

Endocannabinoid turnover (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Stephen P.H. Alexander¹, Patrick Doherty², Christopher J. Fowler³, Jürg Gertsch⁴ and Mario van der Stel⁵

1. University of Nottingham, UK
2. King's College London, UK
3. University Hospital of Umeå, Sweden
4. University of Bern, Switzerland
5. Leiden University, The Netherlands

Abstract

The principle endocannabinoids are 2-acylglycerol esters, such as [2-arachidonoylglycerol](#) (2-AG), and *N*-acylethanolamines, such as [anandamide](#) (*N*-arachidonylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. Mechanisms for release and re-uptake of endocannabinoids are unclear, although potent and selective inhibitors of facilitated diffusion of endocannabinoids across cell membranes have been developed [19]. [FABP5](#) (Q01469) has been suggested to act as a canonical intracellular endocannabinoid transporter *in vivo* [12]. For the generation of [2-arachidonoylglycerol](#), the key enzyme involved is diacylglycerol lipase (DAGL), whilst several routes for [anandamide](#) synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [49]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has recently been identified as a cytosolic enzyme, [PLA2G4E](#) (Q3MJ16) [43]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism via cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [4, 16, 51].

Contents

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Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

Endocannabinoid turnover

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=943>

N-Acylethanolamine turnover

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=273>

Enzymes

NAPE-PLD(*N*-Acylphosphatidylethanolamine-phospholipase D)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1398>

FAAH(Fatty acid amide hydrolase)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1400>

FAAH2(Fatty acid amide hydrolase-2)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1401>

NAAA(*N*-Acylethanolamine acid amidase)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1402>

2-Acylglycerol ester turnover

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=944>

Enzymes

DAGL α (Diacylglycerol lipase α)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1396>

DAGL β (Diacylglycerol lipase β)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1397>

MAGL(Monoacylglycerol lipase)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1399>

ABHD6($\alpha\beta$ -Hydrolase 6)

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2919>

$\alpha\beta$ -Hydrolase 12

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3070>

References

1. Aaltonen N, Savinainen JR, Ribas CR, Rönkkö J, Kuusisto A, Korhonen J, Navia-Paldanius D, Häyrynen J, Takabe P and Käsänen H *et al.*. (2013) Piperazine and piperidine triazole ureas as ultrapotent and highly selective inhibitors of monoacylglycerol lipase. *Chem. Biol.* **20**: 379-90 [PMID:23521796]
2. Ahn K, Johnson DS, Fitzgerald LR, Liimatta M, Arendse A, Stevenson T, Lund ET, Nugent RA, Nomanbhoy TK and Alexander JP *et al.*. (2007) Novel mechanistic class of fatty acid amide hydrolase inhibitors with remarkable selectivity. *Biochemistry* **46**: 13019-30 [PMID:17949010]
3. Ahn K, Johnson DS, Mileni M, Beidler D, Long JZ, McKinney MK, Weerapana E, Sadagopan N, Liimatta M and Smith SE *et al.*. (2009) Discovery and characterization of a highly selective FAAH inhibitor that reduces inflammatory pain. *Chem. Biol.* **16**: 411-20 [PMID:19389627]
4. Alexander SP and Kendall DA. (2007) The complications of promiscuity: endocannabinoid action and metabolism. *Br. J. Pharmacol.* **152**: 602-23 [PMID:17876303]
5. Bachovchin DA, Ji T, Li W, Simon GM, Blankman JL, Adibekian A, Hoover H, Niessen S and Cravatt BF. (2010) Superfamily-wide portrait of serine hydrolase inhibition achieved by library-versus-library screening. *Proc. Natl. Acad. Sci. U.S.A.* **107**: 20941-6 [PMID:21084632]
6. Baggelaar MP, Maccarrone M and van der Stelt M. (2018) 2-Arachidonoylglycerol: A signaling lipid with manifold actions in the brain. *Prog. Lipid Res.* **71**: 1-17 [PMID:29751000]
7. Bisogno T, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, Matias I, Schiano-Moriello A, Paul P and Williams EJ *et al.*. (2003) Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. *J. Cell Biol.* **163**: 463-8 [PMID:14610053]
8. Blankman JL, Simon GM and Cravatt BF. (2007) A comprehensive profile of brain enzymes that hydrolyze

- the endocannabinoid 2-arachidonoylglycerol. *Chem. Biol.* **14**: 1347-56 [PMID:18096503]
9. Bühler KM, Huertas E, Echeverry-Alzate V, Giné E, Moltó E, Montoliu L and López-Moreno JA. (2014) Risky alcohol consumption in young people is associated with the fatty acid amide hydrolase gene polymorphism C385A and affective rating of drug pictures. *Mol. Genet. Genomics* **289**: 279-89 [PMID:24407958]
 10. Cajanus K, Holmström EJ, Wessman M, Anttila V, Kaunisto MA and Kalso E. (2016) Effect of endocannabinoid degradation on pain: role of FAAH polymorphisms in experimental and postoperative pain in women treated for breast cancer. *Pain* **157**: 361-9 [PMID:26808012]
 11. Chang JW, Niphakis MJ, Lum KM, Coggnetta 3rd AB, Wang C, Matthews ML, Niessen S, Buczynski MW, Parsons LH and Cravatt BF. (2012) Highly selective inhibitors of monoacylglycerol lipase bearing a reactive group that is bioisosteric with endocannabinoid substrates. *Chem. Biol.* **19**: 579-88 [PMID:22542104]
 12. Chicca A, Nicolussi S, Bartholomäus R, Blunder M, Aparisi Rey A, Petrucci V, Reynoso-Moreno IDC, Viveros-Paredes JM, Dalghi Gens M and Lutz B *et al.*. (2017) Chemical probes to potently and selectively inhibit endocannabinoid cellular reuptake. *Proc. Natl. Acad. Sci. U.S.A.* **114**: E5006-E5015 [PMID:28584105]
 13. Cisar JS, Weber OD, Clapper JR, Blankman JL, Henry CL, Simon GM, Alexander JP, Jones TK, Ezekowitz RAB and O'Neill GP *et al.*. (2018) Identification of ABX-1431, a Selective Inhibitor of Monoacylglycerol Lipase and Clinical Candidate for Treatment of Neurological Disorders. *J. Med. Chem.* **61**: 9062-9084 [PMID:30067909]
 14. Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR and Lichtman AH. (2001) Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc. Natl. Acad. Sci. U.S.A.* **98**: 9371-6 [PMID:11470906]
 15. Fiskerstrand T, H'mida-Ben Brahim D, Johansson S, M'zahem A, Haukanes BI, Drouot N, Zimmermann J, Cole AJ, Vedeler C and Bredrup C *et al.*. (2010) Mutations in ABHD12 cause the neurodegenerative disease PHARC: An inborn error of endocannabinoid metabolism. *Am. J. Hum. Genet.* **87**: 410-7 [PMID:20797687]
 16. Fowler CJ. (2007) The contribution of cyclooxygenase-2 to endocannabinoid metabolism and action. *Br. J. Pharmacol.* **152**: 594-601 [PMID:17618306]
 17. Ghafouri N, Tiger G, Razdan RK, Mahadevan A, Pertwee RG, Martin BR and Fowler CJ. (2004) Inhibition of monoacylglycerol lipase and fatty acid amide hydrolase by analogues of 2-arachidonoylglycerol. *Br. J. Pharmacol.* **143**: 774-84 [PMID:15492019]
 18. Giang DK and Cravatt BF. (1997) Molecular characterization of human and mouse fatty acid amide hydrolases. *Proc. Natl. Acad. Sci. U.S.A.* **94**: 2238-42 [PMID:9122178]
 19. Haj-Dahmane S, Shen RY, Elmes MW, Studholme K, Kanjiya MP, Bogdan D, Thanos PK, Miyauchi JT, Tsirka SE and Deutsch DG *et al.*. (2018) Fatty-acid-binding protein 5 controls retrograde endocannabinoid signaling at central glutamate synapses. *Proc. Natl. Acad. Sci. U.S.A.* **115**: 3482-3487 [PMID:29531087]
 20. Johnson DS, Stiff C, Lazerwith SE, Kesten SR, Fay LK, Morris M, Beidler D, Liimatta MB, Smith SE and Dudley DT *et al.*. (2011) Discovery of PF-04457845: A Highly Potent, Orally Bioavailable, and Selective Urea FAAH Inhibitor. *ACS Med Chem Lett* **2**: 91-96 [PMID:21666860]
 21. Johnston M, Bhatt SR, Sikka S, Mercier RW, West JM, Makriyannis A, Gatley SJ and Duclos Jr RI. (2012) Assay and inhibition of diacylglycerol lipase activity. *Bioorg. Med. Chem. Lett.* **22**: 4585-92 [PMID:22738638]
 22. Kamat SS, Camara K, Parsons WH, Chen DH, Dix MM, Bird TD, Howell AR and Cravatt BF. (2015) Immunomodulatory lysophosphatidylserines are regulated by ABHD16A and ABHD12 interplay. *Nat. Chem. Biol.* **11**: 164-71 [PMID:25580854]
 23. Karbarz MJ, Luo L, Chang L, Tham CS, Palmer JA, Wilson SJ, Wennerholm ML, Brown SM, Scott BP and Apodaca RL *et al.*. (2009) Biochemical and biological properties of 4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine-1-carboxylic acid phenylamide, a mechanism-based inhibitor of fatty acid amide hydrolase. *Anesth. Analg.* **108**: 316-29 [PMID:19095868]

24. Keith JM, Apodaca R, Tichenor M, Xiao W, Jones W, Pierce J, Seierstad M, Palmer J, Webb M and Karbarz M *et al.*. (2012) Aryl Piperazinyl Ureas as Inhibitors of Fatty Acid Amide Hydrolase (FAAH) in Rat, Dog, and Primate. *ACS Med Chem Lett* **3**: 823-7 [PMID:24900385]
25. Keith JM, Apodaca R, Xiao W, Seierstad M, Pattabiraman K, Wu J, Webb M, Karbarz MJ, Brown S and Wilson S *et al.*. (2008) Thiadiazolopiperazinyl ureas as inhibitors of fatty acid amide hydrolase. *Bioorg. Med. Chem. Lett.* **18**: 4838-43 [PMID:18693015]
26. Keith JM and Liu J. (2011) Modulators of fatty acid amide hydrolase. Patent number: WO2011139951 A1.
27. Kiss LE *et al.*. (2010) Pharmaceutical compounds. Patent number: WO2010074588 A2.
28. Kiss LE, Ferreira HS, Beliaev A, Torrao L and Bonafacio MJ Learmonth DA.. (2011) Design, synthesis, and structure–activity relationships of 1,3,4-oxadiazol-2(3H)-ones as novel FAAH inhibitors. *MedChemComm.* **2**: 889-894
29. Knight MA, Hernandez D, Diede SJ, Dauwese HG, Rafferty I, van de Leemput J, Forrest SM, Gardner RJ, Storey E and van Ommen GJ *et al.*. (2008) A duplication at chromosome 11q12.2-11q12.3 is associated with spinocerebellar ataxia type 20. *Hum. Mol. Genet.* **17**: 3847-53 [PMID:18801880]
30. Li W, Blankman JL and Cravatt BF. (2007) A functional proteomic strategy to discover inhibitors for uncharacterized hydrolases. *J. Am. Chem. Soc.* **129**: 9594-5 [PMID:17629278]
31. Lim ET, Raychaudhuri S, Sanders SJ, Stevens C, Sabo A, MacArthur DG, Neale BM, Kirby A, Ruderfer DM and Fromer M *et al.*. (2013) Rare complete knockouts in humans: population distribution and significant role in autism spectrum disorders. *Neuron* **77**: 235-42 [PMID:23352160]
32. Liu Q, Tonai T and Ueda N. (2002) Activation of N-acylethanolamine-releasing phospholipase D by polyamines. *Chem. Phys. Lipids* **115**: 77-84 [PMID:12047899]
33. Long JZ, Li W, Booker L, Burston JJ, Kinsey SG, Schlosburg JE, Pavón FJ, Serrano AM, Selley DE and Parsons LH *et al.*. (2009) Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. *Nat. Chem. Biol.* **5**: 37-44 [PMID:19029917]
34. Long JZ, Nomura DK, Vann RE, Walentiny DM, Booker L, Jin X, Burston JJ, Sim-Selley LJ, Lichtman AH and Wiley JL *et al.*. (2009) Dual blockade of FAAH and MAGL identifies behavioral processes regulated by endocannabinoid crosstalk in vivo. *Proc. Natl. Acad. Sci. U.S.A.* **106**: 20270-5 [PMID:19918051]
35. M NK, V B S C T, G K V, B CS, Guntupalli S and J S B. (2016) Molecular characterization of human ABHD2 as TAG lipase and ester hydrolase. *Biosci. Rep.* **36**: [PMID:27247428]
36. Marrs WR, Blankman JL, Horne EA, Thomazeau A, Lin YH, Coy J, Bodor AL, Muccioli GG, Hu SS and Woodruff G *et al.*. (2010) The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. *Nat. Neurosci.* **13**: 951-7 [PMID:20657592]
37. Migliore M, Habrant D, Sasso O, Albani C, Bertozzi SM, Armirotti A, Piomelli D and Scarpelli R. (2016) Potent multitarget FAAH-COX inhibitors: Design and structure-activity relationship studies. *Eur J Med Chem* **109**: 216-37 [PMID:26774927]
38. Migliore M, Pontis S, Fuentes de Arriba AL, Realini N, Torrente E, Armirotti A, Romeo E, Di Martino S, Russo D and Pizzirani D *et al.*. (2016) Second-Generation Non-Covalent NAAA Inhibitors are Protective in a Model of Multiple Sclerosis. *Angew. Chem. Int. Ed. Engl.* **55**: 11193-7 [PMID:27404798]
39. Miller MR, Mannowetz N, Iavarone AT, Safavi R, Gracheva EO, Smith JF, Hill RZ, Bautista DM, Kirichok Y and Lishko PV. (2016) Unconventional endocannabinoid signaling governs sperm activation via the sex hormone progesterone. *Science* **352**: 555-9 [PMID:26989199]
40. Navia-Paldanius D, Savinainen JR and Laitinen JT. (2012) Biochemical and pharmacological characterization of human α/β -hydrolase domain containing 6 (ABHD6) and 12 (ABHD12). *J. Lipid Res.* **53**: 2413-24 [PMID:22969151]
41. Niphakis MJ, Cognetta 3rd AB, Chang JW, Buczynski MW, Parsons LH, Byrne F, Burston JJ, Chapman V and Cravatt BF. (2013) Evaluation of NHS carbamates as a potent and selective class of endocannabinoid hydrolase inhibitors. *ACS Chem Neurosci* **4**: 1322-32 [PMID:23731016]
42. Nuzzi A, Fiasella A, Ortega JA, Pagliuca C, Ponzano S, Pizzirani D, Bertozzi SM, Ottonello G, Tarozzo G and Reggiani A *et al.*. (2016) Potent α -amino- β -lactam carbamic acid ester as NAAA inhibitors. Synthesis and structure-activity relationship (SAR) studies. *Eur J Med Chem* **111**: 138-59 [PMID:26866968]

43. Ogura Y, Parsons WH, Kamat SS and Cravatt BF. (2016) A calcium-dependent acyltransferase that produces N-acyl phosphatidylethanolamines. *Nat. Chem. Biol.* **12**: 669-71 [PMID:27399000]
44. Parkkari T, Haavikko R, Laitinen T, Navia-Paldanius D, Ryttilahti R, Vaara M, Lehtonen M, Alakurtti S, Yli-Kauhaluoma J and Nevalainen T *et al.*. (2014) Discovery of triterpenoids as reversible inhibitors of α/β -hydrolase domain containing 12 (ABHD12). *PLoS ONE* **9**: e98286 [PMID:24879289]
45. Petersen G and Hansen HS. (1999) N-acylphosphatidylethanolamine-hydrolysing phospholipase D lacks the ability to transphosphatidylate. *FEBS Lett.* **455**: 41-4 [PMID:10428468]
46. Ribeiro A, Pontis S, Mengatto L, Armirotti A, Chiurchiù V, Capurro V, Fiasella A, Nuzzi A, Romeo E and Moreno-Sanz G *et al.*. (2015) A Potent Systemically Active N-Acylethanolamine Acid Amidase Inhibitor that Suppresses Inflammation and Human Macrophage Activation. *ACS Chem. Biol.* **10**: 1838-46 [PMID:25874594]
47. Roughley S, Walls S, Hart T, Parsons R, Brough P, Graham C and Macias A. (2009) Azetidine derivatives. Patent number: WO2009109743 A1.
48. Savinainen JR, Saario SM and Laitinen JT. (2012) The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. *Acta Physiol (Oxf)* **204**: 267-76 [PMID:21418147]
49. Simon GM and Cravatt BF. (2010) Characterization of mice lacking candidate N-acyl ethanolamine biosynthetic enzymes provides evidence for multiple pathways that contribute to endocannabinoid production in vivo. *Mol Biosyst* **6**: 1411-8 [PMID:20393650]
50. Sirrs S, van Karnebeek CD, Peng X, Shyr C, Tarailo-Graovac M, Mandal R, Testa D, Dubin D, Carbonetti G and Glynn SE *et al.*. (2015) Defects in fatty acid amide hydrolase 2 in a male with neurologic and psychiatric symptoms. *Orphanet J Rare Dis* **10**: 38 [PMID:25885783]
51. Snider NT, Walker VJ and Hollenberg PF. (2010) Oxidation of the endogenous cannabinoid arachidonoyl ethanolamide by the cytochrome P450 monooxygenases: physiological and pharmacological implications. *Pharmacol. Rev.* **62**: 136-54 [PMID:20133390]
52. Solorzano C, Zhu C, Battista N, Astarita G, Lodola A, Rivara S, Mor M, Russo R, Maccarrone M and Antonietti F *et al.*. (2009) Selective N-acylethanolamine-hydrolyzing acid amidase inhibition reveals a key role for endogenous palmitoylethanolamide in inflammation. *Proc. Natl. Acad. Sci. U.S.A.* **106**: 20966-71 [PMID:19926854]
53. Tanaka M, Moran S, Wen J, Affram K, Chen T, Symes AJ and Zhang Y. (2017) WWL70 attenuates PGE2 production derived from 2-arachidonoylglycerol in microglia by ABHD6-independent mechanism. *J Neuroinflammation* **14**: 7 [PMID:28086912]
54. Thorel MF, Krichevsky M and Lévy-Frébault VV. (1990) Numerical taxonomy of mycobactin-dependent mycobacteria, emended description of *Mycobacterium avium*, and description of *Mycobacterium avium* subsp. *avium* subsp. nov., *Mycobacterium avium* subsp. *paratuberculosis* subsp. nov., and *Mycobacterium avium* subsp. *silvaticum* subsp. nov. *Int. J. Syst. Bacteriol.* **40**: 254-60 [PMID:2397193]
55. Tsuboi K, Hilligsmann C, Vandevoorde S, Lambert DM and Ueda N. (2004) N-cyclohexanecarbonylpentadecylamine: a selective inhibitor of the acid amidase hydrolysing N-acylethanolamines, as a tool to distinguish acid amidase from fatty acid amide hydrolase. *Biochem. J.* **379**: 99-106 [PMID:14686878]
56. Tsuboi K, Ikematsu N, Uyama T, Deutsch DG, Tokumura A and Ueda N. (2013) Biosynthetic pathways of bioactive N-acylethanolamines in brain. *CNS Neurol Disord Drug Targets* **12**: 7-16 [PMID:23394527]
57. Tuo W, Leleu-Chavain N, Spencer J, Sansook S, Millet R and Chavatte P. (2017) Therapeutic Potential of Fatty Acid Amide Hydrolase, Monoacylglycerol Lipase, and N-Acylethanolamine Acid Amidase Inhibitors. *J. Med. Chem.* **60**: 4-46 [PMID:27766867]
58. Ueda N, Yamanaka K and Yamamoto S. (2001) Purification and characterization of an acid amidase selective for N-palmitoylethanolamine, a putative endogenous anti-inflammatory substance. *J. Biol. Chem.* **276**: 35552-7 [PMID:11463796]
59. van Esbroeck ACM, Janssen APA, Cognetta 3rd AB, Ogasawara D, Shpak G, van der Kroeg M, Kantae V, Baggelaar MP, de Vrij FMS and Deng H *et al.*. (2017) Activity-based protein profiling reveals off-target

- proteins of the FAAH inhibitor BIA 10-2474. *Science* **356**: 1084-1087 [PMID:28596366]
60. Wan M, Cravatt BF, Ring HZ, Zhang X and Francke U. (1998) Conserved chromosomal location and genomic structure of human and mouse fatty-acid amide hydrolase genes and evaluation of clasper as a candidate neurological mutation. *Genomics* **54**: 408-14 [PMID:9878243]
 61. Wei BQ, Mikkelsen TS, McKinney MK, Lander ES and Cravatt BF. (2006) A second fatty acid amide hydrolase with variable distribution among placental mammals. *J. Biol. Chem.* **281**: 36569-78 [PMID:17015445]
 62. Whibley AC, Plagnol V, Tarpey PS, Abidi F, Fullston T, Choma MK, Boucher CA, Shepherd L, Willatt L and Parkin G *et al.*. (2010) Fine-scale survey of X chromosome copy number variants and indels underlying intellectual disability. *Am. J. Hum. Genet.* **87**: 173-88 [PMID:20655035]
 63. Xie S, Borazjani A, Hatfield MJ, Edwards CC, Potter PM and Ross MK. (2010) Inactivation of lipid glyceryl ester metabolism in human THP1 monocytes/macrophages by activated organophosphorus insecticides: role of carboxylesterases 1 and 2. *Chem. Res. Toxicol.* **23**: 1890-904 [PMID:21049984]