Endocannabinoid-metabolising enzymes

Overview: The principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (*N*-arachidonoylethanolamine, AEA), thought to be generated on demand rather than stored. For 2AG, the key enzyme involved is diacylglycerol lipase (DGL), while several routes for AEA synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD). Inactivation of these endocannabinoids appears to occur predominantly through monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH) for 2AG and AEA, respectively. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism via cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities (see Alexander & Kendall, 2007; Fowler, 2007, Snider *et al*., 2009).

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	*N*-Acylphosphatidylethanolamine-phospholipase D
Preferred abbreviation	DGLα	DGLβ	NAPE-PLD
E.C.	3.1.1.-	3.1.1.-	–
Other names	Neural stem cell-derived dendrite regulator	KCCR13L	–
Ensembl ID	ENSG00000134780	ENSG00000164535	ENSG00000161048
Selective inhibitors (pIC_{50})	Tetrahydrolipstatin (7.2, Bisogno *et al.* (2003), RHC80267	Tetrahydrolipstatin (7.0, Bisogno *et al*., 2003), RHC80267	–

NAPE-PLD activity appears to be enhanced by polyamines in the physiological range (Liu *et al*., 2002), but fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999) unlike phosphatidylcholine-specific phospholipase D.

Nomenclature	Monoacylglycerol lipase	Fatty acid amide hydrolase-1	Fatty acid amide hydrolase-2	*N*-Acylethanolamine acid amidase
Preferred abbreviation	MGL	FAAH1	FAAH2	NAAA
E.C.	3.1.1.23	3.5.1.–	3.5.1.–	3.5.1.–
Other names	HU-K5, lysophospholipase homolog	Oleamide hydrolase, anandamide hydrolase, FAAH	–	Acid ceramidase-like protein, *N*-acylsphingosine amidohydrolase-like, N-palmitoylethanolamine acid amidase
Ensembl ID	ENSG00000074416	ENSG00000117480	ENSG00000165591	ENSG00000138744
Substrate potency order	2OG = 2AG >> AEA (Ghafouri *et al*., 2004)	AEA > ODA > OEA > PEA (Wei *et al*., 2006)	ODA > OEA > AEA > PEA (Wei *et al*., 2006)	PEA > MEA > SEA ≥ OEA > AEA (Ueda *et al*., 2001)
Selective inhibitors (pIC_{50})	JZL184 (8.1, Long *et al*., 2009)	PF750 (6.3–7.8, Ahn *et al*., 2007), JNJ1661010 (7.8, Keith *et al*., 2008), URB597 (6.3–7.0, Wei *et al*., 2006), OL135 (7.4, Wei *et al*., 2006)	URB597 (7.5–8.3, Wei *et al*., 2006), OL135 (7.9, Wei *et al*., 2006)	CCP (5.3, Tsuboi *et al*., 2004)

Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents (Wei *et al*., 2006). Additional enzymes (ABHD6 [ENSG00000163686] and ABHD12 [ENSG00000100997]) thought to be able to hydrolyse 2AG in brain membranes have been identified (Blankman *et al*., 2007). Although these have been incompletely defined, WWL70 has been described to inhibit ABHD6 selectively with a pIC_{50} value of 7.2 (Li *et al*., 2007).

Abbreviations: **2AG**, 2-arachidonoylglycerol; **2OG**, 2-oleoylglycerol; **AEA**, anandamide; **CCP**, *N*-cyclohexylcarbonylpentadecylamine; **DGL**, diacylglycerol lipase; **FAAH**, fatty acid amide hydrolase; **JNJ1661010**, 4-(3-phenyl-[1,2,4] thiadiazol-5-yl)-piperazine-1-carboxylic acid phenylamide; **JZL184**, 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate; **MGL**, monoacylglycerol lipase; **MEA**, *N*-myristoylethanolamine; **NAAA**, *N*-acylethanolamine acid amidase; **NAPE-PLD**, *N*-acylphosphatidylethanolamine-phospholipase D; **ODA**, octadec(9,10*Z*)enamide; **OEA**, *N*-oleoylethanolamine **OL135**, 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-phenylheptane; **PEA**, *N*-palmitoylethanolamine; **PF750**, *N*-phenyl-4-(quinolin-3-ylmethyl)piperidine-1-carboxamide; **RHC80267**, 1,6-bis (cyclohexyloximinocarbonylamino)hexane; **SEA**, *N*-stearoylethanolamine; **URB597**, cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester; **WWL70**, 4′-carbamoylbiphenyl-4-yl methyl(3-(pyridin-4-yl)benzyl)carbamate

Further Reading

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