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Review

N-acylethanolamine metabolism with special reference to *N*-acylethanolamine-hydrolyzing acid amidase (NAAA)

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ABSTRACT

N-acylethanolamines (NAEs) constitute a class of bioactive lipid molecules present in animal and plant tissues. Among the NAEs, *N*-arachidonoylethanolamine (anandamide), *N*-palmitoylethanolamine, and *N*-oleoylethanolamine attract much attention due to cannabimimetic activity as an endocannabinoid, anti-inflammatory and analgesic activities, and anorexic activity, respectively. In mammalian tissues, NAEs are formed from glycerophospholipids through the phosphodiesterase-transacylation pathway consisting of Ca^{2+}-dependent *N*-acyltransferase and *N*-acylphosphatidylethanolamine-hydrolyzing phospholipase D. Recent studies revealed the presence of alternative pathways and enzymes responsible for the NAE formation. As for the degradation of NAEs, fatty acid amide hydrolase (FAAH), which hydrolyzes NAEs to fatty acids and ethanolamine, plays a central role. However, a lysosomal enzyme referred to as NAE-hydrolyzing acid amidase (NAAA) also catalyzes the same reaction and may be a new target for the development of therapeutic drugs. In this article we discuss recent progress in the studies on the enzymes involved in the biosynthesis and degradation of NAEs with special reference to NAAA.

Contents

Abbreviations: Abh4, α/β-hydrolase 4; 2-AG, 2-arachidonoylglycerol; Ca-NAT, Ca^{2+}-dependent NAT; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; COX, cyclooxygenase; DTT, dithiothreitol; FAAH, fatty acid amide hydrolase; GDE, glycerophosphodiesterase; GFP, green fluorescent protein; GP-NAE, glycerophospho-NAE; HRASLS, HRAS-like suppressor family; iNAT, Ca^{2+}-independent NAT; LPS, lipopolysaccharide; LRAT, lecithin retinol acyltransferase; MAFP, methyl arachidonyl fluorophosphonate; NAAA, NAE-hydrolyzing acid amidase; NAE, *N*-acylethanolamine; NAPE, *N*-acylphosphatidylethanolamine; NAPE-PLD, NAPE-hydrolyzing phospholipase D; NAT, *N*-acyltransferase; Ntn, N-terminal nucleophile; PC, phosphatidylcholine; PCMB, *p*-chloromercuribenzoic acid; PE, phosphatidylethanolamine; PL, phospholipase; PMSF, phenylmethanesulfonyl fluoride; $sPLA_2$, secretory phospholipase A_2; TIG3, tazarotene-induced gene 3.

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1. Introduction

N-acylethanolamines (NAEs) are ethanolamides of long-chain fatty acids and exist in both animal and plant. In animal, *N*-palmitoylethanolamine was first isolated from egg yolks [1], and later from rat and guinea pig tissues such as brain, liver, and skeletal muscle [2]. *N*-palmitoylethanolamine had their pharmacological activities such as anti-inflammatory and anti-anaphylactic properties [3]. Quantitatively major NAEs in mammalian tissues include *N*-palmitoylethanolamine, *N*-stearoylethanolamine, *N*-oleoylethanolamine, and *N*-linoleoylethanolamine (Fig. 1). Schmid and his group thoroughly investigated the biosynthetic and degradative pathways of NAEs in mammals, and showed that NAEs are principally formed from glycerophospholipids via *N*-acylated ethanolamine phospholipids. These earlier biochemical studies on NAEs were comprehensively reviewed by Schmid et al. in 1990 [4]. Thereafter, *N*-arachidonoylethanolamine was isolated from porcine brain as an endogenous ligand of cannabinoid receptor and termed anandamide [5].

The cannabinoid receptor was originally cloned as a G protein-coupled receptor that binds to Δ^9-tetrahydrocannabinol, a psychoactive component in marijuana [6]. Cannabimimetic activities of anandamide include pertussis toxin-sensitive decrease in intracellular cAMP levels, regulation of ion channels such as activation of A-type and inwardly rectifying potassium channels and inhibition of N-type and P/Q-type calcium channels, and the 'cannabinoid tetrad' (sedation, catalepsy, analgesia, and hypothermia) [7–9]. Other polyunsaturated NAEs such as *N*-dihomo-γ-linolenoylethanolamine, *N*-docosatetraenoylethanolamine, and *N*-eicosa-5,8,11-trienoylethanolamine (mead ethanolamide) also showed similar ligand activities [10,11], while monounsaturated and saturated NAEs were almost inactive [12]. Later studies revealed several endogenous lipid molecules acting as agonists of cannabinoid receptors, and these molecules were collectively referred to as endocannabinoids [7]. It is now accepted that anandamide is a partial agonist of cannabinoid receptor of the central type (CB1) and is much less active at the peripheral type receptor (CB2) [13]. Anandamide is also known as a ligand of vanilloid receptor (the transient receptor potential vanilloid type 1, TRPV1) [14]. On the other hand, 2-arachidonoylglycerol (2-AG), which was discovered as another endocannabinoid later than anandamide [15,16], is recognized to be a full agonist of both CB1 and CB2 [13].

Studies on cannabinoid receptor-insensitive NAEs were also developed, which revealed the anti-inflammatory and analgesic activities of *N*-palmitoylethanolamine [17] and the anorexic action of *N*-oleoylethanolamine [18,19]. Derivatives of *N*-oleoylethanolamine may be developed as new anti-obesity drugs [20]. Moreover, the peroxisome proliferator-activated receptor (PPAR)-α [21,22] and the G protein-coupled receptor GPR119 [23] were suggested to mediate signal transduction triggered by these NAEs. It has been a matter of debate if GPR55, another G protein-coupled receptor, is a new cannabinoid receptor [24]. However, a recent study showed that 2-arachidonoyl-lysophosphatidylinositol is the most potent endogenous ligand of GPR55 [25]. *N*-acylphosphatidylethanolamines (NAPEs) are minor components of membrane phospholipids serving as precursors of NAEs. Recently, NAPE was reported to repress food intake [26] and to inhibit macrophage phagocytosis by inhibiting Rac1 and Cdc42 [27].

NAEs including anandamide are not stored in the cell but rather made on demand, and their endogenous levels appear to be regulated directly by enzymes responsible for their formation and degradation. Therefore, these enzymes have attracted much attention to elucidate physiological and pathophysiological significance of NAEs. The enzymes are also noted as potential targets of drug therapy, and their selective inhibitors are anticipated as therapeutic drugs [28]. Recent molecular biological studies reveal not only the principal role of the classical 'phosphodiesterase-transacylation pathway' in NAE formation but also the presence of alternative pathways or enzymes (Fig. 2). The major pathway for degradation of NAEs is their hydrolysis to free fatty acids and ethanolamine (Fig. 3). Fatty acid amide hydrolase (FAAH) plays a central role in this reaction. However, a lysosomal enzyme, which we named

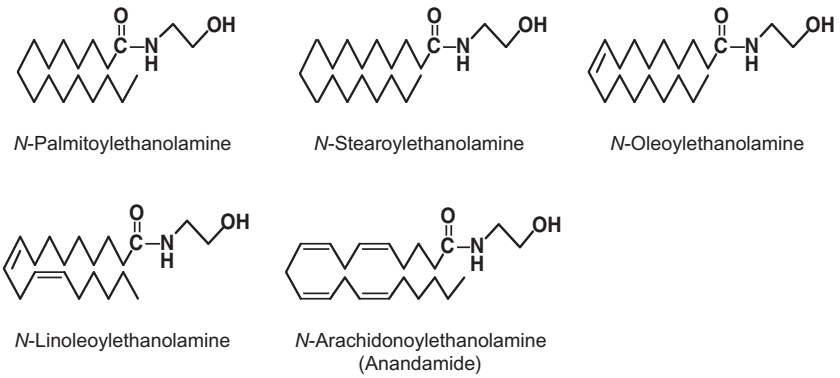

Fig. 1. Representative NAEs.