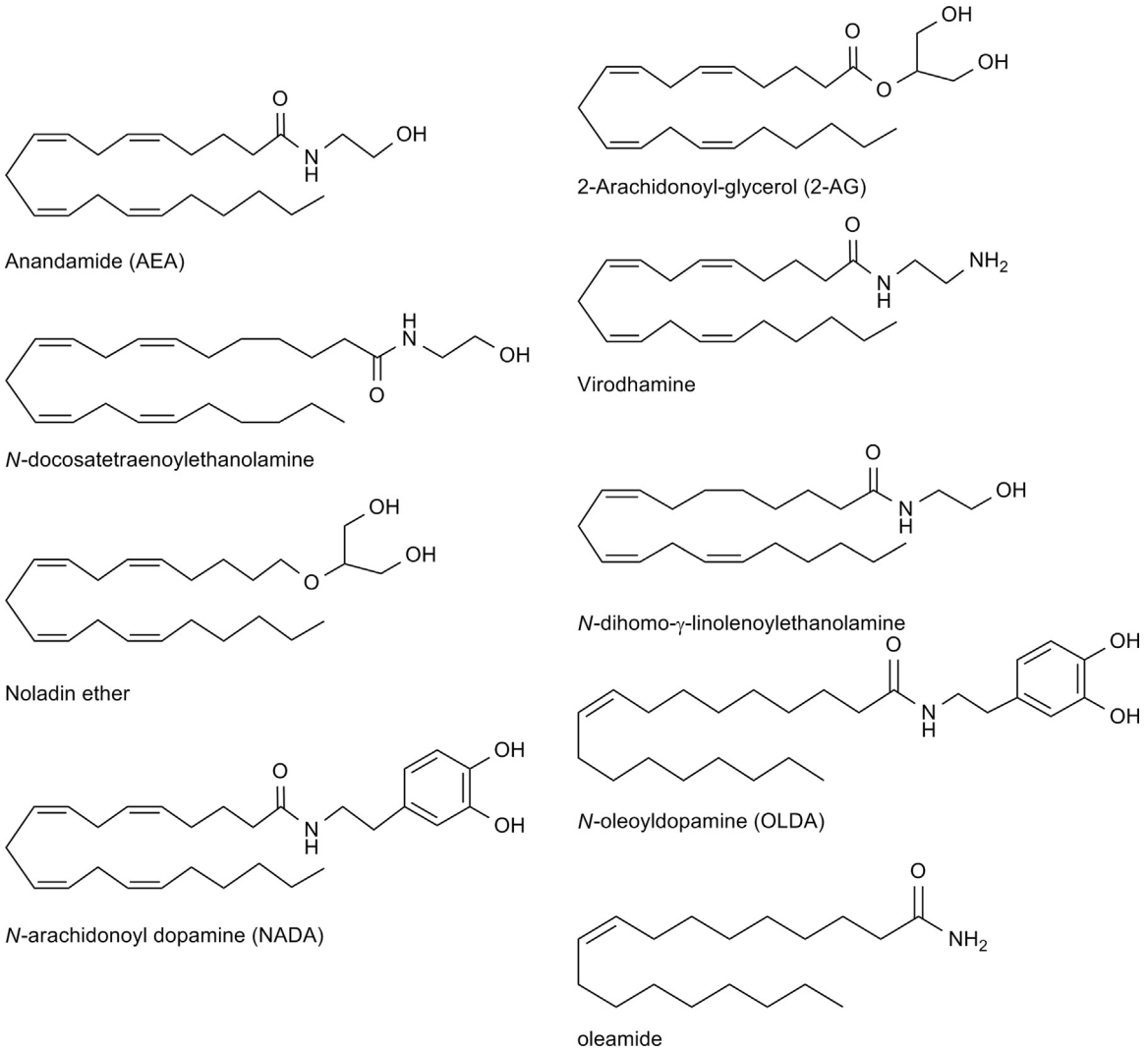

Fig. 1. Structural formulas of endogenous agonists for the cannabinoid receptors. Anandamide (N-arachidonoylethanolamine, AEA), 2-arachidonoyl glycerol (2-AG), O-arachidonoylethanolamine (Virodhamine), Noladin ether, N-arachidonoyldopamine (NADA), are all derived from the *n*-6 LC-PUFA arachidonic acid (20:4[*n*-6]). N-docosatetraenoylethanolamine is derived from docosatetraenoic acid (22:4[4-6]), N-dihomo-γ-linolenoylethanolamine, from gamma-linolenic acid (18:3[*n*-6]). N-oleoyldopamine (OLDA), and oleamide are both derived from the oleic acid (18:1 cis-9).

interact with 'true' cannabinoid receptors (Alexander and Kendall, 2007; Pertwee et al., 2010). Last but not least, biochemical pathways for synthesis and degradation of endocannabinoids and their congeners show several crossroads and connections with those of other bioactive lipids. This not only creates a number of regulatory nodes, but also results in the formation of 'hybrid' structures, including prostamides and other oxidation products, which often display bio-activity themselves (Silvestri et al., 2013; Woodward et al., 2011, 2007, 2013). Taken together, there is growing consensus that an 'expanded' view of the ECS (Fig. 2), also referred to as 'endocannabinoidome' would be more appropriate to study and understand its full dimensions (Maione et al., 2013; Silvestri and Di Marzo, 2013; Witkamp and Meijerink, 2014).

Endocannabinoids, their congeners and metabolites show time- and tissue-specific quantitative fluctuations, which are influenced by various endogenous and environmental factors. This also underlines the involvement of the ECS in various biological processes and multiple diseases and disorders, including pain, anxiety/depression, gastro-intestinal (GI)/liver diseases, cancer, bone diseases, metabolic diseases and obesity. The first decade following its discovery, this pleiotropic character caused great optimism regarding the potential pharmacological targets the ECS seemed to offer. Initially, the most promising areas seemed to be weight management and metabolic diseases. Based on the concept of an apparently 'overactive' ECS, expectations were high about the possibilities to use CB_1 antagonists and inverse agonists to reduce this 'endocannabinoid tone'. Clearly, the failure of rimonabant (in 2008), the first in class CB_1 inverse agonist, because of severe anxiety and depression-related side-effects in predisposed persons (Christensen et al., 2007) came as a shock to the research field and companies working on these compounds. In retrospect, these failures seem to illustrate that it were exactly the central role, vast expanse and dynamic nature of the ECS that contributed to this. However, in spite of these setbacks, the endocannabinoid system in a broader perspective more than ever offers fascinating physiological and pharmacological challenges. With the rapid developments in analytical chemistry and systems biology it has become increasingly possible to comprehend and modulate metabolic pathways of the ECS. This review aims to illustrate recent insights in the endocannabinoid field, focussing on inflammation and its links with other inflammatory mechanisms. As will be shown, targeted modulation of the ECS remains a challenge, but continues to offer interesting therapeutic perspectives.