Published in final edited form as:
Pharmacol Ther. 2017 July ; 175: 35–46. doi:10.1016/j.pharmthera.2017.02.033.

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

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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.

Keywords

monoglyceride lipase; MGL; MAGL; 2-arachidonoyl glycerol; arachidonic acid; cannabinoid receptor; eicosanoids

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 and Isselbacher, 1963) and in adipose tissue (Vaughan et al., 1964) of rats. This activity was later

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Conflict of interest statement
The authors declare that there are no conflicts of interest.

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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 (Tornqvist and Belfrage, 1976; Karlsson et al., 1997). 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 et al., 2011b). Furthermore, MGL's crystal stucture was solved unveiling how the enzyme interacts with membranes, substrates, and inhibitors (Bertrand et al., 2010; Labar et al., 2010a; 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 and 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 (Figure 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 and Cheng, 2009)). MGs can also derive from intracellular TGs stored in cytosolic lipid droplets (Figure 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 (Figure 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 (Stella et al., 1997; Bisogno et al., 1999b). 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 Figure 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 (Tornqvist and Belfrage, 1976; Sakurada and Noma, 1981; Dinh et al., 2002; Blankman et al., 2007). 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).

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 (Long et al., 2009c; Chanda et al., 2010; 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 (Karlsson et al., 2001; Blankman et al., 2007). 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 et al., 2010a; Scalvini et al., 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 X receptor upon ligand binding and thereby activate transcription of genes, most of which are involved in energy metabolism (Grygiel-Górniak, 2014). In wild-type mice, PPARα agonist treatment led to a 6-fold increase in *Mgll* gene expression, a response that was absent in PPARα-deficient mice (Rakhshandehroo et al., 2007).Furthermore, Chon *et al.* demonstrated that

intestinal and hepatic MGL protein levels are induced in mice upon feeding a diet that contains a high amount of fat, indicating nutritional regulation of MGL expression (Chon et al., 2007).

At the posttranslational level, recent data suggest that MGL activity is regulated via sulfenylation of cysteine residues by H_2O_2. The involved cysteines are located in the cap region that controls entry of the substrate into the active site of the enzyme. H_2O_2 exposure leads to a rapid, reversible, non-competitive inhibition of MGL activity. This inhibition may be relevant under conditions associated with increased oxidative stress such as brain ischemia in which increased 2-AG levels may have protective effects (Dotsey et al., 2015).

1.4 Other MG hydrolases

Although MGL is clearly the major enzyme in MG catabolism in most tissues, other MG hydrolases may contribute to this process in cell types or cellular compartments that do not contain MGL. HSL was the first intracellular enzyme characterized with MG hydrolase activity (Fredrikson et al., 1986; Yeaman, 1990). This enzyme is highly expressed in adipose tissue and plays an important role in the mobilization of fatty acids from TG stores. Yet, HSL has substantial MG hydrolase activity and can therefore partially compensate MGL deficiency in lipolysis (Taschler et al., 2011). Fatty acid amide hydrolase (FAAH), responsible for the degradation of the EC arachidonoyl ethanolamine (AEA, also anandamide), was also shown to hydrolyze 2-AG *in vitro* (Goparaju et al., 1998). However, FAAH-deficient mice have unaltered 2-AG levels, questioning a physiological role of FAAH as a MG hydrolase *in vivo* (Cravatt et al., 2001). In 2007, α/β hydrolase domains containing protein 6 and 12 (ABHD6 and ABHD12) were identified as additional MG hydrolases in the brain, accounting for about 15% of total membrane activity (Blankman et al., 2007). Recent reports suggest that ABHD12 is involved in phospholipid rather than MG metabolism. ABHD12 acts as a potent lyso-phosphatidyl serine hydrolase, and human ABHD12 mutations or genetic deletion in mice are associated with the neurodegenerative disease PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract disease) (Fiskerstrand et al., 2010; Blankman et al., 2013). ABHD6 was proposed to acts as the major 2-AG hydrolase in cell types in which MGL is not expressed (Marrs et al., 2010; Alhouayek et al., 2013). Nevertheless, MG hydrolase activity of ABHD6 may also play a role in cells expressing MGL, via distinct cellular distribution of both enzymes. E.g., in neurons, ABHD6 is localized at postsynaptic membranes while MGL is predominantly found presynaptically. Accordingly, ABHD6 may counteract 2-AG formation at the post-synapse (Marrs et al., 2010). Moreover, recent evidence suggests that ABHD6 plays a role in the hydrolysis of MGs esterified in *sn*-1 position, especially 1-palmitoyl glycerol and 1-stearoyl glycerol. Zhao *et al.* suggested that these saturated MG species activate Munc13-1 that is required for the priming of insulin containing vesicles, thereby promoting exocytosis of insulin in pancreatic β-cells (Zhao et al., 2014, 2015). Conversely, inhibition of MGL decreases glucose-stimulated insulin secretion in INS-1 cells and rat islets (Berdan et al., 2016). In contrast to MGL, ABHD6 can also hydrolyze acidic lysophospholipids and the late endosomal/lysosomal lipid bis(monoacylglycero)phosphate (Thomas et al., 2013; Pribasnig et al., 2015). The enzyme co-localizes with acidic organelles and might be therefore involved in the remodeling of outer membranes of these organelles (Pribasnig et al., 2015).

Recently, another member of the ABHD family, namely ABHD2, was identified as a 2-AG hydrolase in spermatozoa. This highly interesting study suggests that ABHD2 is directly activated by progesterone and responsible for the genome-independent action of the hormone via 2-AG signaling (Miller et al., 2016). This observation implicates that lipid-metabolizing enzymes can represent direct targets of hormones. Besides ABHD family members, triglyceride hydrolase 2, rat esterase 4 and 10, carboxyl esterase 1, and neuropathy target esterase have been shown to hydrolyze MG *in vitro* (Lehner and Vance, 1999; van Tienhoven et al., 2002; Xie et al., 2010). While all these hydrolases are active at neutral pH, lysosomal acid lipase was reported to hydrolyze MG in acidic organelles (Sheriff et al., 1995).

2 MGL in endocannabinoid signaling

After initial characterization, MGL returned into the spotlight of research when Dinh *et al.* demonstrated that MGL is the primary enzyme in the brain hydrolyzing 2-AG. This MG species belongs to a class of signaling lipids called ECs which are primarily derivatives of AA. In general, it is thought that Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of *Cannabis sativa* (Gaoni and Mechoulam, 1964), mimics the action of ECs. Δ^9-THC, synthetic cannabinoids, and ECs bind and activate cannabinoid (CB) receptors of which two have been characterized. The CB_1 receptor is expressed mainly in central and peripheral neurons (Howlett et al., 1990), but also in various other cell types including adipocytes and hepatocytes (Pagotto et al., 2006). Its activation is involved in the regulation of various physiological processes including appetite, activity, emotions, pain processing, and energy homeostasis (de Kloet and Woods, 2009; Maccarrone et al., 2011; Silvestri and Di Marzo, 2013; Hasenoehrl et al., 2016). The CB_2 receptor is predominantly expressed in cells of the hematopoietic system and important in the regulation of immune response (Munro et al., 1993; Galiègue et al., 1995). Besides 2-AG, AEA acts as an EC, however its tissue abundance is more than 100 times lower in the brain as compared to 2-AG (Bisogno et al., 1999a). Generally, ECs are produced “on demand” and are rapidly degraded by intracellular enzymes after receptor binding. ECs, together with the two receptors and the EC metabolizing enzymes, constitute the EC system. CB receptors mainly signal through $G_{i/o}$ proteins, inhibit voltage gated Ca^{2+} channels and activate A-type and inwardly rectifying K^+ currents (Howlett, 2005). Whether other receptors, like the orphan G-protein coupled receptor 55 (GPR55) and the transient receptor potential cation channel subfamily V member 1 (TRPV1) are EC-responsive receptors, and contribute to CB_1/CB_2 receptor independent effects of ECs requires further investigation (Di Marzo et al., 1998; Ryberg et al., 2007). Furthermore, PPARs respond to synthetic cannabinoids and ECs, and may mediate some effects (O’Sullivan, 2016).

Although both AEA and 2-AG derive from phospholipids, they have distinct pathways of synthesis and degradation. AEA is generated by a Ca^{2+}-activated N-arachidonoyl-phosphatidylethanolamine selective phospholipase D (NAPE-PLD) (Okamoto et al., 2004), or alternatively by the phospholipase ABHD4 and glycerophospho-diesterase 1 (Simon and Cravatt, 2008). AEA and other N-acyl ethanolamines are hydrolyzed by FAAH (Cravatt et al., 2001; Deutsch et al., 2002). AEA synthesis and degradation pathways are reviewed in detail elsewhere (Cascio and Marini, 2015).

2-AG is synthesized by the consecutive action of a PLC generating 2-arachidonoyl DG which is further hydrolyzed by *sn*-1 specific DAGLs. Very recently, DDH domain containing 2 has been shown to possess DG hydrolase activity and its overexpression in CHO cells results in an increased generation of 2-AG (Araki et al., 2016). 2-AG may undergo different metabolic pathways resulting in inactivation or in the generation of other signaling molecules. The strong increase in 2-AG levels in MGL-knockout (ko) mice implicates that most of the EC is degraded by hydrolysis. However, 2-AG can be phosphorylated to lyso-phosphatidic acid by MG kinase(s) (Simpson et al., 1991) and metabolized by cyclooxygenase-2 (COX-2) resulting in the formation of prostaglandin glycerol esters (Gopez et al., 2005; Telleria-Diaz et al., 2010). Alternatively, 2-AG may be acylated by acyltransferases to generate DG (Yen et al., 2002, 2003, Cao et al., 2003, 2007). A schematic overview of 2-AG synthesis and degradation is illustrated in Figure 2.

2.1 MGL blockade and CB receptor desensitization

Within recent years, different strategies have been established to investigate the physiological role of MGL *in vivo*. Several MGL inhibitors have been synthetized that block MGL activity, as reviewed extensively elsewhere (Labar et al., 2010b; Kohnz and Nomura, 2014) (Table 1), and different genetically modified mouse models have been generated (Table 2). One of the first selective inhibitors developed was JZL184 which inhibits MGL by irreversible active site carbamylation (Long et al., 2009c). JZL184 inhibits around 90% of 2-AG hydrolase activity in the brain and leads to strong accumulation of 2-AG and other MGs 30 min after administration (Long et al., 2009c). However, MGs did not increase in all tissues which could either indicate that MGL activity is compensated by other MG hydrolases in certain tissues or that JZL184 shows a tissue-specific distribution pattern and MGL is not fully inhibited in all tissues (Long et al., 2009a).

The *in vivo* effects of MGL inhibitors have been investigated using the “tetrad test for cannabinoid activity” which consists of four individual tests: analgesia, sedation, catalepsy, and hypothermia (Wiley and Martin, 2003). Acute blockade of MGL induces analgesia, hypomotility, and hypothermia, while catalepsy was not observed (Long et al., 2009c). The effects of JZL184 are dependent on CB_1 receptor activation since they were absent in CB_1 receptor-deficient (CB_1-ko) mice. None of the MGL inhibitors developed so far produced catalepsy which might require the inhibition of both MGL and FAAH as shown with the dual inhibitor JZL195 (Long et al., 2009b). However, these results clearly demonstrate that CB_1 receptor agonists and MGL inhibitors have similar effects *in vivo*.

As mentioned above, MGL-ko mice exhibit dramatically increased 2-AG levels in the brain and in peripheral tissues. Notably, increased 2-AG levels do not evoke cannabimimetic effects in these mice as observed in response to acute inhibitor treatment. The reason for this discrepancy is that chronically elevated 2-AG in MGL-ko mice causes desensitization of CB_1 receptors in the brain similar to what may occur in response to chronic, heavy cannabis abuse (González et al., 2005; Borgelt et al., 2013). Accordingly, MGL-deficiency is associated with decreased CB_1 receptor density, reduced CB_1 receptor ligand binding (Chanda et al., 2010; Schlosburg et al., 2010), and resistance to the hypometabolic effects of CB receptor agonists (Taschler et al., 2011). A recent study suggests that chronically

increased 2-AG induced basal CB_1 receptor/$G_{i/o}$ signaling in the brain but dampened agonist-evoked responses (Navia-Paldanius et al., 2015). Impaired CB_1 receptor signaling due to desensitization in the brain is accompanied by increased β-arrestin 2 binding and a significant reduction of ERK1/2 phosphorylation in different brain regions, such as the amygdala, medial prefrontal cortex, and hippocampus (CA1 and CA3), but not in the cerebellum (Imperatore et al., 2015). Interestingly, β-arrestin2 mediated CB_1 receptor desensitization was observed in brain areas controlling emotional and stress related states, pain sensation, memory and learning, whereas brain areas associated with motor function were not affected by desensitization. Receptor internalization/desensitization is a process generally observed for G-protein coupled receptors, and the CB_1 receptor was shown to internalize only minutes after receptor activation in cell culture (Hsieh et al., 1999). Recently, also desensitization of peripherally expressed CB_1 receptors in the enteric nervous system has been demonstrated by chronic pharmacological inhibition or genetic deletion of MGL. While MGL-ko mice show normal gut motility under physiological conditions, they are insensitive to CB receptor agonist- induced intestinal hypomotility (Taschler et al., 2015). Whether CB_1 receptor activity/expression is impaired in other peripheral tissues and non-neuronal cells remains elusive.

In contrast to the CB_1 receptor, data on CB_2 receptor desensitization/internalization are scarce. Previous reports suggest that CB_2 receptors are not desensitized in MGL-ko mice. Chanda *et al.* showed by CB receptor agonist binding studies that CB_2 receptor density is unaltered in the spleen, however, a functional characterization of the receptor activity was not performed (Chanda et al., 2010). In a more recent study, Vujic *et al.* suggest that CB_2 receptors are not desensitized in MGL-ko macrophages isolated from mice on an ApoE-deficient background. These conclusions are based on Ca^{2+}-flux experiments in response to 2-AG stimulation (Vujic et al., 2016). Yet, cell culture experiments show that CB_2 receptors undergo internalization after activation (Grimsey et al., 2011). Since 2-AG is a physiologically relevant agonist of CB_2 receptors, it is reasonable to assume that also these receptors desensitize in MGL-ko mice. Thus, careful evaluation of inhibitor concentrations may be the key to avoid CB receptor desensitization upon MGL inhibition. Indeed, while the injection of JZL184 at concentrations of 8mg/kg mouse and higher over a period of 5 days causes CB_1 receptor desensitization (Schlosburg et al., 2010), similar to observations in MGL-ko mice, the injection of 4mg/kg mouse did not promote CB_1 receptor desensitization (Kinsey et al., 2013). Burston et al. investigated the effects of acute and chronic MGL inhibition in a rat model of osteoarthritis. Repeated administration of MJN110 at high doses (5mg/kg) resulted in anti-nociceptive tolerance whereas lower concentrations (1mg/kg) preserved antinociception (Burston et al., 2016).

Despite CB_1 receptor desensitization caused by chronic MGL inhibition, blockade of the enzyme has still protective effects in a variety of pathophysiological states such as inflammation and neurodegeneration, mostly via CB_1 receptor independent mechanisms as discussed in the following section (Nomura et al., 2011b; Viader et al., 2015; Grabner et al., 2016).

3 MGL in inflammation and pain

Cannabinoids have a long history as analgesics (Touw, 1981; Mechoulam and Parker, 2013) and research of the last decades suggests close connections between the EC system and inflammation (Turcotte et al., 2015). MGL is a highly interesting target for the treatment of inflammation since it conversely regulates 2-AG and AA levels in several tissues (Dinh et al., 2002; Long et al., 2009c). Accordingly, MGL deficiency exerts a dual anti-inflammatory function. First, MGL ablation leads to augmented 2-AG levels, leading to increased CB receptor activation. Activation of CB_1 or CB_2 receptors by endogenous or exogenous agonists has been shown to have beneficial effects on various diseases harboring an inflammatory component (Klein, 2005; Turcotte et al., 2015). Second, MGL limits AA availability causing CB receptor independent anti-inflammatory effects in the brain and some peripheral tissues (Figure 2). Notably, cytosolic PLA2 (cPLA2) has been considered as mainly responsible for mobilizing AA for prostaglandin synthesis in the brain (Buczynski et al., 2009). Yet, cPLA2-deficient mice do not show a reduction in brain free AA levels indicating that other enzymes mediate this process (Rosenberger et al., 2003). Upon characterization of mice treated with the MGL inhibitor JZL184, a significant, dose dependent reduction in brain AA was observed (Long et al., 2009c). This effect was also confirmed in MGL-deficient mice (Chanda et al., 2010; Schlosburg et al., 2010). Further, it was demonstrated that global genetic deletion or pharmacological inhibition of MGL protects mice from LPS-induced neuroinflammation independent of CB receptor activation, due to reduced AA availability for prostaglandin synthesis (Nomura et al., 2011b). Diminished prostaglandin levels attenuate cytokine production and microglia activation (Nomura et al., 2011b). Since then, numerous studies demonstrated beneficial effects of MGL ablation on various disease models harboring an inflammatory component. These effects are mediated by CB receptor dependent and/or independent effects. MGL inhibition improves pathologies of Parkinson’s (Nomura et al., 2011b) and Alzheimer’s disease (Chen et al., 2012; Piro et al., 2012), multiple sclerosis (Pryce et al., 2013; Hernández-Torres et al., 2014), and Down syndrome (Lysenko et al., 2014). Interestingly, MGL in neurons and astrocytes equally contributes to brain AA availability upon inflammatory stimuli, while MGL in microglia plays a minor role (Viader et al., 2015; Grabner et al., 2016). In peripheral tissues, MGL inhibition leads to attenuated liver (Cao et al., 2013), lung (Costola-de-Souza et al., 2013), and muscle injury (Jiang et al., 2015). MGL deficiency also extenuates colitis and related systemic inflammation (Alhouayek et al., 2011).

Pharmacological inhibition of MGL thus represents a highly interesting strategy to treat inflammation. To date, the majority of anti-inflammatory drugs used are COX inhibitors, prescribed in many of the aforementioned diseases. As an example, pharmacological inhibition or genetic deletion of COX-1 has beneficial effects on neuroinflammation and neurodegenerative disorders (Choi et al., 2008; Vlad et al., 2008; Choi and Bosetti, 2009). A severe drawback of COX inhibitors however is that they cause gastrointestinal (GI) injury (Singh, 1998; Ng and Chan, 2010). Side effects of selective COX-2 inhibitors (coxibs) are less severe in the GI tract, however, wide usage of these drugs is restricted owing to cardiovascular complications (Cannon and Cannon, 2012). Inhibition of MGL could thus represent an anti-inflammatory strategy, which avoids adverse effects of COX inhibition.

The beneficial effects of MGL ablation are thereby comparable to those of COX inhibitors, however, MGL inhibition by JZL184 does not lead to GI injury, but protects from COX-1 inhibitor induced GI damage (Kinsey et al., 2011a). Recently, a Phase 1b study has been initiated to evaluate the effects of a single dose of the orally active human MGL inhibitor ABX-1431 (ABIDE Therapeutics) for the treatment of functional dyspepsia.

Cannabinoids and (naturally occurring) COX inhibitors have a long common history, likely being the first analgesics used by humans. To date, it is well established that CB receptor agonists exhibit analgesic effects (Manzanares et al., 2006; Fine and Rosenfeld, 2013). Concordantly, pharmacological MGL inhibition leads to anti-nociceptive effects in various models of pain, including inflammatory, neuropathic, thermal, and chemically induced pain in a 2-AG/CB_1 receptor dependent manner (Kinsey et al., 2009; Long et al., 2009c; Guindon et al., 2011; Woodhams et al., 2012; Ghosh et al., 2013; Griebel et al., 2015). The orally active MGL inhibitor SAR127303 has been reported to produce anti-nociceptive properties and even repeated administration caused no tolerance since the effects were maintained in the formalin test. However, the authors also demonstrate that inhibition of MGL impaired memory performance (Griebel et al., 2015). Interestingly, administration of the highly selective MGL inhibitor KML29 produces analgesia without cannabimimetic side effects, its chronic administration, however, leads to CB_1 receptor desensitization, as similarly observed for other MGL inhibitors (Ignatowska-Jankowska et al., 2014). Also, genetic mouse models of MGL deficiency, do not show analgesic properties due to constantly increased 2-AG levels and subsequent CB_1 receptor desensitization (Chanda et al., 2010; Schlosburg et al., 2010), as mentioned previously. Nevertheless, by combining anti-inflammatory and anti-nociceptive properties, MGL inhibitors may represent a promising strategy to counteract inflammation and pain.

4 MGL in metabolic disorders

Metabolic syndrome is a major public health care concern and combines several pathological conditions, including abdominal obesity, elevated blood pressure, insulin resistance and high blood glucose, high serum TG and low high-density lipoprotein levels. It is closely associated with the risk to develop type 2 diabetes and cardiovascular disease. A large number of studies implicates that metabolic disorders are associated with the EC system. In general, activation of CB_1 receptors is associated with increased lipid deposition, increased lipogenesis, hyperphagy, and hypomotility as reviewed in (Quarta et al., 2011). In line, acute treatment of mice with isopropyl dodecylfluorophosphonate (IDFP), an inhibitor of MGL and FAAH, caused hepatic steatosis and impaired glucose tolerance by CB_1 receptor dependent and independent mechanisms (Ruby et al., 2011). Moreover, a single administration of JZL184 (40mg/kg) significantly increased food intake (Woodhams et al., 2012). In contrast, CB_1-ko mice are resistant to diet induced obesity, hepatic steatosis and insulin resistance. These effects are mostly caused by reduced caloric intake and increased energy expenditure (Cota et al., 2003; Quarta et al., 2010). Similarly, CB_1 receptor blockade with rimonabant (Acomplia®), a selective inverse CB_1 receptor agonist (Rinaldi-Carmona et al., 1994), ameliorates hepatic steatosis and dyslipidemia in obese mice and rats (Gary-Bobo et al., 2007; Osei-Hyiaman et al., 2008; Tam et al., 2010). Important evidence was provided by studies in obese and diabetic patients treated with rimonabant. The drug promoted weight

loss and improved cardiovascular risk factors (Van Gaal et al., 2005; Scheen et al., 2006). Yet, rimonabant was withdrawn from the market due to serious side-effects such as depression and even suicidal tendencies (Christensen et al., 2007). Based on these observations, it can be assumed that inactivation of MGL increases EC signaling, promoting obesity and co-morbidities. Yet, MGL-ko mice are lean and show no alterations in plasma lipid parameters in the fed state while fasted animals exhibit reduced plasma glycerol and TG levels. Moreover, MGL-deficiency protects from high fat diet (HFD) induced insulin resistance despite similar weight gain (Taschler et al., 2011). A more recent study suggests that MGL-ko mice exhibit decreased body weight and fat mass upon HFD feeding (Douglass et al., 2015). It is important to mention that the fat rich diets used in both studies vary in fat content (55% vs 25% fat w/w), possibly explaining the discrepancy in diet induced obesity. Also, Douglass *et al.* demonstrated even higher differences in body fat mass when using a diet with lower fat content (4,3% w/w) (Douglass et al., 2015). Together, these observations suggest that the metabolic effects of MGL inactivation cannot be explained by hyperactivation of the EC system. As mentioned above, MGL is involved in TG hydrolysis in adipocytes, and reduced lipolysis is known to counteract the development of insulin resistance (Boden, 2011). Furthermore, MGL inactivation has anti-inflammatory effects and insulin resistance is associated with inflammation in insulin-sensitive tissues (Samuel and Shulman, 2012). Finally, MGL inactivation can affect lipid signaling independent of CB receptors. 2-oleoyl glycerol (2-OG) has been identified as a ligand of the G-protein coupled receptor GPR119. Activation of this receptor stimulates the intestinal release of incretin hormones, like glucagon-like peptide-1 (GLP-1), having well-known beneficial effects in the development and progression of diabetic complications (Hansen et al., 2011). Important effects of GLP-1 are augmentation of insulin secretion and inhibition of glucagon release. Yet, MGL has also been directly implicated in the regulation of insulin release in pancreatic β-cells. A recently published study suggests that MGL inactivation inhibits glucose-stimulated and depolarization-induced insulin secretion (Berdan et al., 2016). Thus, in addition to changes in EC signaling, MGL inactivation may have complex effects on metabolic disorders by affecting lipolysis, inflammation, incretin and insulin signaling.

Evidence for an important role of MGL in energy homeostasis comes also from animal models overexpressing the enzyme. Transgenic mice that overexpress MGL in the intestine develop obesity and liver steatosis already after three weeks of HFD feeding, caused by decreased energy expenditure and hyperphagia. The authors speculated that 2-AG might act as a satiety signal (Chon et al., 2012). In contrast, other studies demonstrate that 2-AG in the intestine is increased upon fat intake and acts as hunger signal which is abandoned upon local CB_1 receptor antagonism or surgical transection of the vagus nerve (DiPatrizio et al., 2011). Interestingly, this effect seems to be dependent on distinct fatty acids (DiPatrizio et al., 2013). Another study demonstrated that MGL, expressed in the central nervous system (CNS), is able to influence peripheral energy balance (Jung et al., 2012). Transgenic mice overexpressing MGL specifically in the forebrain are resistant to HFD-induced obesity mostly via elevated brown adipose tissue thermogenesis. Interestingly, these mice maintained leanness and insulin sensitivity despite increased food intake and decreased locomotor activity (Jung et al., 2012). Thus, MGL overexpression has different effects on energy homeostasis depending on the site of expression.

EC signaling has also been implicated in the pathogenesis of atherosclerosis. Initially, it was observed that low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice (Steffens et al., 2005). The beneficial effects of Δ^9-THC were completely blocked by a selective CB_2 receptor antagonist, implicating that CB_2 receptors located on immune cells play a central role in this process. Subsequent studies showed that rimonabant has anti-atherosclerotic effects in low density lipoprotein (LDL) receptor–deficient mice (Dol-Gleizes et al., 2008). These effects are due to an enhancement of reverse cholesterol transport (Sugamura et al., 2010). Yet, clinical trials with rimonabant did not show any significant benefit of this agent in preventing progression of atherosclerosis (Nissen et al., 2008). A recent study investigated atherosclerosis-susceptibility of MGL/ApoE double knockout mice. Mice exhibited a body weight gain and plasma lipoprotein profile similar to their wild-type littermates. However, MGL-ko/ApoE-ko mice displayed larger lesion size and changes in plaque composition indicating increased plaque stability (Vujic et al., 2016). Treatment with a CB_2 receptor inverse agonist prevented these changes suggesting that MGL inactivation provokes increased CB_2 receptor signaling.

Together, all these studies emphasize an important role for MGL in the regulation of energy homeostasis. Acute blockade of MGL induces hyperphagy, while long-term blockade of MGL attenuates diet induced obesity and insulin resistance. Therefore, the potential of MGL inhibitors as therapeutic strategy to treat obesity have to be evaluated carefully. The effects of MGL inhibition cannot be limited to changes in EC signaling. Further studies are required to outline MGL's role in the regulation of incretin/insulin secretion and inflammation in insulin-sensitive tissues. Nevertheless, inhibition of MGL might represent an interesting therapeutic option for the treatment of metabolic disease.

5 MGL in stress, emotion, and addiction

EC effects on neuronal transmission have a deep impact on stress response, mood, and emotion (Hill and Gorzalka, 2009; Lutz, 2009). Activation of CB_1 receptors leads to anxiolysis and improves mood and depression like behavior in humans and animal models (Berrendero and Maldonado, 2002; Denson and Earleywine, 2006; Patel and Hillard, 2006). Conversely, administration of the CB_1 receptor inverse agonist rimonabant leads to increased anxiety and depression in humans (Samat et al., 2008). The impact of (endo-)cannabinoid signaling on acute and chronic stress (Riebe and Wotjak, 2011; Hillard, 2014; Morena et al., 2015), emotion (McLaughlin and Gobbi, 2012), mood and depression (Gaetani et al., 2009; Micale et al., 2013) have been extensively reviewed recently, thus we only briefly summarize the role of MGL therein. MGL inhibition by JZL184 exhibits beneficial effects in various behavioral tests of anxiety via elevated 2-AG and activation of CB_1 receptors (Busquets-Garcia et al., 2011; Kinsey et al., 2011b; Sumislawski et al., 2011; Aliczki et al., 2012, 2013; Lomazzo et al., 2015), but impairs short-term fear extinction in mice (Hartley et al., 2016). Reduction of 2-AG levels by genetic deletion of DAGLα leads to increased anxiety which is ameliorated upon restoration by pharmacological MGL inhibition (Shonesy et al., 2014). JZL184 treatment also improves chronic stress-induced depression-like behavior (Zhong et al., 2014) and attenuates plasma corticosterone levels in the early recovery from restraint stress (Roberts et al., 2014). Conversely, CB_1 receptor desensitization in MGL-deficient mice leads to anxiety-like behavior (Imperatore et al.,

2015). Impaired CB_1 receptor signaling could thus be a major drawback of 2-AG elevation by chronic MGL inhibition, as discussed above.

Another pharmacologically highly relevant area of EC action is drug abuse and withdrawal. ECs play a major role in regulating addictive behavior, and their involvement in opioid, nicotine, and alcohol dependence has been extensively investigated (Parolaro et al., 2007; Scavone et al., 2013). Although it has long been known that *Cannabis sativa* ameliorates opioid withdrawal symptoms (Birch, 1889), MGL's particular role therein has been investigated in detail just recently. Several studies demonstrated that the MGL inhibitor JZL184 attenuates Δ^9-THC (Schlosburg et al., 2009), nicotine (Muldoon et al., 2015), and opioid (Ramesh et al., 2011, 2013) withdrawal in mice, but does not improve aversive behavioral aspects of withdrawal (Gamage et al., 2015). Taken together, pharmacological inhibition of MGL represents a promising strategy to ameliorate stress, depression, and drug withdrawal symptoms.

6 MGL in cancer

First evidence for a pathophysiological role of MGL in cancer emerged when Nomura *et al.* demonstrated that MGL was highly elevated in aggressive ovarian, breast and melanoma cancer cells. The enzyme was involved in cellular growth and survival, *in vitro* migration, and invasion of these cells (Nomura et al., 2010). The study suggests that MGL affects tumor growth through involvement of a pool of fatty acids that promotes pathogenicity, and that blockade of MGL reduces this pool leading to decreased cancer cell aggressiveness independently of EC signaling and CB receptor activation (Nomura et al., 2010). Interestingly, several MGL-derived bioactive lipid mediators affecting tumor invasiveness were identified in this study, including lyso-phosphatidic acid and prostaglandin E2. Both lipids are known to promote cancer aggressiveness (Tsujiuchi et al., 2014; O'Callaghan and Houston, 2015), and their supplementation reestablished malignancy of MGL deficient cancer cells (Nomura et al., 2010). In a subsequent study, the group further demonstrated that MGL activity was also high in aggressive prostate cancer cells and that anti-tumorigenic EC signaling was terminated by MGL via free fatty acid reduction and by CB_1 receptor activation (Nomura et al., 2011a). High MGL expression was also detected in nasopharyngeal (Hu et al., 2014) and hepatocellular carcinoma (Zhang et al., 2016; Zhu et al., 2016). Knockdown of MGL inhibited migration of these cells further indicating a tumor-promoting role of MGL. This may also apply for neuroblastoma cells because inhibition of MGL and type II topoisomerase also decreased proliferation (Matuszak et al., 2012).

In contrast, the role of MGL in the oncogenesis of colorectal cancer is controversial. In line with the previous data, Ye *et al.* demonstrated high expression of MGL in colorectal cancerous tissues and a tumor-promoting effect of MGL in colorectal cancer cell lines (Ye et al., 2011). Conversely, Sun *et al.* described reduced MGL expression in colorectal tumor tissues (and also other human malignancies) and a colony formation suppressive effect in MGL overexpressing colon cancer cells (Sun et al., 2013). The authors of this study suggested that the underlying mechanism by which MGL may affect tumor growth could be through constitutive suppression of Akt phosphorylation because shRNA mediated knockdown of MGL expression enhanced phosphorylation of Akt in both HT29 colon

cancer and MDA-MB-231 breast cancer cells (Sun et al., 2013). The discrepancy between these studies is unclear and requires further research on the role of MGL in colorectal cancer.

Taken together, studies in various cancer cell lines suggest that MGL may drive cancer malignancy. However, the picture may be different in colon cancer in which a tumor suppressive role for MGL was proposed. Certainly, more research is needed to define the role of MGL in human malignancies and whether MGL's role involves CB receptor dependent or independent mechanisms.

7 Conclusions and Outlook

Starting from the first description of MGL activity more than 50 years ago, MGL research has shifted from fat breakdown to endocannabinoid signaling and further to AA metabolism. Apparently, MGL has a central function in feeding AA into COX and LOX pathways. The investigation of these pathways will be of paramount importance to understand the role of MGL in various diseases. Accordingly, the pharmacological inhibition of MGL evokes two different effects: First, levels of the EC 2-AG rise, inducing anti-inflammatory and analgesic effects via activation of CB_1 and CB_2 receptors and, second, the pool of AA is lowered counteracting the synthesis of prostaglandins. Based on these mechanisms, MGL inhibitors represent an alternative to COX inhibitors in the treatment of inflammation and pain.

Yet, it has to be considered that the EC system has a major impact on neuronal signaling and consequently CB receptor activation or desensitization upon MGL inhibition may result in adverse psychological effects. Peripherally restricted MGL inhibitors may circumvent this issue. Nevertheless, MGL inhibitors may prove useful in pathologies where moderate adverse effects are acceptable. Studies in various disease models, such as intestinal inflammation, hepatic injury, endotoxemia, insulin resistance, depression and stress, opioid and nicotine withdrawal already suggest that inhibition of MGL may be a powerful anti-inflammatory pharmacological strategy. In addition, MGL inhibitors may have high potential as anticancer drugs, however, studies on the role of MGL in cancer are conflicting and the role of MGL in the metabolism of cancers cells is incompletely understood. Furthermore, it should be kept in mind that MGL not only degrades 2-AG but also other 2-MGs esterified with PUFAs and thus may affect the mobilization of docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA). These PUFAs are precursors of potent inflammation-resolving mediators such as resolvins and protectins. From preclinical studies we have to assume that therapy with MGL inhibitors may cause CB_1 receptor desensitization in long term use which hampers therapeutic success. This obstacle might be overcome by assessing the lowest effective dose avoiding CB_1 receptor desensitization. In conclusion, the therapeutic potential of MGL inhibition is vast and promising, but warrants further research. Since highly selective inhibitors targeting human MGL have been developed, studies in the near future will disclose whether MGL inhibitors can become an alternative to COX inhibitors in the treatment of inflammation, pain, and other disorders.

Funding

This study was supported by Austrian Science Fund (FWF) grants P21166 and KLI 521-B31 and the doctoral program Molecular Enzymology Grant W 09.

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-phosphatidylethanolamine 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

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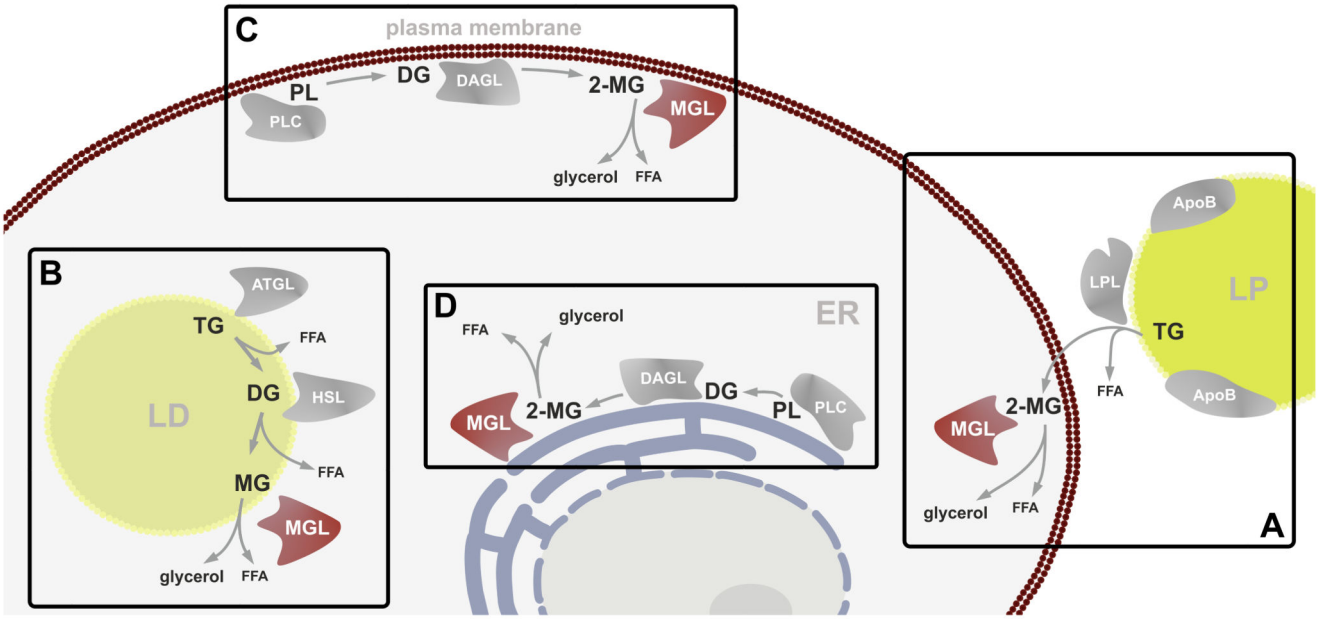

Figure 1. Sources of monoglycerides.

Monoglycerides (MGs) are ubiquitously occurring intermediate lipids derived from various cellular processes. (A) The major extracellular source are triglycerides (TG) from lipoproteins (LP) which are hydrolyzed by lipoprotein lipase (LPL) to generate *sn*-2 monoglycerides (2-MGs). (B) Also, intracellular TGs stored in lipid droplets (LD) are a source of MGs. Sequential hydrolysis of TGs via adipose triglyceride lipase (ATGL) generating free fatty acids (FFAs) and diglycerides (DGs), which are subsequently hydrolyzed by hormone sensitive lipase (HSL) to MGs and FFAs. (C, D) On cellular membranes, including plasma membrane and membranes of the endoplasmic reticulum (ER), 2-MGs are generated from phospholipids (PL) by hydrolysis through phospholipase C (PLC) to DGs and subsequent hydrolysis by diglyceride lipases (DAGL) to MGs.

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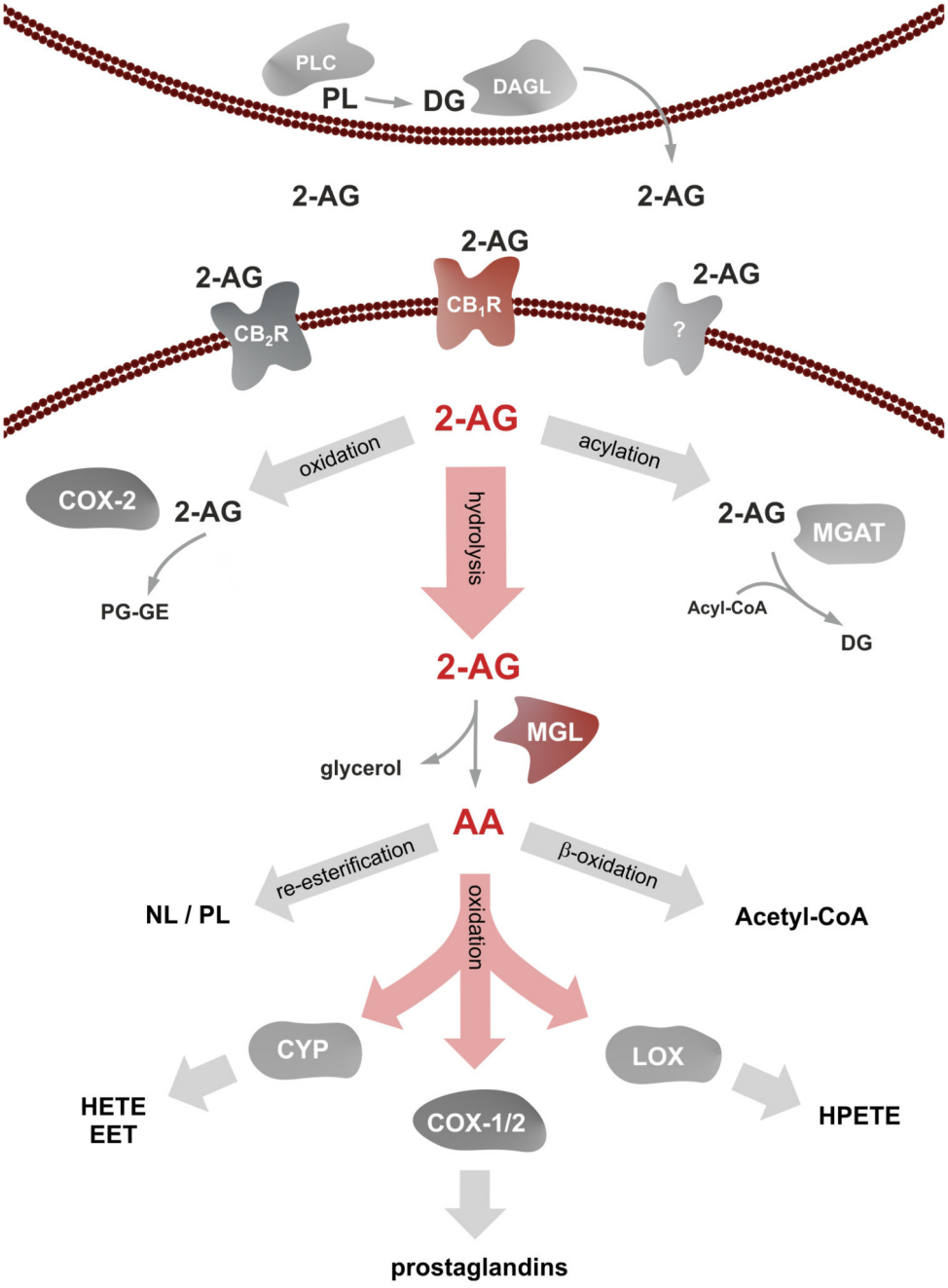

Figure 2. Monoglyceride lipase in 2-arachidonoyl glycerol signaling and arachidonic acid metabolism.

2-AG is generated by hydrolysis of membrane phospholipids (PL) to diglycerides (DGs) by phospholipase C (PLC) and subsequent hydrolysis by diglyceride lipase (DAGL). 2-AG is secreted and binds to CB_1 receptors (CB_1R), CB_2 receptors (CB_2R), or other yet uncharacterized receptors. 2-AG is then metabolized by oxidation through cyclooxygenase 2 (COX-2) generating prostaglandin-glyceryl esters (PG-GE) or acylation through monoacylglycerol acyltransferase (MGAT) to DG. The majority of 2-AG is hydrolyzed by monoglyceride lipase (MGL) to glycerol and arachidonic acid (AA). AA is either re-

esterified into cellular neutral lipid (NL) or PLs or conducted to β-oxidation to generate acetyl-CoA. AA can also be subjected to oxidation by COX-1, COX-2, lipoxygenases (LOX), or cytochrome p450 (CYP) generating important signaling lipids like prostaglandins, hydroxyeicosatetraenoic acid/epoxy-eicosatrienoic acid (HETE, EET), and hydroperoxyeicosatetraenoic acid (HPETE).

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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 et al., 2009c)
OMDM169	Rat/mouse	0.34 μM/7.3μM	(Bisogno et al., 2009)
JZL195 (MGL and FAAH)	Mouse	0.013 and 0.019 μM	(Long et al., 2009b)
KML29	Rat (mouse, human)	0.015 μM	(Chang et al., 2012)
MJN110	Mouse	0.0095 μM	(Chang et al., 2013)
sar127303	Mouse/human	0.0038 and 0.029 μM	(Griebel et al., 2015)

Table 2
Genetic mouse models of MGL deficiency or overexpression

ORIGIN	KNOCKOUT/TRANSGENE	BACKGROUND	OBSERVATION	REFERENCE
MGL-ko	global	129SvEv x C57BL/6J	CB_1 receptor desensitization	(Schlosburg et al., 2010)
MGL-ko	global	C57BL/6NTac	Decreased CB_1 receptor density	(Chanda et al., 2010)
MGL-ko	global	C57BL/6J	Impaired lipolysis Increased insulin sensitivity on HFD CB_1 receptor desensitization	(Taschler et al., 2011)
MGL-ko	global	C57BL/6	Tissue expression analyses of MGL	(Uchigashima et al., 2011)
MGL-ko	global	C57BL/6	Delayed lipid absorption; resistance to HFD induced obesity	(Douglass et al., 2015)
MGL-ko/ApoE-ko	global	C57BL/6J	Increased plaque stability on Western type diet	(Vujic et al., 2016)
MGLflox/GluN2Cre	granula cells	C57BL/6		(Tanimura et al., 2012)
MGLflox/Rosa26-Cre **MGLflox/Eno2-Cre** **MGLflox/GFAP-Cre** **MGLflox/LysM-Cre**	global neurons astrocytes microglia		Astrocytes and neurons collaborate to terminate endocannabinoid signaling; Astrocytes couple 2-AG hydrolysis to neuroinflammatory prostaglandin production	(Viader et al., 2015)
MGLflox/GFAP-Cre	astrocytes	129Sv x C57BL6/J	Protected from LPS induced inflammation	(Grabner et al., 2016)
CaMKIIA-MGL Transgene	forebrain	C57BL/6	Decreased 2-AG in forebrain, resistance to HFD induced obesity	(Jung et al., 2012)
IFABP-MGL Transgene	intestine	SJL, F4-F10	Development of obesity on HFD	(Chon et al., 2012)