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Commentary

Fatty acid amide hydrolase: biochemistry, pharmacology, and therapeutic possibilities for an enzyme hydrolyzing anandamide, 2-arachidonoylglycerol, palmitoylethanolamide, and oleamide

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Abstract

Fatty acid amide hydrolase (FAAH) is responsible for the hydrolysis of a number of important endogenous fatty acid amides, including the endogenous cannabimimetic agent anandamide (AEA), the sleep-inducing compound oleamide, and the putative anti-inflammatory agent palmitoylethanolamide (PEA). In recent years, there have been great advances in our understanding of the biochemical and pharmacological properties of the enzyme. In this commentary, the structure and biochemical properties of FAAH and the development of potent and selective FAAH inhibitors are reviewed, together with a brief discussion on the therapeutic possibilities for such compounds in the treatment of inflammatory pain and ischaemic states.

Keywords: Anandamide; Palmitoylethanolamide; Oleamide; Fatty acid amide hydrolase

1. Introduction

AEA, PEA, and oleamide belong to a class of biologically active endogenous fatty acid amides that have been the subject of increasing interest in recent years [for recent reviews, see Refs. [1–4]]. AEA is found in the brain, and shares many of the behavioral properties of cannabinoids such as Δ^9-tetrahydrocannabinol, producing antinociception, hypothermia, hypomotility, and catalepsy [5]. AEA interacts with cannabinoid CB_1 and CB_2 receptors [see Ref. [6]] and vanilloid receptors [7]. In contrast, PEA does not interact with CB_1 or CB_2 receptors [8], but has been shown to prevent mast cell activation and to reduce inflammatory pain *in vivo* [9–11]. Both AEA and PEA are found in the skin [10], and it has been suggested that PEA acts as an autocoid capable of locally modulating mast cell activation in response to neurogenic inflammatory stimuli such as substance P [12]. Oleamide has been shown to induce sleep in experimental animals [13], possibly as a result of its effects upon $GABA_A$ receptors and voltage-gated Na^+ channels [14].

In 1993, Deutsch and Chin [15] reported in this journal an amidase activity capable of the hydrolysis of AEA (reaction pathway, see Fig. 1). This enzymic activity, which they termed "anandamide amidase," was sensitive to inhibition by the serine protease inhibitor PMSF, and was found in several tissues including the liver and brain [15]. *In vivo*, AEA administered i.v. to mice is transformed rapidly to arachidonic acid, so that most of the AEA reaching the brain has been metabolized by 15 min [16]. Initially, it was not clear whether the enzyme was related to the enzymic activity previously described by Natarajan *et al.* [17] that was capable of metabolizing PEA and other *N*-acylethanolamines. However, once the enzyme was cloned by Cravatt *et al.* [18], it was clear that a single enzyme was responsible for the metabolism of a wide variety of fatty acid amides. This enzyme is now generally termed FAAH.

The demonstration of an AEA-metabolizing activity, while of general scientific interest, was not of pharmacological importance until it was demonstrated that functional inhibition of the enzyme led to a significant potentiation of the actions of AEA, i.e. that the enzyme represented an important metabolic pathway *in vivo*. It is possible, for example, that other metabolic pathways for AEA (such as the oxidative pathways mediated by cyclooxygenase-2 and

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Abbreviations: AEA, anandamide, arachidonyl ethanolamide; PEA, palmitoylethanolamide, *N*-(2-hydroxyethyl) hexadecamide; FAAH, fatty acid amide hydrolase; CB, cannabinoid; PMSF, phenylmethylsulfonyl fluoride; MAFP, methyl arachidonyl fluorophosphonate; methAEA, arachidonyl-1′-hydroxy-2′-propylamide; and NSAIDs, nonsteroidal anti-inflammatory drugs.

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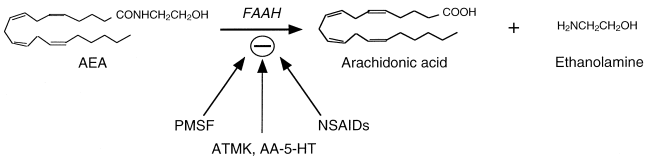


Fig. 1. Reaction pathway of FAAH with AEA as substrate. In the scheme are examples of compounds that have been shown to inhibit the enzyme: PMSF, phenylmethylsulfonyl fluoride; ATMK, arachidonoyl trifluoromethylketone; AA-5-HT, arachidonyl-serotonin; and NSAIDs, nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin.

lipoxygenases; for a review, see Ref. [19]) are of greater importance. However, in 1997, Compton and Martin [20] reported that pretreatment of mice with PMSF, at doses that did not produce behavioral effects *per se*, potentiated 5- to 10-fold three out of the four behavioural actions of AEA investigated in the "tetrad" of tests used to identify cannabimimetic agents (see Fig. 2). This was mirrored by an increased brain level of AEA following its i.v. administration. Thus, the concentration of AEA in the brain following a dose of 10 mg/kg, i.v., was 0.13 ± 0.02 and 1.94 ± 0.67 μg/g for control and PMSF-pretreated animals, respectively [21]. PMSF also potentiated the effects of AEA upon electrically evoked contractions of a myenteric plexus preparation from guinea-pig small intestine [22]. In contrast, PMSF had considerably less effect upon the response in this preparation to *R*-methAEA, which is a poor substrate for FAAH [22]. Compton and Martin [20] concluded from their study that "these findings with PMSF underscore the importance of metabolism in the actions of anandamide" and thus indicate that FAAH inhibition may be a useful pharmacological strategy in potentiating the actions of this and other

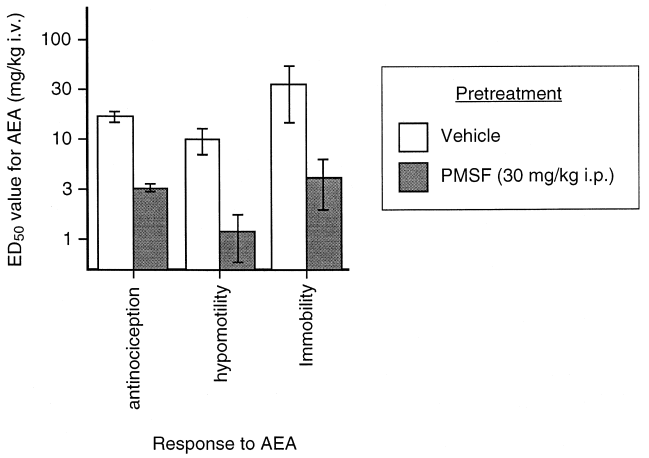


Fig. 2. Effect of PMSF upon the behavioural responses to AEA in mice. PMSF, at a dose that did not produce effects *per se* upon the behavioural parameters measured, was administered 10 min prior to AEA, and the behaviours were measured 5–15 min later, depending upon the test. Antinociception refers to tail flick latency. Shown are means ± SEM of the ED_{50} values, derived from at least six mice in each treatment group. PMSF did not potentiate the hypothermic effects of AEA. Figure drawn from data of Compton and Martin [20].

fatty acid amides. In this commentary, the authors will discuss the structure and biochemical properties of FAAH before describing recent advances in the synthesis of potent and selective FAAH inhibitors. Finally, therapeutic possibilities for FAAH inhibitors will be discussed briefly.

2. Structure and biochemical properties of FAAH

2.1. Cellular and subcellular localization of FAAH

FAAH is distributed widely throughout the body, and is found in brain, liver, testes, uterus, kidney, ocular tissues, spleen, and possibly lung, but not in skeletal muscle or heart [15,18,23–27]. Within the brain, FAAH expression varies from region to region, with the highest activities being found in the globus pallidus and hippocampus, and the lowest in the medulla [23,28,29]. The sensitivity of FAAH to different inhibitors is similar in different brain regions [29]. Expression of FAAH in large neurons and in non-neuronal epithelial cells in the choroid plexus has been reported [30,31]. Across the brain and in the retina, FAAH has a cellular localization complementary (although with little or no actual co-localization) to the CB_1 receptors [28,32,33]. Rabbit platelets can metabolize AEA to arachidonic acid in a PMSF-sensitive manner [34], although in human platelets the preferred route of metabolism of AEA is by a lipoxygenase pathway [35]. Very little expression of FAAH mRNA is found in rat platelets, in contrast to the situation for circulating rat macrophages [36]. In human polymorphonuclear leukocytes, AEA is metabolized both by a lipoxygenase pathway and possibly by FAAH (since arachidonic acid is the product, although inhibitor data and/or western blot data to confirm enzyme identity have not been published) [35]. Human lymphocytes express an enzyme identified by western blotting and RT–PCR as FAAH [37].

Most investigations into FAAH activity have been undertaken using mammalian cells and tissue. However, FAAH is found in both sea urchin ovaries [38] and chicken brain [39]. Among cultured cells, FAAH activity is found, for example, in rat C6 glioma, mouse N_{18}TG2 neuroblastoma, and RBL-2H3 basophilic leukemia cells, but not in human HeLa epithelioid carcinoma or monkey COS-7 kidney fibroblast-like cells [15,40,41]. Human HMC-1 mast cells showed FAAH activity only when 5-lipoxygenase activity was inhibited [42].

FAAH is a membrane-bound enzyme that in the brain is found associated with synaptosomal, mitochondrial, microsomal, and myelin fractions [25,28,43–45]. The inhibitor sensitivities of FAAH derived from these fractions appear to be very similar [45]. With regard to the pH profile of FAAH, an early study gave a pH optimum of about pH 9 for the partially purified microsomal enzyme from pig brain [43]. A similar pH optimum was seen for microsomal FAAH obtained from mouse N_{18} neuroblastoma cells [46]

and rat forebrain membranes [28], as well as for FAAH from rat basophilic leukemia cells [47], cow brain [48], and sea urchin ovaries [38]. In contrast, Desarnaud *et al.* [23] found a pH optimum between 6 and 8 for AEA metabolism by rat brain microsomal FAAH.

2.2. Substrate specificity of FAAH

K_M values for AEA hydrolysis by FAAH ranging from 0.8 to 180 μM have been reported [25,28,40,46,48–51]. However, as pointed out by Omeir et al. [48], "The K_M and V_{max} values . . . must be considered approximate in view of the interfacial enzyme reaction occurring. . . . (in the enzyme preparations). . . . . whose substrate and product have the potential to form micelles which in turn may affect the enzyme activity." This observation may provide a partial explanation for differences in substrate specificities seen in the literature (see below).

Most authors have used AEA as the prototypical substrate for FAAH and demonstrated that the enzyme not only can metabolize this substrate but, in addition, catalyses its reverse synthesis from arachidonic acid and ethanolamine [43,52,53]. However, the physiological importance of this reverse pathway is unclear, since high concentrations of ethanolamine and arachidonic acid are required for it to occur. FAAH has a wide substrate specificity and is capable of metabolizing a wide variety of AEA analogues [50,51] and other fatty acid amides such as PEA and oleamide [see, for example, Refs. [18,23,40,45]] as well as the endocannabinoid 2-arachidonoylglycerol [51,54]. The enzyme is also able to distinguish between optical isomers of meth-AEA, the (*S*)-enantiomer being hydrolysed with a K_M value approximately 4-fold lower than the (*R*)-enantiomer [51]. However, there appears to be a wide divergence in relative activities reported in the literature, although most authors agree that AEA is among the most readily metabolized substrates (see Fig. 3A for the substrate specificity of rat liver FAAH expressed in COS-7 cells). Thus, for example, relative V_{max} values for AEA and oleamide in 100,000 g microsomes from rabbit brain were 5.5 ± 1.3 and 5.8 ± 0.8 nmol·(mg protein)$^{-1}$·min^{-1} [55]. In contrast, in a 100,000 g pellet obtained from mouse neuroblastoma cells, AEA was more readily metabolized than oleamide (V_{max} values of 2.3 vs 0.94 nmol·(mg protein)$^{-1}$·min$^{-1,}$ respectively [46]). The difference is even more apparent for PEA where rates of hydrolysis relative to AEA of 1% up to 82% have been reported in different studies [23,44]. Whether these differences reflect differences in assay conditions or the possible heterogeneity of FAAH is not fully elucidated. However, Ueda *et al.* [47] recently described an enzymic activity with a pH optimum of ~5 in human CMK megakaryoblastic cells. The enzyme hydrolysed both AEA and PEA, but was two orders of magnitude less sensitive to PMSF than FAAH from rat basophilic leukemia cells, and was not inhibited by the substrate analogue MAFP [47]. Chicken brain FAAH is also less sensitive to PMSF than its rodent equivalent, although in this case it retains its sensitivity to the substrate analogues oleyl trifluoromethylketone and diazomethyl-arachidonyl ketone [39].

2.3. Molecular structure of FAAH

FAAH was first successfully cloned from rat liver by Cravatt *et al.* [18]. The authors demonstrated that the cloned enzyme, which had a deduced 579 amino acid sequence and was capable of the metabolism of several fatty acid amides (Fig. 3A), contained a region rich in serine, glycine, and alanine residues that is highly homologous to the "amidase signature" found in a family of bacterial and fungal amidases [EC 3.5.1.4; see Ref. [56]]. Mouse, human, and pig FAAH were cloned subsequently and showed a high degree of homology to the rat enzyme, with almost completely conserved amidase consensus sequences [18,57,58] (see Fig. 3B).

The finding that PMSF is a potent inhibitor of FAAH activity implicates serine residues as crucial for catalytic activity, since PMSF sulfonylates the hydroxyl groups of serine residues. Within the amidase signature sequence of FAAH, there are several serine groups, and the catalytic activity of FAAH is greatly reduced by mutation of the serine groups at 217 and 241 to alanine ([41,57–60]; see Fig. 3B). Further experiments using an irreversible FAAH inhibitor, ethoxy oleolyl fluorophosphonate, identified S241 as the catalytic nucleophile of the enzyme [59]. More recent mutagenesis studies have shed further light on catalytically and/or structurally important amino acid residues in the FAAH molecule [60].

3. FAAH inhibitors

Initial studies into the inhibitor sensitivity of FAAH identified a number of "standard" compounds that were capable of blocking enzyme activity. These included PMSF, arachidonic acid, diisofluorophosphate, *p*-bromophenacyl-bromide, iodoacetic acid, *p*-hydroxymercuribenzoate, thimerosal, $CuSO_{4,}$ and $HgCl_2$ [15,25,28,40,50]. While these compounds have been invaluable for the general characterization of FAAH, they are, of course, not candidates for therapeutic strategies. Two separate approaches, however, have defined inhibitors of FAAH that may be of therapeutic use. These are discussed below.

3.1. Arachidonic acid and oleic acid derivatives

There are now a considerable number of publications reporting inhibitors of FAAH based upon the synthesis of arachidonic acid and other fatty acid derivatives (see Table 1 for some example compounds). Early studies led to a number of potent FAAH inhibitors such as arachidonoyl trifluoromethyl ketone, which was designed as a transition state inhibitor [61]. However, these compounds often lack

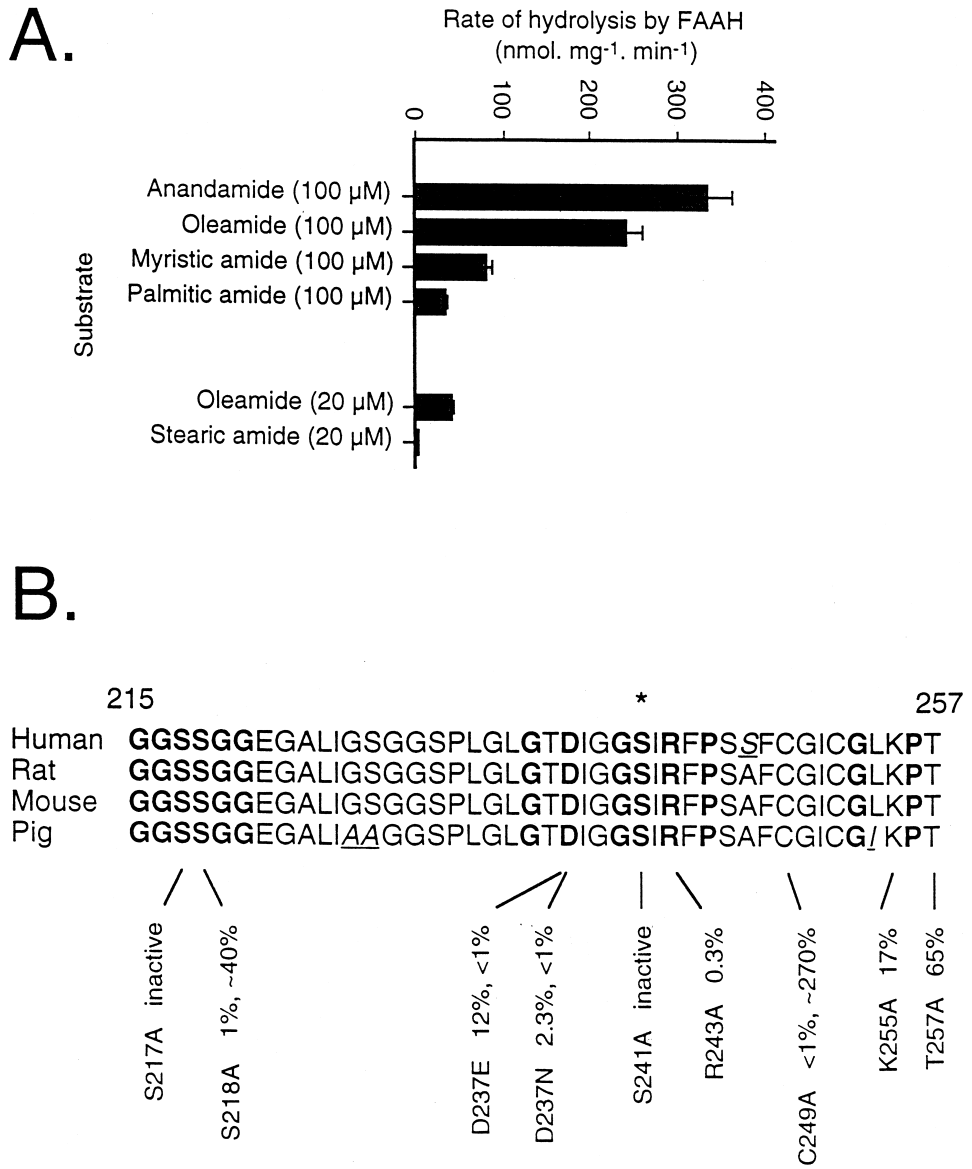
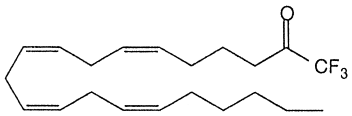
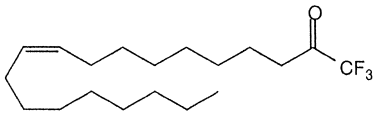
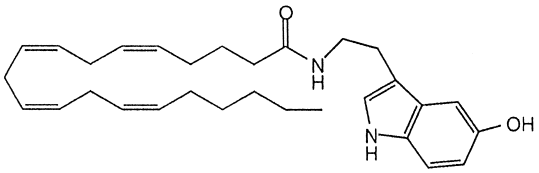
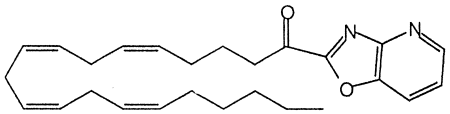
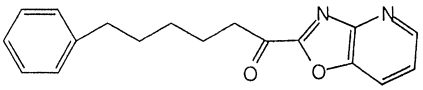
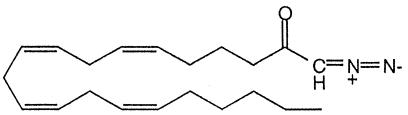
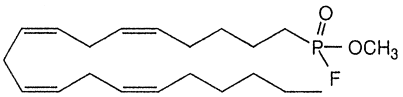
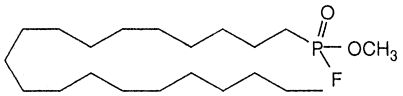


Fig. 3. (A) Relative rates of hydrolysis of a series of fatty acid amides for FAAH cloned from rat liver plasma membranes and expressed in COS-7 cells (figure drawn from Table 1 of Cravatt *et al.* [18]; the sample size or nature of the error bars [SD or SEM] was not indicated in the article). (B) Deduced amino acid sequences for FAAH cDNAs from four species across the amidase signature sequence as defined by Patricelli *et al.* [59]. The serine residue at position 241, the catalytic nucleophile of the enzyme, is marked with an asterisk. Italic/underlined residues indicate those residues that differ between the four species [18,57,58]. Residues marked in bold style are common to other amidase signature sequence enzymes [see Ref. [59]]. Under the sequence are given mutations and the activity as percent of the corresponding wild-type enzyme. Among mutations outside the signature sequence, K142A results in a complete loss of activity, while E143Q, S152A, D167A, H184Q, H358A, and H449A produce active mutants (48–385% of wild type). The mutant N206A had 11% of wild-type catalytic activity. Mutation data are taken from Ref. [41] (estimated from Fig. 3 and, when active, indicated by the "~" symbol) and Refs. [58–60]. The large difference between the two studies investigating the C249A mutation may reflect a difference in the species (rodent vs pig) used to generate the wild-type FAAH [41,58].

selectivity for FAAH vs. cannabinoid receptors, thus limiting their usefulness *in vivo* in delineating the pharmacological importance of FAAH. Thus, for example, arachidonoyl trifluoromethyl ketone (the most potent of the inhibitors found in the study of Koutek *et al.* [61]), produced a complete inhibition of AEA hydrolysis (and increased the level of AEA in N_{18}TG2 neuroblastoma cells) at a concentration of 7.5 μM. In later studies, IC_{50} values for arachidonoyl trifluoromethyl ketone ranging between 230 nM and 3 μM were reported [43,46,49,62]. However, the compound blocked the binding of [^{3}H]CP-55,940 to cannabinoid CB_1 receptors over the same concentration range [61,62].

Other compounds, however, show better selectivities for FAAH. Based on the finding that PMSF inhibited FAAH [15], a series of fatty acid sulfonyl fluorides were synthesised by Deutsch *et al.* [62]. Of these, palmitylsulfonyl fluoride (AM374) inhibited FAAH with an IC_{50} value of 13 nM and blocked the binding of [^{3}H]CP-55,940 to cannabi-

Table 1
Examples of fatty acid-derived FAAH inhibitors

Structure	K_i/IC_{50}	Name/Reference
	IC_{50} 0.23–3 μM (transition-state inhibitor)	Arachidonoyl trifluromethyl ketone (ATMK) [61] [IC_{50} values from Refs. 43, 46, 49, 62]
	K_{iapp} 1.2 nM (transition-state inhibitor)	Oleoyl trifluromethyl ketone [65]
	IC_{50} 12 μM (time-dependent non-covalent inhibition)	Arachidonoyl-serotonin (AA-5-HT) [63]
	K_i 1 nM (mechanism not elucidated)	Compound 38 of [68]
	K_i human 94 pM (mechanism not elucidated)	Compound 53 of [68]
	IC_{50} 0.5–6 μM (time-dependent, irreversible)	Diazomethylarachidonoyl ketone [69,71]
	IC_{50} 1–3 nM (irreversible)	Methyl arachidonoyl fluorophosphonate (MAFP) [70,71]
	IC_{50} 137 nM (mechanism not elucidated)	O-1624 [72]

noid CB_1 receptors with an IC_{50} value of 520 nM [62]. Arachidonoyl-serotonin was found to be a tight-binding (albeit non-covalent) inhibitor of FAAH with an IC_{50} value (in the absence of preincubation) of 12 μM without obvious effects on the function of either phospholipase A_2 or cannabinoid receptors [63]. In contrast, arachidonoyl dopamine interacted with both FAAH and cannabinoid CB_1 receptors [64].

Inhibitory effects of oleamide derivatives have also been reported. Patterson *et al.* [65] reported the FAAH inhibitory efficacy of a series of oleamide derivatives with K_{iapp} values varying from 1.2 nM to 6 μM. A linkable version of the most potent compound, oleoyl trifluoromethyl ketone was produced and used for the affinity purification of FAAH [18]. This research group has subsequently synthesized a large number of compounds with varying fatty acid chain lengths of different degrees of saturation and with different substitutions (trifluoromethyl ketone and α-keto heterocycles), the most potent of which inhibited recombinant human FAAH with a K_i value of 94 pM [66–68]. Although information on the selectivity of these compounds versus cannabinoid receptors was not provided, it is to be hoped that such inhibitors will be useful for *in vivo* studies of FAAH function.

Arachidonyl-derived irreversible inhibitors of FAAH, such as diazomethylarachidonyl ketone and MAFP have been described [69–71]. Both of these compounds have limited selectivity vis-á-vis the cannabinoid CB_1 receptor and, in the case of MAFP, phospholipase A_2. An oleoyl analogue of MAFP, ethoxy oleoyl fluorophosphonate, also acts as an irreversible inhibitor of FAAH [59]. Recently, a series of analogues of MAFP have been described, which retain the ability to inhibit FAAH, but which have a wide variation in affinity towards cannabinoid CB_1 receptors [72]. Of these the saturated equivalent of MAFP, O-1624, was found to have modest selectivity versus the cannabinoid CB_1 receptors, but potentiated the antinociceptive effects of AEA without a corresponding potentiation of the effects of either 2-arachidonoylglycerol or Δ^9-tetrahydrocannabinol [72]. Whether this compound is a reversible or an irreversible inhibitor of FAAH awaits elucidation. The lack of effect upon the response to 2-arachidonoylglycerol is interesting given that this compound is at least as good a substrate as AEA towards FAAH [50,53]. The most likely explanation is that FAAH is not the major metabolic enzyme for exogenously administered 2-arachidonoylglycerol. Indeed, other metabolic enzymes involved in the metabolism of this endocannabinoid have been characterized [36,54].

Irreversible inhibitors of FAAH have a number of potential uses, over and above their utility in labeling studies of FAAH mutants [41,59], such as determining the half-life for the synthesis of the enzyme *in vivo* in different brain regions and subcellular fractions. In addition, the ability of reversible competitive inhibitors to protect against irreversible inhibition gives a valid *in vivo* measure of their pharmacokinetic properties and potencies: *ex vivo* experiments measuring the activity remaining invariably involve inhibitor dilution as a result of homogenate preparation and hence an underestimate of the true level of inhibition. These types of studies using irreversible inhibitors have proven very successful for other enzymes [see Refs. [73] and [74] for data with monoamine oxidase as an example]. However, the presently available irreversible inhibitors may not all be suitable for such studies. There are problems of stability with diazomethylarachidonyl ketone, and the potential toxicity of MAFP and related compounds [see Ref. [72]] is a major factor limiting the utility of these agents for *in vivo* experiments.

The above compounds are examples of exogenously synthesized FAAH inhibitors. However, endogenous substances, such as PEA and oleamide, will also reduce the FAAH-catalyzed hydrolysis of AEA by acting as alternate substrates. This may contribute to the "entourage" effect of these compounds towards endocannabinoids [2,75], whereby they potentiate the tonic effects of endogenous compounds that are active at cannabinoid receptors.

3.2. NSAIDs as inhibitors of FAAH

NSAIDs, such as ibuprofen, aspirin, and indomethacin, have long been used therapeutically for the treatment of inflammation, pain, and fever. In 1997, it was found, using an indirect binding assay, that ibuprofen inhibits the metabolism of AEA by rat brain FAAH [76]. A subsequent study demonstrated that this compound was a mixed-type inhibitor of FAAH at a concentration that, at least in theory, could be reached following oral intake of this drug [49]. Many NSAIDs inhibit FAAH with different potencies, and there is a small degree of stereoselectivity, the *R*-form of ibuprofen (and ketorolac) being superior to the corresponding *S*-forms ([29,45]; see Fig. 4). The most recent addition to this group of FAAH inhibitors is indomethacin, which competitively inhibits rat and chicken brain FAAH with K_i values of 120 and 330 μM, respectively [39]. Although there is no hard evidence that FAAH inhibition contributes to the therapeutic actions of these NSAIDs, these findings have raised the notion that a combined FAAH/cyclooxygenase-2 inhibitor might be a useful strategy for the treatment of pain. In this respect, D'Ambra *et al.* [77] reported that pravadoline, which acts both as an inhibitor of cyclooxygenase and as an agonist at cannabinoid receptors, showed a greater antinociceptive efficacy than found for other NSAIDs.

4. Therapeutic possibilities for FAAH inhibitors

Given the myriad number of effects of AEA, PEA, and oleamide [see Refs. [1–4]] and the finding that FAAH inhibition potentiates the effects of exogenous AEA [20–22,71,78], it would be easy to suggest a number of disease states whereby FAAH inhibitors may be of use therapeutically. However, such an approach would be more appropriate in the discussion of the therapeutic application of FAAH-resistant compounds with AEA-, PEA- or oleamide-like actions. The effect of FAAH inhibition upon endogenous fatty acid amide function may be more subtle. Thus, Martin *et al.* [72] reported that although both compounds

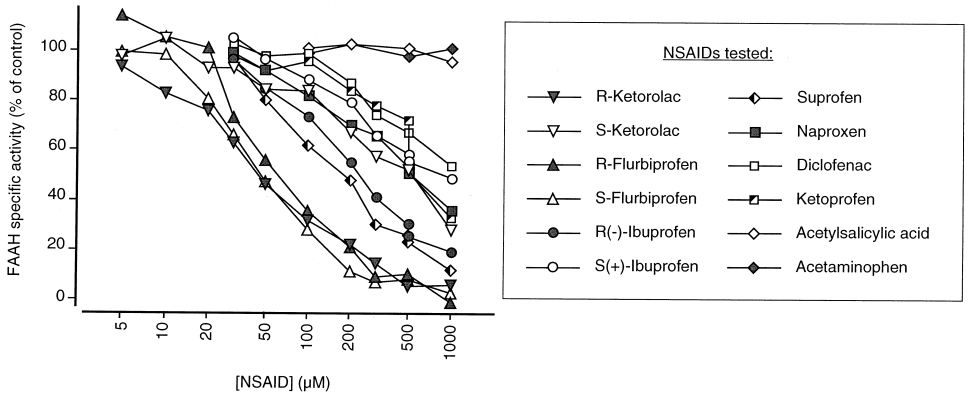


Fig. 4. Effect of a series of NSAID compounds upon the activity of rat brain FAAH measured with AEA as substrate. Redrawn from data of Refs. [29] and [49] (means of 3–7 experiments).

O-1623 and O-1624 were able to reduce the activity of spinal cord FAAH, only the latter significantly increased the levels of AEA. The finding that arachidonoyl-serotonin lacks cannabimimetic activity *in vivo* [63] would suggest that FAAH inhibition does not increase AEA levels in normal animals sufficiently to activate cannabinoid receptors (assuming, of course, that the bioavailability of this compound is reasonable). However, such an argument would suggest that prevention of endocannabinoid metabolism only contributes to a minor extent in the "entourage" effects of PEA and oleamide [2,75].

While it is debatable whether FAAH inhibition will affect the function of fatty acid amides in normal states, there is an exciting possibility that FAAH inhibition may be beneficial in certain inflammatory states. The levels of AEA and PEA are normally low, but have been shown to be greatly increased in conditions of cellular stress, such as after ischaemia [[79,80]; see also [81]]. There are reports that both AEA and PEA have beneficial effects in inflammatory pain conditions [9–11], and somewhat contradictory studies suggesting neuroprotective actions to short neurotoxic insults [82–85]. More recently, it has been demonstrated in an animal model of multiple sclerosis where brain and spinal levels of AEA are increased and where AEA has beneficial effects on spasticity, that the FAAH inhibitor AM374 (palmitylsulfonyl fluoride) *per se* also reduces spasticity [86]. Although the potentially hazardous consequences of FAAH inhibition given the cytotoxic effects of AEA still need to be considered [see Refs. [37] and [87]], it is quite possible that FAAH inhibitors, by prolonging the life of the fatty acid amides produced endogenously during these conditions, may prove to be of therapeutic value.

5. Conclusion

It is just 8 years since Deutsch and Chin [15] reported in this journal the enzyme-catalyzed degradation of AEA to produce arachidonic acid and ethanolamine. In that short time, interest in FAAH has increased steadily, and the original article has been cited on 237 different occasions (as of May 2001). It is to be hoped that the availability of potent and selective FAAH inhibitors will allow the elucidation of the role played by this enzyme, and the investigation as to whether such compounds have therapeutic value.

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