Pharmacological Research 86 (2014) 11–17

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Advances in the discovery of *N*-acylethanolamine acid amidase inhibitors

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ARTICLE INFO

Article history:
Received 27 February 2014
Received in revised form 23 April 2014
Accepted 24 April 2014
Available online 4 May 2014

Keywords:
N-Acylethanolamine acid amidase
Fatty acid ethanolamides
Palmitoylethanolamide
Pain
Inflammation
NAAA inhibitors

Chemical compounds studied in this article:
Palmitoylethanolamide (PubChem CID: 4671)
Oleoylethanolamide (PubChem CID: 5283454)
N-Pentadecylbenzamide (PubChem CID: 44398681)
N-Pentadecylcyclohexancarboxamide (PubChem CID: 44398718)
Pentadecylamine (PubChem CID: 17386)
3-Phenyl-1-pyrrolidin-1-ylpropan-1-one (PubChem CID: 1533088)
N-[(3*S*)-2-Oxooxetan-3-yl]-3-phenylpropanamide (PubChem CID: 25227533)
N-[(3*S*)-2-Oxooxetan-3-yl]-4-phenylbenzamide (PubChem CID: 46899632)
5-Phenylpentyl *N*-[(2*S*,3*R*)-2-methyl-4-oxooxetan-3-yl]carbamate (PubChem CID: 57523549)
(4-Phenylphenyl)methyl *N*-[(2*S*,3*R*)-2-methyl-4-oxooxetan-3-yl]carbamate (PubChem CID: 73291988)

ABSTRACT

N-Acylethanolamine acid amidase (NAAA) is a cysteine amidase that hydrolyzes saturated or monounsaturated fatty acid ethanolamides, such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA). PEA has been shown to exert analgesic and anti-inflammatory effects by engaging peroxisome proliferator-activated receptor-α. Like other fatty acid ethanolamides, PEA is not stored in cells, but produced on demand from cell membrane precursors, and its actions are terminated by intracellular hydrolysis by either fatty acid amide hydrolase or NAAA. Endogenous levels of PEA and OEA have been shown to decrease during inflammation. Modulation of the tissue levels of PEA by inhibition of enzymes responsible for the breakdown of this lipid mediator may represent therefore a new therapeutic strategy for the treatment of pain and inflammation. While a large number of inhibitors of fatty acid amide hydrolase have been discovered, few compounds have been reported to inhibit NAAA activity. Here, we describe the most representative NAAA inhibitors and briefly highlight their pharmacological profile. A recent study has shown that a NAAA inhibitor attenuated heat hyperalgesia and mechanical allodynia caused by local inflammation or nerve damage in animal models of pain and inflammation. This finding encourages further exploration of the pharmacology of NAAA inhibitors.

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http://dx.doi.org/10.1016/j.phrs.2014.04.011
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1. Introduction

The amides of long-chain fatty acids with ethanolamine, or fatty acid ethanolamides (FAEs), are a family of bioactive lipids that participate in the control of multiple physiological functions, including pain and inflammation [1–4]. Polyunsaturated FAEs such as arachidonoylethanolamide (anandamide, Fig. 1) are endogenous agonists for G protein-coupled cannabinoid receptors and participate in the control of stress-coping responses and pain initiation [1,5]. On the other hand, monounsaturated and saturated FAEs, such as oleoylethanolamide (OEA, Fig. 1) and palmitoylethanolamide (PEA, Fig. 1), are potent or moderately potent agonists of the peroxisome proliferator-activated receptor-α (PPAR-α), a member of the nuclear receptor superfamily, which is responsible for most of their analgesic and anti-inflammatory properties [4,6,7].

FAEs are not stored in cells, but rather are produced on demand from cell membrane precursors [8–10]. OEA and PEA are generated in many mammalian tissues, including neurons [11] and innate immune cells [12], where a selective phospholipase, *N*-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) releases them by cleaving their membrane precursor, *N*-acylphosphatidylethanolamine [13]. The actions of these lipid messengers are terminated by enzyme-mediated hydrolysis, which is catalyzed by two known intracellular lipid amidases: *N*-acylethanolamine acid amidase (NAAA, previously referred to as *N*-acylethanolamine hydrolyzing acid amidase) [14–16] and fatty acid amide hydrolase (FAAH) [17,18]. These enzymes share the ability to cleave lipid amide bonds, but differ in primary structure, substrate selectivity, and cellular localization. NAAA is a cysteine hydrolase that belongs to the *N*-terminal nucleophile (Ntn) family of enzymes [15,16,19], and bears a significant degree of sequence homology with the choloylglycine hydrolases, which share the ability to cleave non-peptide amide bonds [20]. NAAA displays a strong preference for saturated FAEs such as PEA [15], while FAAH, a member of the amidase signature family of serine hydrolases, displays broader substrate selectivity, but hydrolyzes preferentially monounsaturated and polyunsaturated FAEs such as anandamide and OEA [17]. Moreover, NAAA seems to be mainly localized to the lysosomal compartment of macrophages [21], whereas FAAH is a membrane-bound enzyme that is found on the outer face of mitochondria and endoplasmic reticulum of most mammalian cells [22].

Like other Ntn enzymes, such as acid ceramidase, a lysosomal enzyme that hydrolyses ceramide to sphingosine and fatty acid [23,24], NAAA is activated by auto-proteolysis, which occurs at acidic pH and generates a catalytically competent form of the enzyme [25]. Comparison of the primary structure of NAAA with those of the other members of the choloylglycine hydrolase family followed by site-directed mutagenesis experiments have unequivocally identified cysteine 131 (Cys-131) in mice, or cysteine 126 (Cys-126) in humans, as the catalytic residue responsible for both auto-proteolysis and FAE hydrolysis [26,27]. The proposed mechanism of amide bond hydrolysis by Ntn enzymes consists in the attack of the catalytic *N*-terminal residue on the amide with formation of an acyl enzyme, followed by acyl enzyme hydrolysis with regeneration of the catalytically competent enzyme [28,29]. According to this mechanism, the thiol group of the catalytic cysteine of NAAA would react with substrate with the formation of a thioester bond. Acylation of Cys-126 of human NAAA by β-lactones, a class of NAAA inhibitors, was recently demonstrated by mass spectrometry experiments [30,31].

The pharmacology of PEA has been extensively investigated [32]. The compound inhibits peripheral inflammation and mast cell degranulation [33,34], and exerts strong anti-nociceptive effects in rat and mouse models of acute and chronic pain [1,34–36]. Moreover, in mice it suppresses pain behaviors induced by tissue injury, nerve damage or inflammation [4]. These properties are dependent on PPAR-α activation, since they are absent in PPAR-α-deficient mice, blocked by PPAR-α antagonists and mimicked by synthetic PPAR-α agonists [4,37]. The finding that PEA might attenuate skin inflammation and neuropathic pain in humans is highly significant and warrants additional clinical investigation [38,39].

Endogenous levels of PEA and OEA (but not anandamide) undergo marked changes during inflammation. Stimulation with pro-inflammatory agents such as lipopolysaccharide (LPS) or carrageenan decreases PEA (and OEA) content in various cells and tissues of rodents [3,27,40–42]. The observation that synovial fluid from patients with rheumatoid arthritis and osteoarthritis contains lower amounts of PEA adds clinical relevance to previous findings [43]. The decrease in the cellular levels of PEA and OEA following an inflammatory stimulus is reversed by pharmacological blockade of NAAA-mediated FAE hydrolysis [27,44,45]. Moreover, protecting endogenous PEA and OEA from NAAA-catalyzed degradation in vivo has recently been reported to attenuate hyperalgesic and allodynic states elicited in mice and rats by local inflammation or nerve damage [46].

The previous findings suggest that sustaining the levels of PEA by inhibition of intracellular NAAA activity might represent a novel approach to control inflammation and pain. The search for NAAA inhibitors is still in its infancy, and has developed mainly through two approaches. The first one relies on the modification of the structure of one of the natural substrates, PEA, with the goal of discovering derivatives that are able to inhibit enzyme activity while showing selectivity versus other lipid amide-hydrolyzing enzymes, such as FAAH. The second approach focuses on compounds containing chemical functionalities that are known to react with the thiol group of cysteine, referred to as “cysteine warheads”, in order to inactivate the catalytic cysteine in the catalytically competent form of the enzyme, thus inhibiting its activity.

To date, a number of compounds originating from the two approaches have been discovered to inhibit NAAA activity with various potencies and selectivity. In this respect, it is important to point out that assay conditions should always be considered when comparing compounds’ potencies. In fact, median inhibitory concentration (IC_{50}) values may change depending on whether the compounds are tested in cell-free, homogenates, or whole-cell assays. This review will describe the most representative inhibitors and will briefly highlight their pharmacological profile.

2. Analogs of PEA

The search for inhibitors of NAAA activity relied at first on the structure of the natural substrate, PEA. Analogs of PEA were prepared by modification or replacement of the amidic function. Different amides and various retroamides, esters, and retroesters of palmitic acid (Fig. 2) were synthesized and evaluated for their ability to inhibit NAAA activity and their selectivity versus FAAH [47,48].

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