ENDOCANNABINOIDS: THEIR ROLES IN BIOLOGY AND MEDICINE

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Summary

Endocannabinoids are endogenous ligands and activators of cannabinoid receptors. These bioactive lipids are currently categorized into two main families: *N*-acylethanolamines and acylesters, being *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), respectively, their main representatives. Furthermore, several studies suggested that AEA may also act on other targets, such as vanilloid and peroxisome proliferator-activated receptors. Many of the biological actions of endocannabinoids are controlled by key agents responsible for their synthesis, transport and degradation, forming all together the "endocannabinoid system". In the past decade, this system has been involved in a broad range of physiological functions, including control of mood, anxiety, depression, cardiovascular tone, energy metabolism, bone remodelling, skin homeostasis and reproduction, as well as in a growing number of pathological conditions, both in the central and peripheral nervous systems and in

peripheral organs. On this basis, it has been suggested that the endocannabinoid system may serve as an attractive therapeutic target for the treatment of different human disorders.

1. Introduction

The recreational value of cannabis (*Cannabis sativa*) preparations is known to most people, largely as a result of the explosion in its use in the late 1960s. Indeed, marijuana is still one of the most widespread illicit drugs of abuse in the world. The plant produces more than 420 compounds, including ~80 terpeno-phenol substances termed "phytocannabinoids". Among them, Δ^9-tetrahydrocannabinol (THC) (Figure 1) is the primary psychoactive component and is thought to mediate most of the effects associated with marijuana smoking. Other phytocannabinoids have emerged as bioactive substances, endowed with central or peripheral activities, like cannabidiol (CBD), trans-Δ^9-tetrahydrocannabivarin (THCV), and cannabigerol (CBG), all shown in Figure 1. The growing interest towards these new plant derivatives is due to minimal (if any) psychotropic effects of some of them (especially CBD), while leading to a modulation of the endocannabinoid system that holds promise for next generation therapeutics.

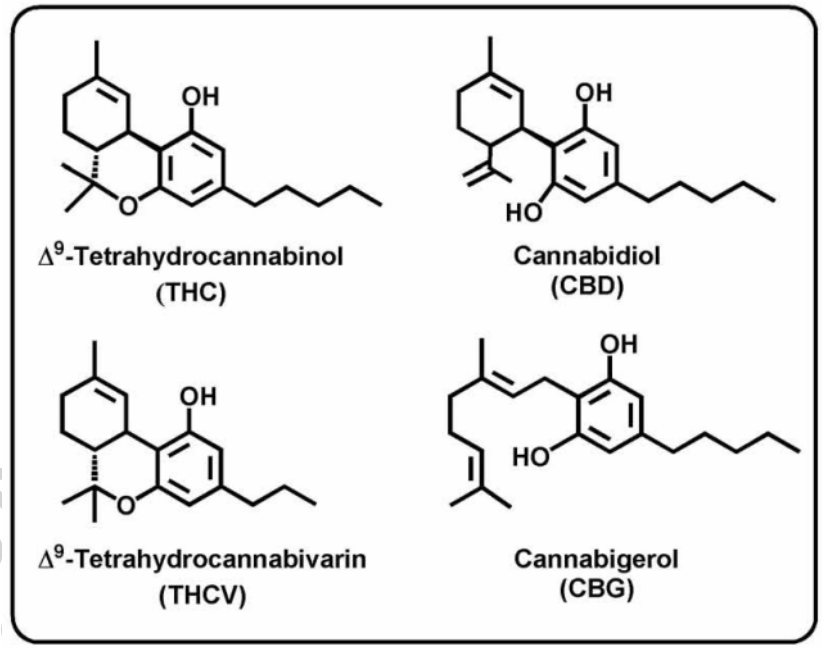

Figure 1. Chemical structures of some prominent phytocannabinoids

The stringent structural characteristics that plant-derived substances must possess, in order to exert their psychotropic effects, advocated the presence of a specific, high-affinity binding site for these lipids. Not surprisingly, the first membrane receptor for THC was identified in rat brain, and its distribution was consistent with the pharmacological properties of psycotropic cannabinoids; therefore, it was designated as type-1 cannabinoid (CB_1) receptor. A second THC-binding receptor was identified a few years later in spleen and immune cells, and was called type-2 cannabinoid (CB_2) receptor. The properties of CB_1 and CB_2 have been recently described in extensive reviews, and will be recapitulated later in this article.

Shortly after the discovery of CB_1 and CB_2 several bioactive lipids, collectively termed "endocannabinoids (eCBs)", have been shown to act as their endogenous ligands. These compounds comprise a family of unsaturated fatty acid derivatives that include *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) as the best studied members of fatty acid amides (FAAs) and monoacylglycerols (MAGs), respectively. In addition, *N*-arachidonoyldopamine (NADA), 2-arachidonoylglycerylether (noladin ether) and *O*-arachidonoylethanolamine (virodhamine) (Figure 2) have been shown to behave as cannabimimetic compounds, although their pharmacology is as yet poorly understood.

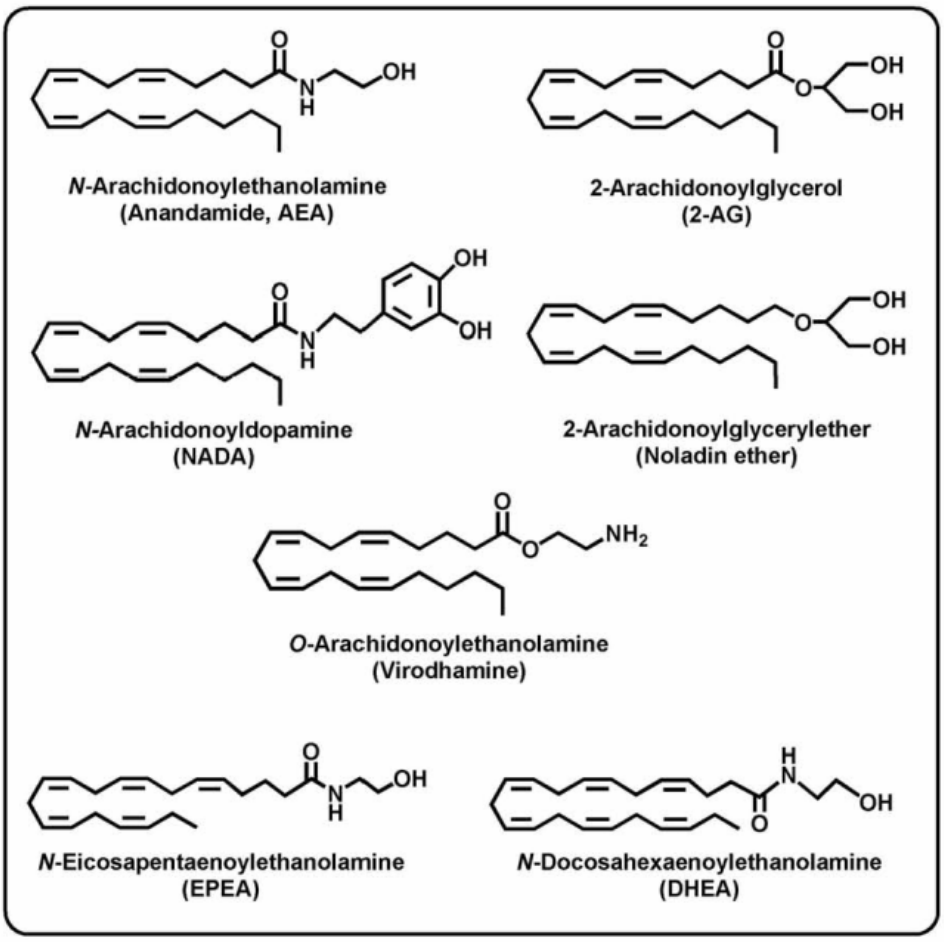

Figure 2. Chemical structures of the major endocannabinoids

Interestingly, new ethanolamide derivatives of two metabolically important -3 fatty acids (eicosapentaenoic and docosahexaenoic acids) have been demonstrated in animal tissues; they are eicosapentaenoyl ethanolamide (EPEA) and docosahexaenoyl ethanolamide (DHEA), shown in Figure 2, that activate CB_1 and CB_2 in prostate cancer cells with significant potency. On this basis, EPEA and DHEA are condidered *bona fide* eCBs.

In contrast to polyunsaturated FAAs, saturated and monounsaturated FAAs appear to be inactive at CB receptors, yet they show a variety of biological activities. *N*-Palmitoylethanolamine (PEA) is an anti-inflammatory, anti-convulsant and anti-

proliferative agent, *N*-oleoylethanolamine (OEA) is an appetite-suppressor, and *N*-stearoylethanolamine (SEA) is an immunomodulator that also induces apoptosis of glioma cells and shows anorexic effects. In particular, OEA and PEA are better considered "endocannabinoid-like" compounds, because they do not activate directly CB receptors, but rather prolong the activity of true eCBs within the cell by an "entourage effect". The chemical structures of OEA, SEA and PEA are shown in Figure 3.

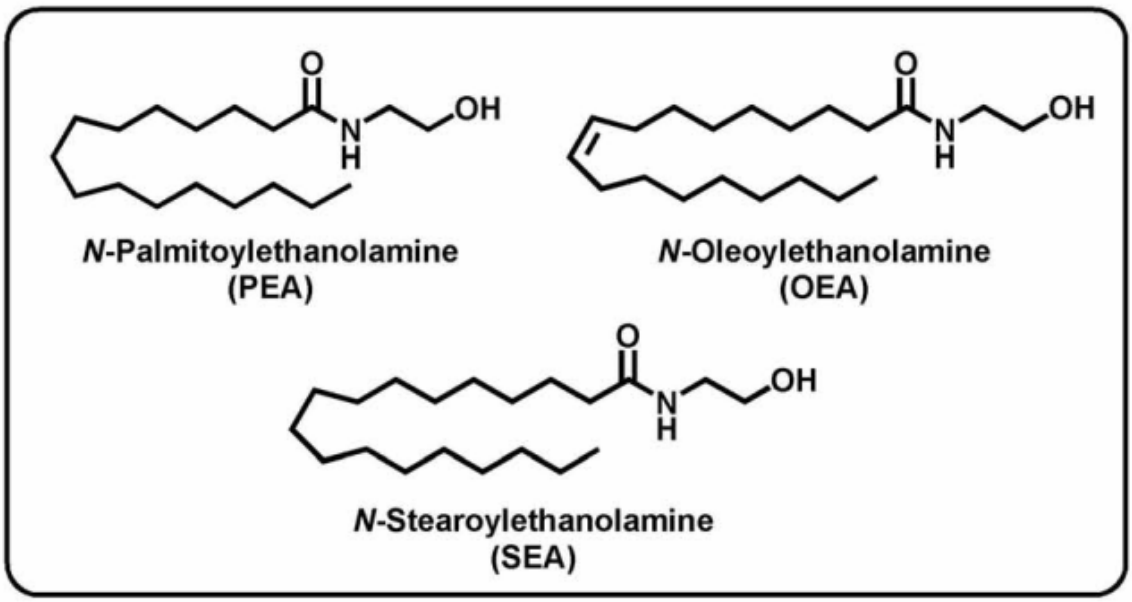

Figure 3. Chemical structures of some prominent "endocannabinoid-like" compounds

AEA and 2-AG bind to and activate both CB_1 and CB_2, that are G protein-coupled receptors (GPCR) localized in the central nervous system and in peripheral tissues. Recent evidence suggests that some eCBs might also bind to and activate GPR55, an orphan GPCR that might be a novel "type-3 cannabinoid (CB_3)" receptor. Furthermore, AEA binds also to transient receptor potential vanilloid 1 (TRPV1) channels, as well as to nuclear receptors like peroxisome proliferator-activated receptors (PPARs).

The biological actions of AEA and 2-AG are controlled through not yet fully characterized cellular mechanisms, that include key agents responsible for AEA and 2-AG synthesis, like the *N*-acyl-phosphatidylethanolamines (NAPE)-hydrolyzing phospholipase D (NAPE-PLD) and the *sn*-1-specific diacylglycerol lipase (DAGL), respectively; or degradation, like the fatty acid amide hydrolase (FAAH) and the monoacylglycerol lipase (MAGL), respectively. These enzymes, together with other congeners of AEA and 2-AG, the cannabinoid receptors and a purported "endocannabinoid membrane transporter (EMT)", form the "endocannabinoid system (ECS)", schematically depicted in Figure 4. The main features of the ECS elements are detailed in the following sections.

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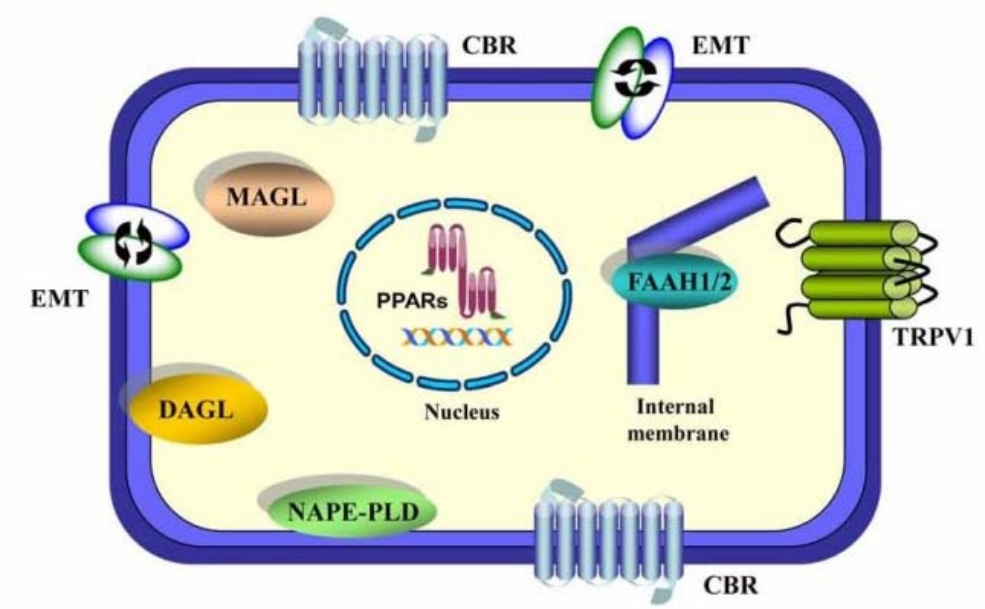

Figure 4: Scheme illustrating the main elements of the endocannabinoid system

2. Endocannabinoid System

2.1 Endocannabinoids

The eCBs are bioactive substances structurally different from THC or other phytocannabinoids. Yet, the first eCB to be isolated from pig brain, termed anandamide (AEA) from the Sanskrit word "ananda" for inner bliss, was shown to share with THC three pharmacophores that allow a specific interaction with CB_1 receptors (Figure 5).

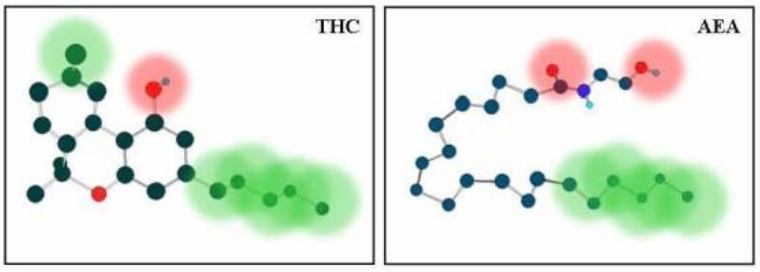

Figure 5: Structural similarities between THC and AEA: electron density and arrangements of the three pharmacophores, i.e. moieties that interact with CB receptors

The second eCB to be found was 2-AG: in 1995 isolated it from rat brain, and independently from canine gut. The chemical structures of AEA and 2-AG are shown in Figure 2.

eCBs are present in the central nervous system (CNS) and also in peripheral tissues, but exhibit important differences in their quantitative distribution as well as in their properties as endogenous agonists for cannabinoid receptors; 2-AG is more abundant than AEA in the brain and behaves as a full agonist of CB_1 and CB_2, while AEA acts as a partial agonist of CB_1 and as a weak partial agonist/antagonist of CB_2.

AEA levels may vary from 4- to 6-fold in different regions of the rat brain, with the highest levels in the striatum and brainstem and the lowest levels in the cerebellum and cortex. AEA is produced in regions of both rat and human brains where CB_1 is highly represented (hippocampus, cerebellum, and striatum) and also in the thalamus, a region that is sparse in CB_1. AEA levels in the brain are equivalent to those of other neurotransmitters such as dopamine and serotonin, but at least 10-fold lower than the levels reported for γ-aminobutyric acid (GABA) and glutamate.

AEA has also been found in peripheral tissues like human and rat spleen, which expresses high levels of CB_2. Small amounts of AEA were also detected in human serum, plasma, cerebrospinal fluid and in human immune cells that circulate in peripheral blood.

In many brain regions the levels of 2-AG are 2 to 3 orders of magnitude higher than those of AEA, however caution has to be raised on the possibility that different detection protocols, or even artifactual production of eCBs might contribute to alter the detected amounts. In this context, it seems noteworthy that a recent study has shown that the extracellular concentrations of AEA and 2-AG are both in the nanomolar range, suggesting that these two compounds have a similar availability for their CB receptor-mediated biological actions.

On the other hand, the spatial distribution of the two eCBs is similar in different regions of the brain. In fact, the highest concentrations of 2-AG were found in the brainstem, medulla, limbic forebrain, striatum, and hippocampus, and the lowest levels in the cortex, diencephalon, mesencephalon, hypothalamus, and cerebellum. Therefore, much alike AEA, no strict correlation exists between the endogenous tone of 2-AG and CB_1 distribution. 2-AG was also detected in the peripheral system, i.e. in the sciatic nerve, lumbar spinal cord, and lumbar dorsal root ganglion cells, as well as in immune cells. More generally, it should be stressed that 2-AG found in cells and tissues does not necessarily stimulate CB receptors, as this eCB can also act at the crossroads of several metabolic pathways.

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2.2 Biosynthesis of Endocannabinoids

Any molecule acting as an endogenous mediator of physiological and pathological responses needs mechanisms for its biosynthesis. In particular, for AEA the first hypothesis was that this compound is not stored in secretory vesicles, like classical neurotransmitters, but is formed “on demand” from membrane phospholipid precursors in a Ca^{2+}-dependent manner. Recent evidence, both for AEA and 2-AG, seems to expand this model that underestimates the complexity of eCB metabolic routes. In fact, intracellular storage organelles and intracellular transporters have been demonstrated for AEA, and distinct intracellular pools have been suggested for 2-AG.

The relevance of the intracellular distribution (or “trafficking”) of eCBs will be discussed later on in this review. Of course, it is possible that the multiple pathways that contribute to eCBs production might act in distinct tissues and under different pathophysiological conditions, making it even more challenging to disclose the regulatory mechanisms of eCBs metabolism.

2.2.1 Biosynthesis of AEA

The family of FAAs, of which AEA is the prototype member, has been known long before the identification of AEA and the appreciation of its prominent biological activity. It was demonstrated that FAAs are mainly biosynthesized from membrane phospholipids through a common two-step pathway, termed "the transacylation-phosphodiesterase pathway". In particular, the AEA precursor is *N*-arachidonoylphosphatidylethanolamine (NArPE), which originates from the transfer of arachidonic acid from the *sn*-1 position of phospholipids to the *N*-position of phosphatidylethanolamine (PE), catalyzed by *trans*-acylase activity. NArPE is then cleaved by the *N*-acyl-phosphatidylethanolamines (NAPE)-hydrolyzing phospholipase D (NAPE-PLD), which releases AEA and phosphatidic acid (Figure 6).

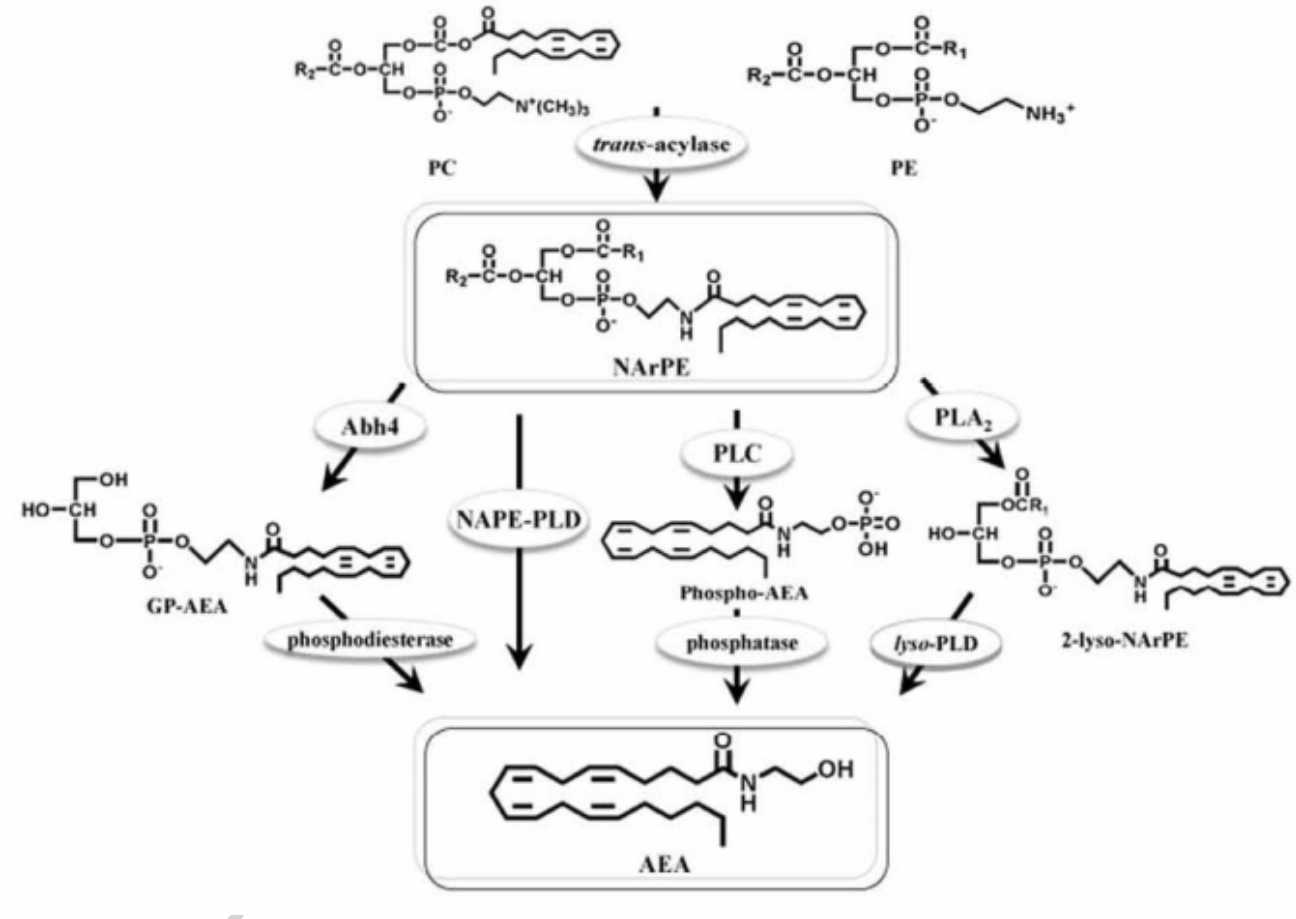

Figure 6: Major biosynthetic pathways of anandamide. Abh4, alpha/beta-hydrolase 4; NArPE, *N*-arachidonoylphosphatidylethanolamine; NAPE-PLD, *N*-acyl-phosphatidylethanolamines (NAPE)-hydrolyzing phospholipase D; PE, phosphatidylethanolamine; PC, phosphocholine; PLC, phospholipase C

This biosynthetic pathway is in agreement with the different percentages of FAAs in various tissues, because their concentrations may reflect the amounts of different fatty acids esterified on the *sn*-1 position of phospholipids. Although a specific *trans*-acylase has not yet been identified, a NAPE-PLD has been cloned from mouse, rat and human tissues and classified as a member of zinc metallo-hydrolase family of the β-lactamase

fold. The enzyme is composed of 393 amino acids, binds 1 or 2 zinc ions per subunit, and is localized on the cell membrane.

Recently, a number of different routes have been described in macrophages and brain extracts for the transformation of NArPE into AEA. Firstly, a phospholipase C-dependent conversion to phospho-AEA, followed by its hydrolysis to AEA by the tyrosine phosphatase PTPN22. Secondly, the action of alpha/beta-hydrolase 4 (Abh4) as a *lyso*-phospholipase/phospholipase B for the formation of glycerol-phospho-AEA (GP-AEA), which is then converted into AEA by a phosphodiesterase. Yet another possible pathway for AEA biosynthesis, independent of NAPE-PLD, involves the conversion of NArPE into 2-*lyso*-NArPE by a soluble form of phospholipase A_2, followed by the action of a *lyso*-phospholipase D. These alternative routes for AEA biosynthesis are summarized in Figure 6. It should be recalled that the existence of multiple biosynthetic pathways for AEA stemmed from data showing that mice lacking *nape-pld* gene (knockout (-/-) mice) displayed profound reductions in very long-chain saturated and monounsaturated FAAs in the central nervous system, but unaltered levels of poly-unsaturated FAAs, including AEA. Additionally, these observations represented a proof of concept that at least a dual strategy to control the biosynthesis of long chain saturated and poly-unsaturated FAAs was developed by the cell.

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