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Review

Orphan endogenous lipids and orphan GPCRs: A good match

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ABSTRACT

A large and growing family of over 70 endogenous lipids of the basic structure *N*-acyl amide has been identified during the last 10 years. Only a few of these lipids have been characterized for biological activity, however, those that have shown a wide-range of activity may act at G-protein coupled receptors (GPCRs). Like orphan GPCRs that are identified as being in the genome and expressed in tissue, the majority of these endogenous lipids many produced throughout the body, some predominately in nervous tissue, remain orphaned. Here, we give a brief history of these orphan lipids and highlight the activity of *N*-arachidonoyl glycine, and farnesyl pyrophosphate at the orphan receptors GPR18 and GPR92, respectively, as well as summarizing the biological and pharmacological data for the recently identified *N*-palmitoyl glycine that suggests activity at a novel GPCR. Working to deorphanize both lipids and GPCRs together provides a unique opportunity for a greater understanding of cellular signaling and a challenge to find them all a home.

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Contents

1. Matching endogenous lipid ligands with GPCRs lead to the discovery of orphan lipids

The lipophilic phytocannabinoid, Δ^9-tetrahydrocannabinol (THC), was identified from cannabis in 1965 by Mechoulam and Gaoni [1]. Δ^9-THC and other lipids extracted from the cannabis plant [2] where shown to activate G-protein coupled receptors [for review see [3]] leading to the hypothesis that an endogenous ligand, likely a lipid, must be produced. An endogenous analog to Δ^9-THC was identified in Mechoulam's group in 1992 [4] from porcine brain and named anandamide after the transliteration of the Sanskrit word *ananda* meaning bliss, and the amide bond between the acyl chain, arachidonic acid, and the amine, ethanolamine. This endogenous cannabinoid, *N*-arachidonoyl ethanolamine (AEA, Fig. 1A) shares a molecular structure with the growing family of novel endogenous *N*-acyl amide signaling molecules with a wide-range of cellular signaling potential [5]. Both Δ^9-THC and AEA were shown to activate the G-protein coupled cannabinoid receptor 1 and induce several physiological and behavioral outcomes including hypothermia, analgesia, hypoactivity and catalepsy [1,4]. Additional characteristics of AEA include binding to the GPCR cannabinoid receptor 2 and activating the transient receptor potential vanilloid type-1 channel ($TRPV_1$) [6,7]. A second endogenous cannabinoid lipid, 2-arachidonoyl glycerol (2-AG), which also binds both cannabinoid receptors, was later identified in rat brain and canine gut [8,9]. The field of endogenous cannabinoid research has exploded during the last decade and our understanding of basic neurophysiology, immune function, memory, appetite, and pain [for reviews see: [3,10–14]] have grown from these humble beginning. These two endogenous lipids paved the way for the

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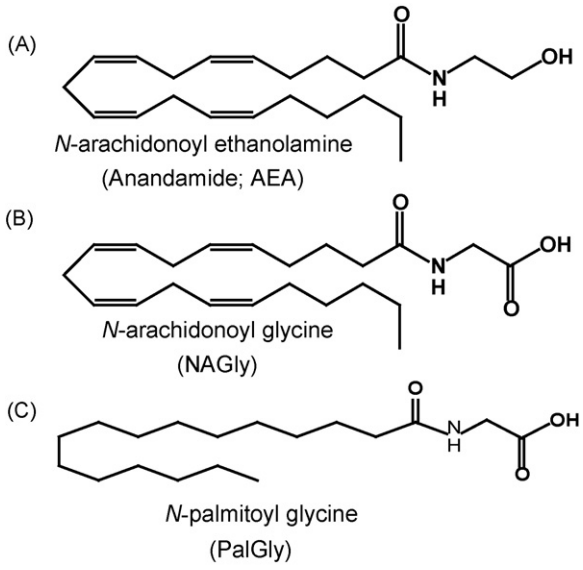

Fig. 1. Molecular structure of the endocannabinoid, *N*-arachidonoyl ethanolamine (AEA) (A). (B and C) Endogenous structural analogs of AEA, *N*-arachidonoyl glycine and *N*-palmitoyl glycine.

identification of a growing family of lipids often referred to as endocannabinoids/endovanilloids and are primarily *N*-acyl amides in structure. In this report we will discuss of this family of "orphan" lipids and two of the GPCRs for which a few of them have found a match. Given the number of orphan lipids now identified and the number of still orphan GPCRs the combination of the two systems will likely provide novel and important insights into cell signaling.

2. Identification of a large family of endogenous *N*-acyl amides: orphan lipids

Sumner Burstein and colleagues suggested that *N*-arachidonoyl glycine (NAGly; Fig. 1B) was a putative endogenous compound in 1997 [15]. The methodologies used in the isolation and measurements of AEA in biological samples (lipid extractions and HPLC/MS/MS) enabled the search for other *N*-acyl amides of similar structure, which were hypothesized to have comparable function. Thus, Huang and colleagues [16] isolated three novel *N*-acyl amide molecules in the brain and periphery: NAGly, *N*-arachidonoyl GABA, and *N*-arachidonoyl alanine. Subsequent work identified *N*-acyl dopamines; *N*-arachidonoyl dopamine, *N*-palmitoyl dopamine, *N*-stearoyl dopamine and *N*-oleoyl dopamine [17,18]. In addition, other research groups identified and characterized *N*-arachidonoyl serine [19] and the *N*-acyl taurines [20]. We continued the identification of the *N*-acyl glycines by way of *N*-palmitoyl glycine (PalGly) [21] plus another four *N*-acyl-glycines from oleoyl, linoleoyl, stearoyl, and docosahexaenoyl acyl groups conjugated to glycine [22]. Tan and colleagues while in the lab of the late Walker [23,24] further demonstrated structural and chromatographic matches for 54 synthesized *N*-acyl amino acid standards to endogenous compounds isolated in brain. Like the *N*-acyl ethanolamine, glycines, dopamines, and taurines that have been identified (Fig. 2), these novel endogenous lipids are extended members of the *N*-acyl amide families in that the acyl chains are typically C16, C18, C20 or C22 with 0–6 double bonds and each conjugated to an amino acid. These compounds represent a collection of orphan signaling molecules whose biological activity remains unknown. *N*-Oleoyl ethanolamine and *N*-palmitoyl ethanolamine (the oleic and palmitic acid amide analogs of the endocannabinoid, AEA) were deorphaned by the GPCRs, 119 [25] and GPR55 [26], respectively, and this is discussed in another paper in this special edition by Kunos and colleagues. Systematic characterization of each of these orphan lipids at orphan GPCRs will open the door to understanding how these novel lipids work in the brain.

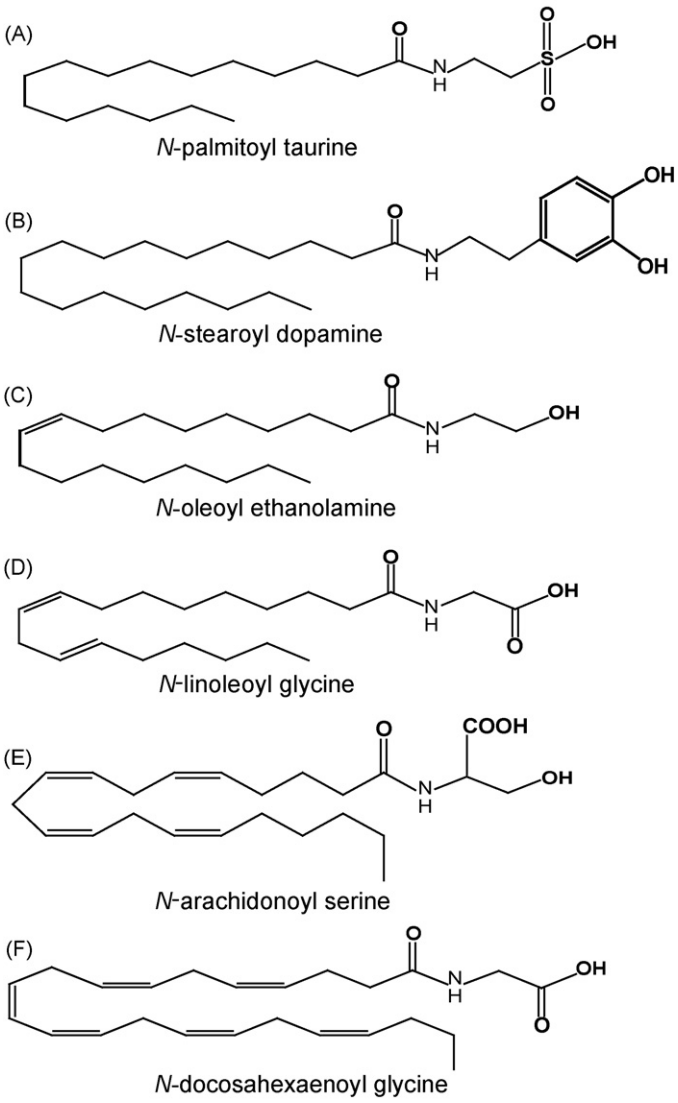

Fig. 2. Examples of *N*-acyl amides that have been identified endogenously and whose targets are still being characterized. Each of these endogenous compounds is a conjugation of an acyl chain ranging from 16 to 24 carbons in length and contains either 0 or 6 double bonds to a simple amine. (A) *N*-Palmitoyl taurine may activate TPRV1 or TRPV4 receptors [20], (B) *N*-stearoyl dopamine is located in mammalian striatum [18], (C) *N*-oleoyl ethanolamine activates GPR119 and plays a role in appetite regulation [38], (D) *N*-linoleoyl glycine is present in most tissues with highest abundance in lung [22], (E) *N*-arachidonoyl serine is present throughout the body and plays a role in vascular function [19] and (F) *N*-docosahexaenoyl glycine is present in most tissues with highest abundance in skin [22].

2.1. GPR18

The orphan GPCR, GPR18, consists of 331 amino acids and is located in humans, rodents, and canine on chromosome 13 [27]. Studies by Kohno et al. [28] found that low concentrations ($EC_{50} \sim 20$ nM) of NAGly activate GPR18. NAGly differs from AEA by the oxidation state of the carbon beta to the amido nitrogen (Fig. 1B); a modification that drastically reduces its activity at both cannabinoid receptors [29]. Therefore, when NAGly was shown to produce antinociceptive and anti-inflammatory effects in a variety of pain models, it was hypothesized to be through an alternative receptor [16,30–32]. Consistent with the anti-inflammatory effects of NAGly, GPR18 is highly expressed in peripheral blood leukocytes