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Monoglyceride lipase as a drug target: At the crossroads of arachidonic acid metabolism and endocannabinoid signaling

Gernot F. Grabner [a], Robert Zimmermann [a,c], Rudolf Schicho [b,c,*], Ulrike Taschler [a]

[a] Institute of Molecular Biosciences, University of Graz, Graz, Austria
[b] Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria
[c] BioTechMed Graz, Graz, Austria

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ABSTRACT

Monoglyerides (MGs) are short-lived, intermediary lipids deriving from the degradation of phospho- and neutral lipids, and monoglyceride lipase (MGL), also designated as monoacylglycerol lipase (MAGL), is the major enzyme catalyzing the hydrolysis of MGs into glycerol and fatty acids. This distinct function enables MGL to regulate a number of physiological and pathophysiological processes since both MGs and fatty acids can act as signaling lipids or precursors thereof. The most prominent MG species acting as signaling lipid is 2-arachidonoyl glycerol (2-AG) which is the most abundant endogenous agonist of cannabinoid receptors in the body. Importantly, recent observations demonstrate that 2-AG represents a quantitatively important source for arachidonic acid, the precursor of prostaglandins and other inflammatory mediators. Accordingly, MGL-mediated 2-AG degradation affects lipid signaling by cannabinoid receptor-dependent and independent mechanisms. Recent genetic and pharmacological studies gave important insights into MGL's role in (patho-)physiological processes, and the enzyme is now considered as a promising drug target for a number of disorders including cancer, neurodegenerative and inflammatory diseases. This review summarizes the basics of MG (2-AG) metabolism and provides an overview on the therapeutic potential of MGL.

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Abbreviations: ABHD, α/β hydrolase domain containing protein; Δ^9-THC, Δ^9-tetrahydrocannabinol; 2-AG, 2-arachidonoyl glycerol; 2-OG, 2-oleoyl glycerol; DGAT, acyl-CoA:diacylglycerol acyltransferase; MGAT, acyl-CoA:monoacylglycerol acyltransferase; ATGL, adipose triglyceride lipase; AA, arachidonic acid; AEA, arachidonoyl ethanoamine; CB, cannabinoid; CNS, central nervous system; COX, cyclooxygenase; cPLA2, cytosolic phospholipase A2; DAGL, diglyceride lipase; DG, diglyceride; EC, endocannabinoid; FAAH, fatty acid amide hydrolase; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GPR55, G-protein coupled receptor 55; HFD, high-fat diet; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; LDL, low density lipoprotein; MAGL, monoacylglycerol lipase; MGL, monoglyceride lipase; MG, monoglycerides; NAPE-PLD, *N*-arachidonoyl-phosphatidylehtanolamine selective phospholipase D; PPAR, peroxisome proliferator activated receptor; PHARC, polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract disease; PLC, phospholipase C; PUFA, polyunsaturated fatty acid; TRPV1, transient receptor potential cation channel subfamily V member 1; TG, triglyceride.

* Corresponding author at: Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria.
E-mail address: rudolf.schicho@medunigraz.at (R. Schicho).

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1. Introduction

1.1. Milestones in monoglyceride lipase research

Early work from the 1960s suggested the presence of a distinct enzymatic activity that hydrolyzes monoglycerides (MGs) to glycerol and fatty acids in the intestine (Senior & Isselbacher, 1963) and in adipose tissue (Vaughan, Berger, & Steinberg, 1964) of rats. This activity was later ascribed to monoglyceride lipase [MGL, also known as monoacylglycerol lipase (MAGL)], a 33 kDa serine hydrolase that cleaves MGs at neutral pH (Kupiecki, 1966). Subsequently, MGL was purified, cloned, and enzymatically characterized (Karlsson, Contreras, Hellman, Tornqvist, & Holm, 1997; Tornqvist & Belfrage, 1976). The enzyme harbors an alpha/beta hydrolase fold and a catalytic triade with an active serine located within a GXSXG consensus sequence commonly found in lipases (Karlsson et al., 1997). MGL returned into the spotlight of research when Dinh et al. demonstrated that it degrades 2-arachidonoyl glycerol (2-AG), the most abundant endocannabinoid (EC) in the body (Dinh et al., 2002). This finding led to the development of powerful tools used today in MGL research, including selective MGL inhibitors (Table 1) and genectic mouse models of MGL deficiency or overexpression (Table 2). Thereby, MGL was identified as the major enzyme providing arachidonic acid (AA) for eicosanoid synthesis in certain tissues (Nomura, Morrison, et al., 2011). Furthermore, MGL's crystal stucture was solved unveiling how the enzyme interacts with membranes, substrates, and inhibitors (Bertrand et al., 2010; Labar, Bauvois, et al., 2010; Schalk-Hihi et al., 2011). Genetic as well as pharmacological studies gave important insights into MGL's role in (patho-)physiological processes, and the enzyme is now considered as a promising therapeutic target for the treatment of a number of disorders including cancer, neurodegenerative and inflammatory diseases.

1.2. Overview on monoglyceride metabolism

MGs are short-lived lipids deriving from intra- and extracellular sources. The extracellular quantitatively most important source of MGs are triglyceride-(TG)-rich lipoproteins since lipoprotein lipase (LPL) hydrolyzes TGs in *sn*-1- and *sn*-3-position, generating 2-MG species (Goldberg & Merkel, 2001). Similarly, digestion of dietary TG by pancreatic lipase results in the generation of 2-MG (Lowe, 1994). Extracellularly generated MGs are internalized by cells and may be degraded by MGL (Fig. 1A) or re-esterified to TG by acyl-CoA:monoacylglycerol and acyl-CoA:diacylglycerol acyltransferase (MGAT and DGAT) reactions. The latter pathway is specifically important in the small intestine where MGAT enzymes synthesize about 80% of the TG incorporated into chylomicrons (reviewed in (Shi & Cheng, 2009)). MGs can also derive from intracellular TGs stored in cytosolic lipid droplets (Fig. 1B). These TGs are hydrolyzed by the sequential action of two lipases. The first and rate-limiting step is catalyzed by adipose triglyceride lipase (ATGL) generating diglycerides (DGs) and fatty acids. These DGs are then hydrolyzed by hormone-sensitive lipase (HSL), releasing another fatty acid and thereby generating MG (Schweiger et al., 2006). Finally, MGL cleaves the last fatty acid off the MG and releases glycerol. Membrane bound glycerophospholipids are precursors for the generation of MGs (Fig. 1C, D). Glycerophospholipids are hydrolyzed by phospholipase C (PLC) to generate DGs which are further metabolized by *sn*-1-specific DG lipases (DAGLα and DAGLβ) (Bisogno et al., 2003) to generate 2-MG (Bisogno, Melck, De Petrocellis, & Di Marzo, 1999; Stella, Schweitzer, & Piomelli, 1997). This is the major pathway for the generation of the EC 2-AG. AA and other polyunsaturated fatty acids (PUFAs) are commonly found esterified in *sn*-2 position of glycerophospholipids and TGs. Accordingly, by degrading 2-MG from different sources, MGL can affect PUFA metabolism. It is currently unknown whether also 2-AG, deriving from TG of extra- or intracellular sources, can contribute to EC signaling. As summarized in Fig. 1, the heterogeneity of MG sources correlates with the subcellular distribution of MGL. The enzyme has been shown to localize to plasma membranes, endoplasmic reticulum, and lipid droplets (Blankman, Simon, & Cravatt, 2007; Dinh et al., 2002; Sakurada & Noma, 1981; Tornqvist & Belfrage, 1976). Upon over-expression of MGL in cells, it equally distributes between membrane and cytosolic fractions (Dinh et al., 2002). However, brain tissue fractionation revealed that more than 90% of endogenous MGL activity is found in the membrane fraction (Blankman et al., 2007).

Table 1
MGL inhibitors.

Inhibitor	Organism	IC_{50}	Reference
URB602	Rat/mouse	28 μM	Hohmann et al. (2005)
NAM	Rat/mouse	0.14 μM	Saario et al. (2005)
JZL184	Mouse /(rat, human)	0.008 μM	Long, Weiwei, et al. (2009)
OMDM169	Rat/mouse	0.34 μM/7.3 μM	Bisogno et al. (2009)
JZL195 (MGL and FAAH)	Mouse	0.013 and 0.019 μM	Long, Nomura, Vann, et al. (2009)
KML29	Rat (mouse, human)	0.015 μM	Chang et al. (2012)
MJN110	Mouse	0.0095 μM	Chang, Cognetta, Niphakis, Cravatt, and Cravatt (2013)
sar127303	Mouse/human	0.0038 and 0.029 μM	Griebel et al. (2015)

1.3. Biochemical properties, tissue distribution, and regulation of MGL

MGL is capable of hydrolyzing MG species with different fatty acid chain length and saturation. The enzyme has no positional preference for *sn*-1(3) or 2-MGs, yet a slight preference for MG species containing unsaturated fatty acids (Ghafouri et al., 2004; Vandevoorde et al., 2005). Recent data suggest that MGL also degrades prostaglandin glycerol esters which represent still poorly characterized inflammatory mediators (Savinainen et al., 2014). Finally, MGL has been implicated in non-oxidative ethanol metabolism by hydrolyzing fatty acid ethyl esters which are produced in the body in response to alcohol consumption (Heier et al., 2016).

Genetic as well as pharmacological inactivation of MGL in mice causes a strong increase of MGs in many tissues including brain, liver, adipose tissue, intestine, and others, demonstrating a major role of the enzyme in MG catabolism (Chanda et al., 2010; Long, Weiwei, et al., 2009; Schlosburg et al., 2010). Accordingly, MGL is expressed in many cell types of various tissues. In mice, highest expression is observed in brown and white adipose tissue (Karlsson et al., 1997) and the brain (Dinh et al., 2002). MGL is expressed throughout the major cell types of the brain, including neurons, astrocytes, oligodendrocytes, and to a lower extent in microglia (Dinh et al., 2002; Stella, 2004). Several studies demonstrated the existence of MGL proteins with different molecular weight by Western Blot analysis. In murine adipose tissue, liver, heart, lung, spleen, kidney, and adrenal glands, a single MGL band is observed at 33 kDa, whereas in skeletal muscle, MGL can be detected at 40 kDa. In testis, MGL is found at 30 kDa, and in the brain even two bands are observed at 33 and 35 kDa (Blankman et al., 2007; Karlsson et al., 2001). Although it is not fully understood how these variations occur, they very likely derive from differential use of start codons in the 5′ leader sequence of the *Mgll* gene as well as alternative splicing (Karlsson et al., 2001). The existence of different splice variants might also explain the variation in the subcellular localization of MGL. For human *Mgll*, splice variants have been described that lack exon 5 which encodes for the cap region which is implicated in substrate selectivity and membrane localization (Bertrand et al., 2010; Labar, Bauvois, et al., 2010; Scalvini, Piomelli, & Mor, 2016).

Surprisingly, little is known about the regulation of MGL. At the transcriptional level, microarray analysis of murine liver revealed that MGL expression is regulated via the transcription factor peroxisome proliferator activated receptor α (PPARα) (Rakhshandehroo et al., 2007). PPARs are nuclear receptors that heterodimerize with retinoid