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Biosynthesis, degradation, and pharmacological importance of the fatty acid amides

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Abstract

The identification of two biologically active fatty acid amides, *N*-arachidonoylethanolamine (anandamide) and oleamide, has generated a great deal of excitement and stimulated considerable research. However, anandamide and oleamide are merely the best-known and best-understood members of a much larger family of biologically-occurring fatty acid amides. In this review, we will outline which fatty acid amides have been isolated from mammalian sources, detail what is known about how these molecules are made and degraded *in vivo*, and highlight their potential for the development of novel therapeutics.

Keywords

N-acylamino acid; *N*-acyldopamine; *N*-acylethanolamine; primary fatty acid amide; N-acylamide

The fatty acid amide bond has long been recognized in nature, being important in the structure of the ceramides [1] and the sphingolipids [2]. The first non-sphingosine based fatty acid amide isolated from a natural source was *N*-palmitoylethanolamine from egg yolk in 1957 [3]. Interest in the *N*-acylethanolamines (NAEs) dramatically increased upon the identification of *N*-arachidonoylethanolamine (anandamide) as the endogenous ligand for the cannabinoid receptors in the mammalian brain [4]. It is now known that a family of NAEs is found in the brain and in other tissues [5,6].

In addition to the NAEs, other classes of fatty acid amides have been characterized, namely the *N*-acylamino acids (NAAs) [7], the *N*-acyldopamines (NADAs) [8] and the primary fatty acid amides (PFAMs) [9,10] (Figure 1). Relative to NAEs, much less is currently known about the NAAs, the NADAs and the PFAMs, except that they are found in biological systems. The goal of this review is to summarize the current state of knowledge regarding the different classes of endogenous fatty acid amides and highlight their potential for drug discovery (see refs. [11-13] for earlier reviews)

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Teaser Sentence Fatty acid amides are a family of mammalian bioactive compounds. These molecules and the enzymes involved in their metabolism provide an opportunity to develop new drugs to treat human disease.

N-Acylethanolamines

A series of long-chain NAEs have been identified in the mammalian brain, the most abundant being *N*-palmitoyl-, *N*-stearoyl- and *N*-oleoylethanolamine [5,11], each compromising ≥25% of total brain NAEs. Other less abundant NAEs found in the brain are anandamide, *N*-linoleoyl-, *N*-linolenoyl-, *N*-dihomo-γ-linolenoyl- and *N*-docosatetraenoylethanolamine [11]. In addition to the brain, the NAEs are widespread in the peripheral tissues [5].

The function of anandamide in mammals is mediated largely by its binding to the CB_1 receptors (K_d = ~80 nM) [14]. Anandamide is also known to bind to CB_2 receptors (K_d = ~500 nM) [14], peroxisome proliferators-activated receptors (PPARα, K_d = 20μM and PPARγ, K_d = 10 μM) [15], to the transient receptor potential (TRP) vanilloid type 1 (TRPV1) channels (K_d ~ 2 μM) [13], and the transient receptor potential channels of melastatin type 8 (TRPM8) (K_d ~ 1 μM) [16]. It is currently unclear how much the binding of anandamide to the non-CB_1 receptors contributes to its total activity *in vivo*.Anandamide is involved in the regulation of body temperature, locomotion, feeding and the perception of pain, anxiety and fear [17-21]. The functions of the other known mammalian NAEs are not as well-established as anandamide, which is ironic given that ananadamide represents only 1-10% of brain NAEs [5,11]. With the exception of *N*-dihomo-γ-linolenoyl-, and *N*-docosatetraenoylethanolamine, the other NAEs do not bind to the CB_1 and CB_2 receptors [13,22,23]. *N*-Oleoylethanolamine binds to PPARα and PPARβ, functioning to inhibit feeding behavior [15,23], as well as the TRPV1 receptor [6], and the G-protein-coupled receptor, GPR119 [24]. Stearoylethanolamine binds to specific, non-CB_1 and CB_2 receptors and yet exhibits activities similar to anandamide [25]. *N*Palmitoylethanolamine is neuroprotective and also modulates pain and inflammation [26]. The anti-inflammatory effect of *N*-palmitoylethanolamine is mediated by its binding to PPARα [26]. Ryberg *et al*. [27] recently found that *N*-palmitoylethanolamine is a ligand for the orphan GPR55 receptor. It has been suggested that at least some of the activities of *N*-palmitoylethanolamine, *N*-oleoylethanolamine and *N*-stearoylethanolamine result from the "entourage effect": cellular levels of anandamide are stabilized or increased because the other NAEs compete with anandamide for enzymatic degradation [22].

The most widely-accepted biosynthetic pathway for NAEs involves the NAPE-specific phospholipase D (NAPE-PLD)-mediated cleavage of *N*-acylphosphatidylethanolamine (NAPE) to the corresponding NAE and phosphatidic acid (PA) (reaction 1 in Figure 2) [28, 29]. NAPE is produced by the *N*-acylation of phosphatidylethanolamine in a reaction catalyzed by a calcium activated transacylase (Figure 3) [28]. Recent evidence suggests that there are other PLD-independent pathways for NAE biosynthesis [30,31]. One alternative pathway involves the phospholipase C-mediated cleavage of NAPE to yield a phospho-NAE (pNAE) which is then cleaved by a phosphatase to yield the NAE and inorganic phosphate (reactions 6 and 7 in Fig. 2). Another alternative pathway involves sequential hydrolysis of the *O*-acyl chains of NAPE to produce free fatty acids and glycerophospho-NAE (GP-NAE) (reactions 2 and 4 in Fig. 2). Simon and Cravatt [30] have found that a serine hydrolase, α/β-hydrolase 4 (Abh4), can catalyze both *O*-deacylation steps required to convert NAPE to GP-NAE. Phosphodiesterase cleavage of GP-NAE will yield the NAE and glycerol 3-phosphate (reaction 5 in Fig. 2). Other possible routes to the NAEs are direct hydrolysis of lysoNAPE (reaction 3 in Fig. 2) or the 2-step conversion of GP-NAE to the NAE *via* phospho-NAE (reactions 8 and 7 in Fig. 2). The PLD-independent pathways for NAE biosynthesis are exciting discoveries, suggesting that the body has redundant "back-up" methods to produce these important bioactive lipid amides that are made "on demand" [12,31]. Future work will determine how these three pathways function to supply the required NAE levels.

Any review of NAE biosynthesis would be incomplete if one last synthetic strategy is not discussed. There is data going back more than 40 years, showing that the NAEs can be produced

in vitro from ethanolamine and free fatty acids, in a reaction that did not require ATP or CoA-SH [32]. The *in vivo* significance of this chemistry is unclear.

NAE degradation is by hydrolysis to fatty acid and ethanolamine: R-CO-NH-CH_2-OH + H_2O → R-COOH + H_2N-CH_2-OH. Three enzymes are known to catalyze this reaction: two fatty acid amide hydrolases (FAAH-1 and FAAH-2) [33] and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) [34]. FAAH-1 and FAAH-2 both hydrolyze NAEs, but have different acyl group specificities. Note that FAAH inhibitors are currently being developed as potential analgesics [35-37].

N-Acyldopamines

A relatively small number of long-chain *N*-fatty acyldopamines have been isolated and characterized from mammalian systems, including *N*-palmitoyl-, *N*-stearoyl-, *N*-oleoyl- and *N*-arachidonoyldopamine. All of these NADAs are found in the mammalian brain, with the highest concentrations in the striatum, hippocampus and cerebellum [38].

N-Arachidonoyldopamine and *N*-oleoyldopamine were first identified as capsaicin-like endovanilloids that bound tightly to the TRPV1 receptor [13,38,39]. As a consequence of their binding to the TRPV1 receptors, both of these *N*-fatty acyldopamines stimulated calcium influx in HEK293 cells over-expressing either rat or human TRPV1 and produced hyperalgesia in rats [38,39]. *N*-Arachidonoyldopamine also binds tightly to the CB_1 receptor (K_d = 250-500 nM) [39,40] and a non-CB_1/CB_2 GPR in the aorta [41].[42] Other endogenous *N*-fatty acyldopamines include *N*-palmitoyldopamine and *N*-stearoyldopamine, both of which bind with to the TRPV1 or CB_1 receptors with relatively low affinity (K_d values >5 μM) [39]. The biological role(s) fulfilled by *N*-palmitoyldopamine and *N*-stearoyldopamine are unclear, but there is evidence that both enhance the activity of *N*-arachidonoyldopamine *via* the entourage effect [42].

In addition to the long-chain *N*-fatty acyldopamines, *N*-acetyldopamine is a known metabolite in mammals. The function of *N*-acetyldopamine is unclear, but it has been shown to inhibit mammalian sepiapterin reductase (an enzyme in the tetrahydrobiopterin biosynthetic pathway) with a K_i = 400 nM [43].

There has been little work on the pathways for the biosynthesis and degradation of the *N*-acyldopamines. *N*-Acetyldopamine is produced by the acetyl-CoA-dependent *N*-acetylation of dopamine [44] and has been found in the urine, kidney and liver [44,45]. It has been proposed that the long-chain *N*-acyldopamines are made *in vivo* in a similar fashion, with the acyl donors being the corresponding acyl-CoA thioesters [38]. Alternatively, the *N*-acyldopamines could be produced by the tyrosine hydroxylase-mediated oxidation of *N*-acyltyrosines (currently unknown metabolites in mammals). Huang *et al*. [38] provide data in support of both biosynthetic pathways.

Degradation of the *N*-acyldopamines is thought to occur by FAAH-catalyzed hydrolysis to the fatty acid and dopamine [38] or *O*-methylation by catechol-*O*-methyltransferase [38]. *N*-Acetyldopamine can serve as a substrate for tyrosinase; thus, the long-chain *N*-acyldopamines could also be oxidized to a quinone by this enzyme [46]. *N*-Acetylnoradrenaline is a known human metabolite [47] suggesting that *N*-acetyldopamine and the longer-chain *N*-acyldopamines could serve as substrates for dopamine β-monooxygenase.

N-Acylamino acids

Mammalian *N*-acylamino acids have a long history, tracing their discovery to the conjugation of glycine to benzoate to form N-benzoylglycine (hippurate) in the 1840s (see Caldwell *et al*.

[7] and reference cited therein). N^{α}-Acetyl conjugates for all 20 of the common amino acids have been identified in mammals. In addition, the N^{α}-acetyl conjugates of other amino acids, including β-alanine, allo-isoleucine, α-aminobutyric acid, GABA, 2-aminooctanoic acid, citrulline and N^{ε}-acetyllysine have also been characterized from mammalian sources [48-61]. With the exception of *N*-acetylglutamate, which serves as an allosteric activator of carbamoyl phosphate synthetase I [62], the *N*-acetylamino acid conjugates are trace metabolites that function in the excretion/detoxification of abnormally high levels of a particular amino acid. [63]Similarly, a set of *N*-isovaleroylamino acids have been identified from patents suffering from isovaleric acidemia, with *N*-isovaleroylglycine being the most abundant metabolite [55, 60,63-65] The function of these *N*-isovaleroylamino acids is also in excretion; one patient suffering from isovaleric academia was excreting 1.7 grams of N-isovaleroylglycine per day [66].

[63][65] *N*-Conjugation of fatty acids to amino acids forming the long-chain N-fatty acylglycines is known, but is relatively uncommon in mammals. [64][55][66]The most common mammalian *N*-fatty acylamino acids are conjugates of glycine, glutamine and taurine (Table 1). Like the shorter chain *N*-acetyl and *N*-isovaleroyl amino acids, the major function of these longer chain amino acid conjugates would appear to be in the detoxification and excretion of xenobiotic carboxylates [7]. Glycine conjugation is particularly important in detoxification and elimination, as a careful analysis of the metabolism of most xenobiotic carboxylates reveals at least a trace of the corresponding *N*-acylglycine conjugate [67]. In fact, the list of *N*-acylglycines shown in Table 1 is incomplete as glycine conjugates of many other carboxylates also have been reported [67,68].

Amino acid *N*-fatty conjugation may function primarily in excretion/detoxification; however, this chemistry does serve other roles in mammals. [69][70]Bile acid conjugation to glycine or taurine increases bile acid solubility, renders the bile acids impermeable to cell membranes and is essential to proper liver function [69]. In addition, β-citrylglutamate may have a role in spermatogenesis [54] and in the differentiation of lens epithelial cells into fiber cells [70].

Most intriguing are the emerging roles of the long-chain *N*-fatty acylamino acids. Milman *et al*. [71] recently isolated and characterized *N*-arachidonoyl-L-serine from bovine brain and showed that this novel *N*-fatty acylserine had vasodilatory properties. We have proposed that the *N*-fatty acylglycines are biosynthetic precursors to the PFAMs, being oxidatively cleaved to the corresponding PFAM and glyoxylate in a reaction catalyzed by peptidylglycine α-amidating monooxygenase (PAM) [72]. Recent evidence suggests that the *N*-fatty acylglycines may serve as more than simple PFAM pathway intermediates and may have independent functions: *N*-oleoylglycine regulates body temperature and locomotion [73], *N*-arachidonoyltaurine activates TRPV1 and TRPV4 calcium channels of the kidney [74], *N*-arachidonoylglycine is an endogenous ligand for the orphan GPR18 receptor, [75], *N*-arachidonoyl-γ-aminobutyric acid is analgesic [76], and *N*-arachidonoylglycine is analgesic, and inhibits FAAH [77] and the GLYT2a glycine transporter [78]. The function(s) served by *N*-arachidonoylalanine is currently not understood. Another set of *N*-acyl amino acid conjugates that warrant some discussion are related to the conjugation of fatty acids to either the α-amino group of an N-terminal glycine residue or to the ε-amino group of internal lysine residue. The most common N-terminal acyl group found in eukaryotes is myristic acid, but other fatty acids, including lauric acid, (*cis*-Δ^5)-tetradecaenoic acid (physeteric acid), (*cis*,*cis*-Δ^5,Δ^8)-tetradecadienoyl, and palmitic acid, have been identified as N-terminal fatty acids [79-81]. Mammalian proteins decorated *via* an amide linkage between the ε-amino group of an internal lysine and myristic acid [82] or palmitic acid [83] have been identified. Proteolytic degradation of N-terminal or ε-acyllysyl lipidated proteins could release the corresponding *N*-acylglycine or N^{ε}-acyllysine, but we could not find any reports showing that such metabolites have been detected in mammals.

One biosynthetic route to the *N*-acylamino acids utilizes the acyl-CoA thioester as the acyl group donor: acyl-CoA + amino acid → *N*-acyl-amino acid + CoA-SH. Enzymes known to catalyze this reaction include *N*-acetylglutamate synthase [62] bile acid coenzyme A:amino acid *N*-acyltransferase (BAAT) for the formation of the bile acid glycine and taurine conjugates [84], acyl-CoA:glycine *N*-acyltransferase (ACGNAT) for the formation of the short-chain and branched chain *N*-acylglycines [85], a peroxisomal acyl-CoA:amino acid *N*-acyltransferase (ACNAT1) for the formation of the *N*-acyltaurines [86], and acyl-CoA: L-glutamine *N*-acyltransferase for the formation of the *N*-acylglutamines [87]. N-Terminal acylation is catalyzed by *N*-myristoyl transferase (NMT), an enzyme which strongly prefers myristoyl-CoA as a substrate, and only transfers the acyl group to the α-amino moiety of an N-terminal glycine. Glycine and the α-amino moiety of other N-terminal amino acids are not NMT substrates [79]. Evidence suggests that myristoyl-CoA or palmitoyl-CoA are also the acyl donors for the acylation of ε-amino group of internal lysine groups [81].

The data regarding the biosynthesis of the long-chain *N*-fatty acylglycines is not clear. N-conjugation of fatty acids to glycine via a fatty acyl-CoA thioester is an attractive possibility. The availabl evidence strongly suggests that ACGNAT does not catalyze this reaction *in vivo*: long-chain acyl-CoA thioesters are not ACGNAT substrates [85], and [87]ACGNAT is found primarily in the liver and kidney [85] while the PFAMs have been isolated from the brain [10].For that matter, ACGNAT is not likely involved in the biosynthesis of other N-fatty acylamino acids as amino acids other than glycine are very poor ACGNAT substrates [88]. Other possible candidates that might catalyze this reaction *in vivo* include bile BAAT, which will produce *N*-fatty acylglycines at a low rate relative to the bile acid conjugates [89], [89]or cytchrome c [90,91]. The recent report that cytochrome c can catalyze the formation of *N*-oleoylglycine and *N*-arachidonoylglycine from the corresponding CoA thioester in a reaction stimulated by H_2O_2 is very intriguing [90,91] and could provide the *in vivo* route to the to the *N*-fatty acylglycines. One last fascinating possible route to the N-fatty acylglycines might be the NAD^+-dependent oxidation of the NAEs to the N-fatty acylglycines by the sequential actions of a fatty alcohol and a fatty aldehyde dehydrogenase [92].

The catabolic fates of the *N*-acylamino acids are not well-defined. FAAH will hydrolyze the *N*-acyltaurines and *N*-arachidonoylglycine to the corresponding fatty acid and amino acid [33,76], but the other *N*-acylamino acids are not degraded by FAAH [77]. We have shown that *N*-acylglycines are biosynthetic precursors to the PFAMs using purified PAM [72] and in PAM-expressing neuroblastoma cells [93][73][92][E1]. Marnett and co-workers have found that the *N*-arachidonoylamino acids are substrates for lipoxygenase and cyclooxygenase *in vitro* [94,95], pointing either to a mechanism for the inactivation of the *N*-arachidonoylamino acids or for the formation of other bioactive, oxidized amino acid conjugates. Clearly, there is much work remaining to better define the pathways of biosynthesis and degradation for the *N*-acylamino acids.

Primary Fatty Acid Amides

Arafat *et al*. [9] first isolated and characterized five PFAMs (palmitamide, palmitoleamide, oleamide, elaidamide and linoleamide) from luteal phase plasma in 1989. Because the function of the PFAMs was initially unknown, interest in these molecules was modest until Cravatt *et al*. [10]isolated oleamide and erucamide from the cerebrospinal fluid (CSF) of cat, rat and human and further demonstrated that the intraperitoneal injection of nanomole quantities of oleamide induced physiological sleep in rats. Research concerning oleamide has progressed rapidly since this first report and, in addition to its role in regulating the sleep/wake cycle, this PFAM has been shown to block gap junction communication in glial cells, to regulate memory processes, to decrease body temperature and locomotor activity, to stimulate Ca^{2+} release, to modulate depressant drug receptors in the CNS, and to allosterically activate the $GABA_A$

receptors and specific serotonin receptor subtypes [see refs.[96,97] for reviews]. Like oleamide, other members of the PFAM are bioactive: linoleamide increases Ca^{2+} flux [98] and inhibits the *erg* current in pituitary cells [99], erucamide stimulates the growth of blood vessels [100] and regulates fluid imbalance [101] and elaidamide might function as an endogenous inhibitor of epoxide hydrolase [102].

The PFAMs are degraded by fatty acid amide hydrolase, being hydrolyzed to the fatty acid and ammonia [6,77]. One of the key unanswered questions regarding the PFAMs is how these novel brain lipid amides are produced in the body. A number of reactions have been proposed to account for PFAM production. Sugiura *et al*. [103] found that FAAH catalyzed the *in vitro* production of oleamide from oleic acid and NH_3. This reaction is unlikely to occur *in vivo* because the K_M for ammonia was high (65 mM), and the pH optimum for oleamide synthesis was > 9. Mouse neuroblastoma $N_{18}TG_2$ cells secrete [1-^{14}C]-oleamide when cultured in the presence of [1-^{14}C]-oleic acid [93,104]; thus, these cells must contain the enzymatic machinery required for oleamide biosynthesis. Oleamide production in the $N_{18}TG_2$ cells increases upon the inhibition of FAAH, providing further evidence against a role for this enzyme in PFAM production *in vivo*. Bisogno *et al*. [104] proposed that PFAMs were produced by phospholipid aminolysis. However, incubation of [^{14}C]-oleic acid-containing phospholipids with NH_4OH in the presence of $N_{18}TG_2$ cell homogenates did not result in the formation of [^{14}C]-oleamide.

Currently, there are two proposed pathways for the biosynthesis of the PFAMs that have some experimental support. One is the direct amidation of fatty acyl-CoA thioesters by ammonia as catalyzed by cytochrome c [105]. The PFAM-synthesizing activity of cytochrome c yields a number of PFAMs, exhibits Michealis-Menton kinetics with a K_M value for oleoyl-CoA of 21μM and a pH optimum of 7.5, and is stimulated by H_2O_2. A second proposed pathway for PFAM biosynthesis involves the PAM-mediated cleavage of *N*-fatty acylglycines [73,94], as mentioned above. We have shown that PAM is expressed in the oleamide-synthesizing $N_{18}TG_2$ cells and further demonstrated that inhibition of PAM in $N_{18}TG_2$ cells results in the accumulation of *N*-oleoylglycine [93,106]. A melding of the two proposed pathways could also lead to PFAMs: first the cytochrome c-mediated production of the *N*-fatty acylglycine followed by PAM oxidation to the corresponding PFAM. As discussed by Mueller and Driscoll [90], there may be more than one pathway for the *in vivo* production of the PFAMs, consistent with the fact that there are at a number of pathways known for the *in vivo* production of the NAEs (Figure 2). Outlined in Figure 4 are potential pathways for the biosynthesis of the PFAMs that metabolically link together the PFAMs to the *N*-fatty acylglycines and the NAEs. The potential conversion of one class of fatty acid amide to another only adds another fascinating dimension to this family of bioactive compounds.

N-Acylamides

N-Acylamides, R_1-CO-NR_2R_3 for which $R_1 \neq H$, represents a broad class of molecules found in mammals (and other organisms) and is beyond the scope of this review. A few examples of mammalian *N*-acylamides are the acetylated polyamines, the ceramides, and sphingomyleins. The identification of *N*-stearoylisopropylamine [107] and the phophocholine-NAE conjugates [108] from mouse brain suggests that many other mammalian fatty acid amides await discovery.

Pharmacological Importance of the Fatty Acid Amides

Because of the broad functions exhibited by the various members of the fatty acid amide family, a wide range of indications could benefit from a fatty acid amide-targeted drug, including cancer, cardiovascular disease, inflammation, pain, drug addition, eating disorders, anxiety, and depression (see refs. [12,13,109,110] for recent reviews). Potential drug targets include

the enzymes involved in fatty acid amide biosynthesis and degradation [111,112], transporters responsible for moving the fatty acid amides across the cell membranes [110], and analogs of the fatty acid amides themselves as agonists or antagonists for their respective receptors (Table 2) [13,113]. As detailed by Felder *et al*. [110], the potential existence of specific transporters for anandamide and the other fatty acid amides is controversial, but accumulating evidence suggests that the simple passive diffusion of the these hydrophobic compounds across the membrane driven by FAAH-hydrolysis is insufficient to account for published anandamide uptake data. The fatty acid amides represent an exciting opportunity for the development of new drugs for the treatment of human disease. Much work remains to be done, but the potential for a fatty acid amide-targeted therapeutic is high.

Conclusion

Fatty acid amides are a large family of structurally-diverse molecules found in humans and other organisms. Because many of these molecules have been shown to be bioactive, particularly in cell signaling, analogs of the fatty acid amides could prove useful as agonists or antagonists for their respective receptors. The enzymes involved in the biosynthesis and degradation, many of which are still poorly defined, also provide an exciting opportunity for the development of new drugs to treat sleep disorders, anxiety, depression, cardiovascular disease, and cancer.

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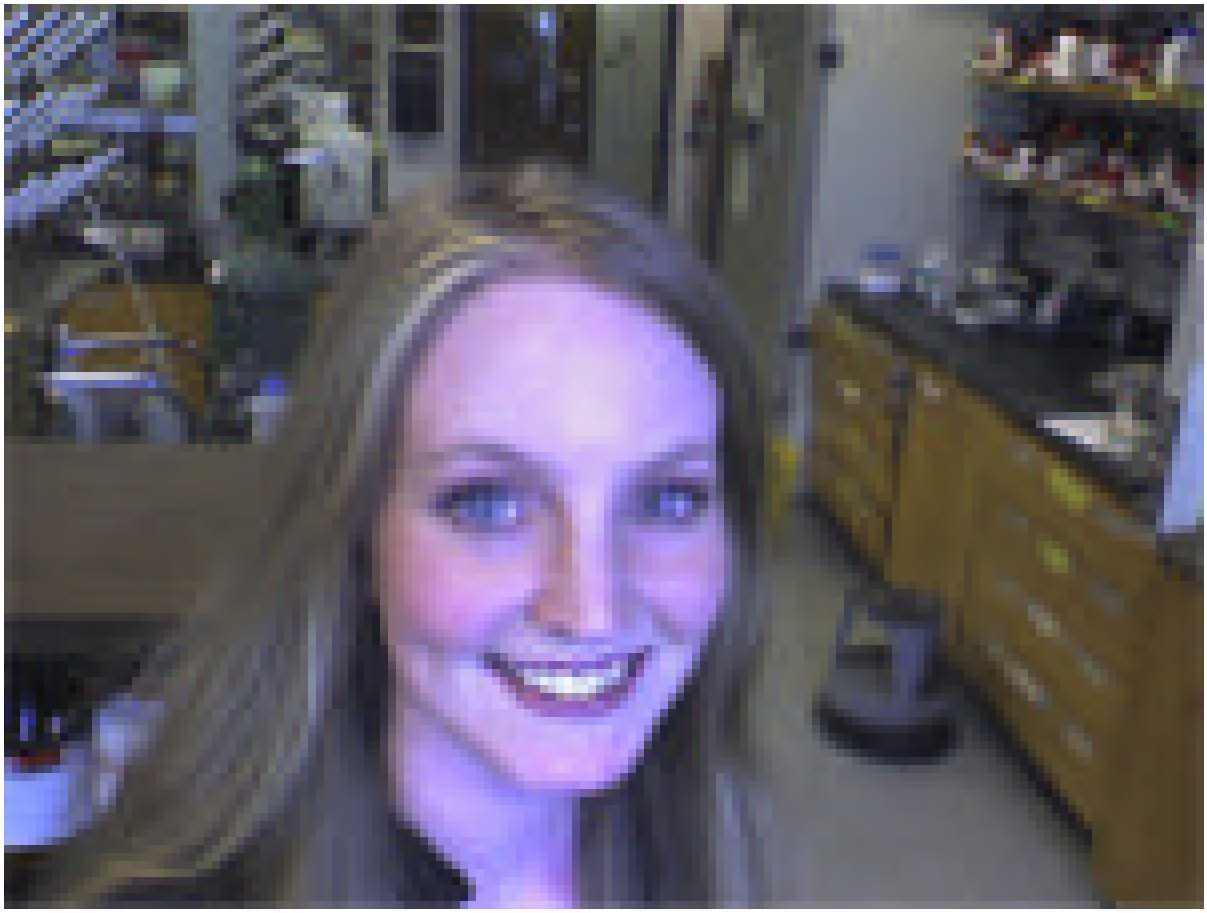

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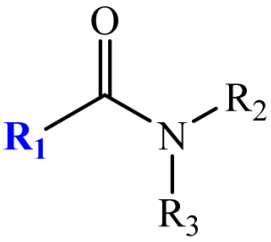
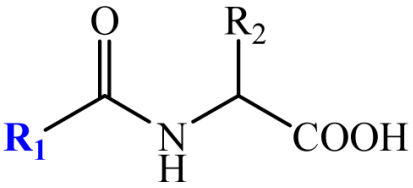
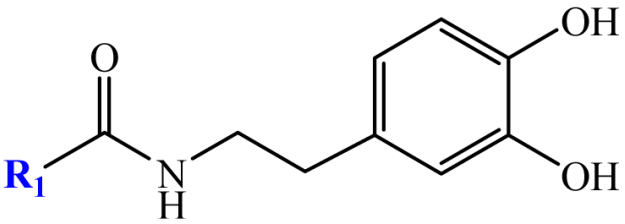
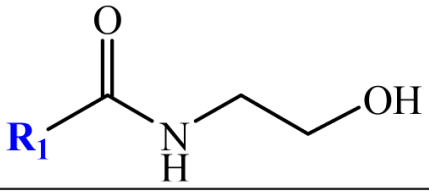
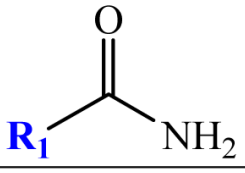
Fatty Acid Amide	Structure
N-Acylamide (NAM)	
N-Acylamino acid (NAA)	
N-Acyldopamine (NDA)	
N-Acylethanolamines (NAE)	
Primary fatty acid amides (PFAM)	

Figure 1.
The Structures of the Fatty Acid Amides [a]R_2 represents the functional groups that define the different amino acids The arrow points to carbon-2 in the fatty acid chain. R_1 is an acyl group, making these structures fatty acids. R_2 and R_3 are also acyl groups.

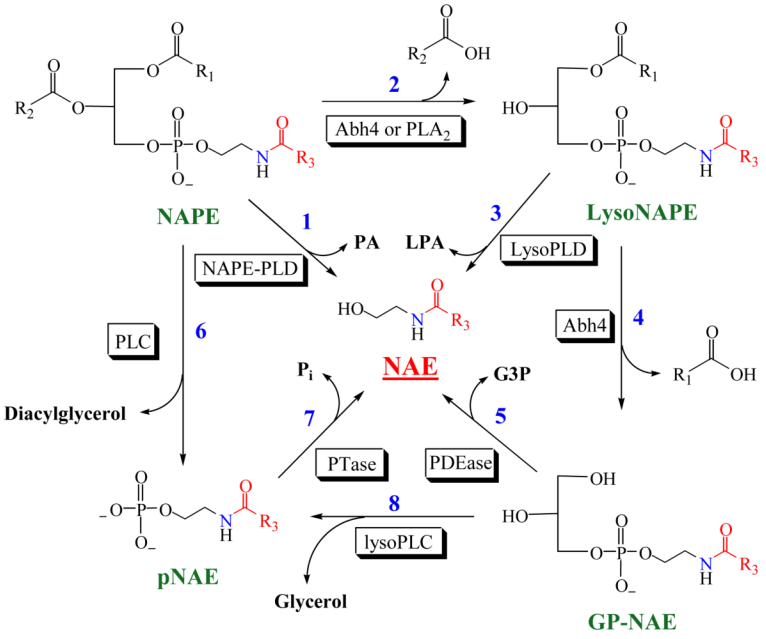


Figure 2.

Biosynthetic Pathways for *N*-Acylethanolamines (NAEs) The enzymes catalyzing the individual reactions are in the shaded boxes and the numbers that refer to reactions in the text are in **bold blue**. The reader is referred to Simon and Cravatt [23] and Liu *et al*. [31] for greater details on NAE biosynthesis. *Abdh4*, α,β-hydrolase 4, *G3P*, glycerol-3-phosphate, *LPA*, lysophosphatic acid, *LysoPLD*, lysophospholipase D, *NAPE-PLD*, NAPE-specific phospholipase D, *PA*, phosphatidic acid, *PDEase*, phosphodiesterase, PLA_2, phopholipase A_2, *PLC*, phopholipase C, *PTase*, phosphatase (most likely tyrosine phosphatase, PTPN22, or inositol-5′-phosphatase, SHIP1, *in vivo*)

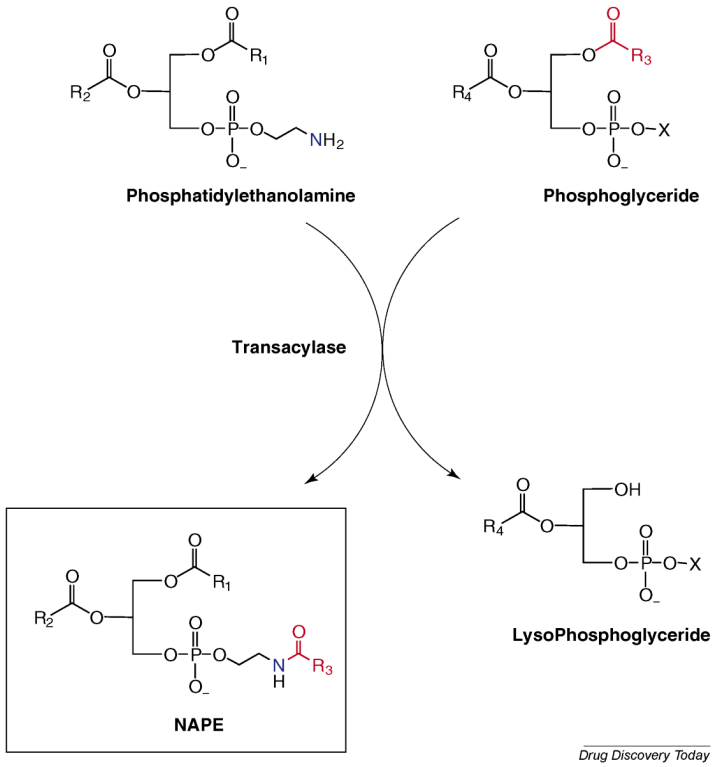


Figure 3.
Biosynthesis of the *N*-Acylphosphatidylethanolamine (NAPE)

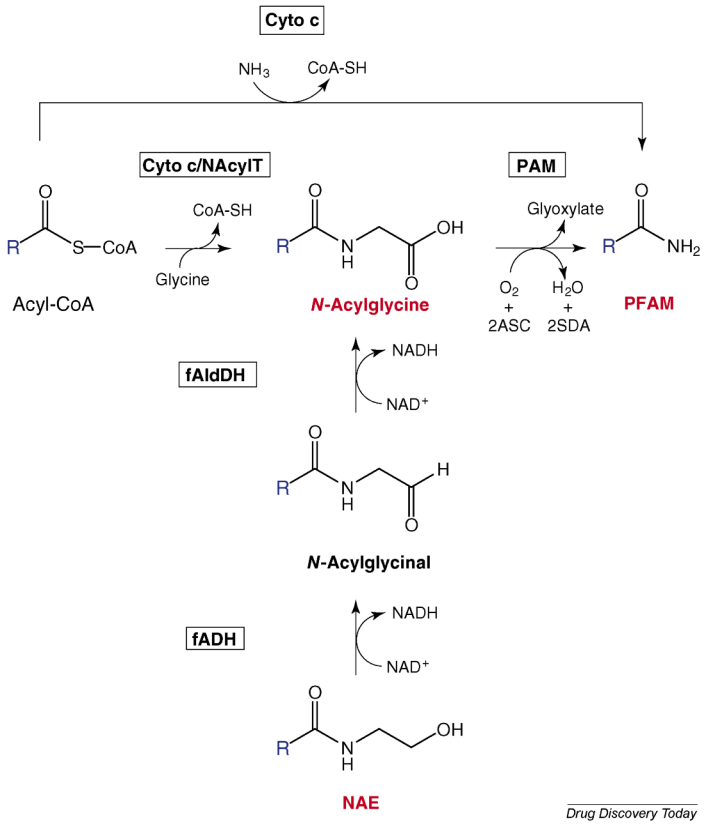


Figure 4.

Proposed Biosynthetic Pathways for the Primary Fatty Acid Amides (PFAMs) The enzymes catalyzing the individual reactions are in the shaded boxes and the fatty acyl group are represent by the **bold blue "R"**. The fatty acid amides discussed in this review are highlighted in red. The reader is referred to Mueller and Driscoll [73] and Merkler *et al*.[74] for greater details on PFAM biosynthesis. *ASC*, ascorbic acid, *Cyto c*, cytochrome c, *fADH*, fatty alcohol dehydrogenase, *fAldDH*, fatty aldehyde dehydrogenase, *NAcylT*, a novel acyl-CoA:*N*-amino acid transferase, *PAM*, peptidyglycine α-amidating monooxygenase, *SDA*, semidehydroascorbic acid

Table 1

Mammalian N-Fatty Acylamino Acids

Amino Acid[b]	N-Acyl Group	References
Alanine	Arachidonoyl	[76]
γ-*Aminobutyric acid*	Arachidonoyl	[76]
Glutamic Acid	β-Citryl and phenylacetyl	[54,55,114]
Glutamine	Phenylacetyl, other arylacetyls, and 4-phenylbutyryl	[55,114]
Glycine[c]	Arachidonoyl, benzoyl, butyryl, bile acids, decanoyl, hexanoyl, isobutyryl, 2-methylbutyryl, 3-methylcrotonyl, octanoyl, phenylacetyl and other arylacetyls, propionyl, suberyl, and tiglyl	[7,55,57,65,76,84,115]
Isoleucine	Lactyl	[116]
Leucine	Lactyl	[116]
Phenylalanine	Succinoyl	[117]
Pyroglutamic acid	Phenylacetyl	[57]
Serine	Arachidonoyl	[71]
Taurine	Bile acids, phenylacetyl and other arylacetyls, long chain, saturaturated acyl groups from C16:0-C26:0[d], long-chain, monounsaturated acyl groups from C18:1-C24:1[d]	[7,84,118]
Valine	Lactyl	[116]

[a] *N*-Acetyl and *N*-isovaleroylamino acids were not included in this table.

[b] Amino acids not commonly found in proteins are italicized.

[c] Included here most of the more common *N*-acylglycine conjugates known. Many others have been identified as metabolites in various organic acid acidemias or in the detoxification of a xenobiotic carboxylate.

[d] Included in the family of long-chain fatty acyl groups found N-conjugated to taurine were odd-numbered acyl chains including C21:0, C21:1, C23:0, C23:1, C25:0, and C25:1. *N*Tricosanoyltaurine was found to be one of the more abundant *N*-acyltaurines in mouse brain [49].

Table 2

[50]Receptors Identified for the Mammalian Bioactive Fatty Acid Amides[a]

A. *N*-Acylethanolamines		
NAE	**Receptors(s)**	**Reference**
Anandamide	CB_1, CB_2, PPARα, PPARγ, TRPV1, and TRPM8	[6,13-16]
N-Dihomo-γlinolenoylethanolamine	CB_1 and CB_2	[119]
5Z,8Z,11Z-Eicosatrienoylethanolamine	CB_1 and CB_2	[119]
N-Oleoylethanolamine	PPARα, PPARγ, TRPV1, and GPR119	[6,15,24]
N-Palmitoylethanolamine	PPARα, GPR55	[15,27]
N-Linolenoylethanolamine	TRPV1	[6]
N-Linoleoylethanolamine	TRPV1	[6]
B. *N*-Acyldopamines		
NDA	Receptors(s)	Reference
N-Arachidonoyldopamine	CB_1, TRPV1, and non-CB_1/CB_2 GPCR (in the aorta)	[38,39,41]
N-Oleoyldopamine	PPARα, PPARγ, and TRPV1	[38,39]
C. *N*-Acylamino acids[b,c]		
NAA Receptors(s)	Reference	*N*-Arachidonoyltaurine
N-Arachidonoyltaurine	TRPV1 and TRPV4	[74]
N-Arachidonoylglycine[c]	GPR18	[75]
D. Primary Fatty Acid Amides		
PFAM	Receptors(s)	Reference
Oleamide	$GABA_A$ receptor, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7	[120-122]

[a] In some cases, the indicated fatty acid amide has not been demonstrated to bind to the listed target by direct binding, but instead has been shown to be an agonist or antagonist to the target using a reporter assay. For exact details, the reader is pointed to the cited references.

[b] While *N*-acetylglutamate is not formally a fatty acid amide, this *N*-acylamino acid binds a protein target as it is an allosteric activator of carbamoylphosphate synthetase I.

[c] Fatty acid conjugation to amino acids serves largely in the detoxification and execretion of xenobiotic carboxylates. Thus, many of the *N*-acylamino acids are likely to bind to a membrane-bound transporter. For example, Wiles *et al*. [78] have recently shown that *N*-arachidonoylglycine inhibits the GLYT2a glycine transporter.