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Therapeutic Potential of Monoacylglycerol Lipase Inhibitors

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Abstract

Marijuana and aspirin have been used for millennia to treat a wide range of maladies including pain and inflammation. Both cannabinoids, like marijuana, that exert anti-inflammatory action through stimulating cannabinoid receptors, and cyclooxygenase (COX) inhibitors, like aspirin, that suppress pro-inflammatory eicosanoid production have shown beneficial outcomes in mouse models of neurodegenerative diseases and cancer. Both cannabinoids and COX inhibitors, however, have untoward effects that discourage their chronic usage, including cognitive deficits and gastrointestinal toxicity, respectively. Recent studies have uncovered that the serine hydrolase monoacylglycerol lipase (MAGL) links the endocannabinoid and eicosanoid systems together through hydrolysis of the endocannabinoid 2-arachidonoylglycerol (2-AG) to provide the major arachidonic acid (AA) precursor pools for pro-inflammatory eicosanoid synthesis in specific tissues. Studies in recent years have shown that MAGL inhibitors elicit anti-nociceptive, anxiolytic, and anti-emetic responses and attenuate precipitated withdrawal symptoms in addiction paradigms through enhancing endocannabinoid signaling. MAGL inhibitors have also been shown to exert anti-inflammatory action in the brain and protect against neurodegeneration through lowering eicosanoid production. In cancer, MAGL inhibitors have been shown to have anti-cancer properties not only through modulating the endocannabinoid—eicosanoid network, but also by controlling fatty acid release for the synthesis of protumorigenic signaling lipids. Thus, MAGL serves as a critical node in simultaneously coordinating multiple lipid signaling pathways in both physiological and disease contexts. This review will discuss the diverse (patho)physiological roles of MAGL and the therapeutic potential of MAGL inhibitors in treating a vast array of complex human diseases.

Keywords

monoacylglycerol lipase; MAGL; mgll; JZL184; endocannabinoid; cannabinoid; eicosanoid; prostaglandin; inflammation; neurodegenerative disease; cancer

Introduction

Cannabinoids and cyclooxygenase (COX) inhibitors have been used therapeutically for centuries collectively to alleviate pain, fever, inflammation, anxiety, depression, convulsions, and lack of appetite (Di Marzo, 2006; Dinarello, 2010; Miner and Hoffhines, 2007). Direct cannabinoid receptor agonists and COX inhibitors also exert protective effects

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in various other pathologies including neurodegenerative diseases, stroke, and ischemia/reperfusion injury (Aid and Bosetti, 2011; Batkai et al., 2007; Romero and Orgado, 2009; Tuma and Steffens, 2012). The active component of marijuana, Δ^9 -tetrahydrocannabinol, acts through cannabinoid receptors type 1 and type 2 (CB1 and CB2) to exert not only medicinal, but also psychoactive effects and cognitive impairments that have made its use controversial (Di Marzo et al., 2004; Ligresti et al., 2009). COX inhibitors which include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, aspirin, or celecoxib act through either blocking both COX1 and COX2 or COX2 alone to lower a cascade of pro-inflammatory arachidonic acid oxidation products, collectively termed eicosanoids, which in-turn act through a host of G-protein coupled receptors to propagate inflammation (Rouzer and Marnett, 2011). However, COX inhibitors also exhibit mechanism-based side effects which include gastrointestinal bleeding for COX1/COX2 dual inhibitors and heightened risk of myocardial infarction for COX2-selective inhibitors that have made their chronic usage undesirable (Mitchell and Warner, 2006). Nonetheless, both cannabinoid-based therapies and NSAIDs are still widely used for therapeutic benefit and represent proven strategies towards combatting inflammation. Additionally, new therapeutic utilities using these strategies are being discovered in basic science research.

We have recently provided compelling evidence linking both the endocannabinoid and eicosanoid pathways together through the serine hydrolase monoacylglycerol lipase (MAGL) (Nomura et al., 2011b). MAGL, through hydrolyzing and degrading an endocannabinoid signaling lipid 2-arachidonoylglycerol (2-AG), releases a major arachidonic acid (AA) precursor pool for the synthesis of pro-inflammatory eicosanoids in specific tissues such as the brain, liver, and lung (Nomura et al., 2011b). In aggressive cancer cells, MAGL supplies the free fatty acids for production of protumorigenic signaling lipids. This review will discuss the diverse biochemical and physiological roles of MAGL and evidence for the therapeutic potential of MAGL inhibitors in combatting a variety of human diseases through bidirectionally manipulating endocannabinoid, eicosanoid, and other lipid signaling pathways (Figure 1).

Biochemical and Physiological Roles of MAGL

MAGL is a serine hydrolase that preferentially hydrolyzes monoacylglycerols to glycerol and fatty acid, with highest expression in brain, white adipose tissue, and liver in mice and is a soluble enzyme that associated with membranes (Ahn et al., 2008; Dinh et al., 2002; Long and Cravatt, 2011). One of these monoacylglycerols is the endocannabinoid 2-AG (Mechoulam et al., 1995; Sugiura et al., 1995). Understanding of the metabolic and (patho)physiological roles of MAGL has been greatly accelerated in recent years due to the synthesis of highly potent and selective *in vivo* efficacious inhibitors such as JZL184, as well as the development of MAGL-deficient ($-/-$) mice (Chanda et al., 2010; Long et al., 2009a; Schlosburg et al., 2010). Pharmacological or genetic inactivation of MAGL lowers 2-AG hydrolytic activity by >80 % in most tissues including the brain while the remaining 20 % of 2-AG hydrolytic activity in brain arises from the uncharacterized serine hydrolases alpha/beta hydrolase domain 6 (ABHD6) and ABHD12 (Blankman et al., 2007; Dinh et al., 2004). Although ABHD6 and ABHD12 may have roles in 2-AG hydrolysis in certain settings, both genetic and pharmacological inactivation of MAGL lead to dramatic elevations in both bulk levels and depolarization-induced interstitial levels of 2-AG in the brain, confirming that MAGL is indeed the primary enzyme involved in degrading 2-AG *in vivo* (Long et al., 2009a; Nomura et al., 2011b; Schlosburg et al., 2010). MAGL blockade shows tissue-specific differences in monoacylglycerol metabolism, with the brain showing the most dramatic elevations in 2-AG and peripheral tissues often showing greater changes in other monoacylglycerols, consistent with the lipolytic role of MAGL as the final step of triglyceride hydrolysis in peripheral tissues (Long et al., 2009b). The endocannabinoid 2-AG

is thought to be formed through hydrolysis of phospholipids by phospholipase C (PLC) β or δ to release diacylglycerols (DAG) and then degradation of DAG by diacylglycerol lipase (DAGL) α or β (Gao et al., 2010; Tanimura et al., 2010). Although the involvement of PLCs in DAG and 2-AG synthesis is not yet fully elucidated, the creation of DAGL α and β -deficient mice has cemented the roles of these enzymes in 2-AG synthesis and endocannabinoid function. Studies have shown that DAGL α is the primary enzyme in brain and spinal cord, whereas DAGL β plays a primary role in the liver with modest roles in the brain for 2-AG synthesis (Gao et al., 2010; Tanimura et al., 2010).

In addition to the role of MAGL in terminating 2-AG signaling, we have recently found that MAGL releases AA, the precursor for pro-inflammatory prostaglandin synthesis in certain tissues. MAGL blockade lowers bulk AA levels in the brain, stoichiometrically to 2-AG elevation, which also results in a reduction of lipopolysaccharide (LPS)-induced pro-inflammatory levels of downstream COX-driven prostaglandin and thromboxane production in the brain (Nomura et al., 2011b). These results were quite surprising since phospholipases have been considered to be the dominant AA-releasing enzyme for prostaglandin production (Buczynski et al., 2009). Instead, there is an anatomical demarcation in enzymes that regulate this process in which MAGL plays this role not only in the brain, but also in the liver and lung, whereas cytosolic phospholipase A2 (cPLA2) is the dominant AA-releasing enzyme in gut, spleen and macrophages (Bonventre et al., 1997; Nomura et al., 2011b). Recently, Jaworski et al. showed that adipose-specific PLA2 (AdPLA2) controls this process in white adipose tissue, also demonstrating that other enzymes beyond cPLA2 may play a role in AA release for prostaglandin biosynthesis (Jaworski et al., 2009). Our results are further supported by substantially reduced AA levels in DAGL α or β $-/-$ mice in brain and liver (Gao et al., 2010).

The endocannabinoid 2-AG is synthesized in postsynaptic neurons and binds to presynaptic CB1 receptors to modulate presynaptic or interneuron release of excitatory or inhibitory neurotransmitters by mediating two forms of retrograde synaptic depression, depolarization-induced suppression of excitation (DSE) and inhibition (DSI) (Pan et al., 2009; Straiker et al., 2009; Straiker and Mackie, 2009; Szabo et al., 2006). MAGL is found on presynaptic terminals, optimally positioned to break down 2-AG that has engaged presynaptic CB1 receptors (Straiker et al., 2009). Acute MAGL blockade with the selective inhibitor JZL184 or with the non-selective inhibitor methyl arachidonyl fluorophosphonate (MAFP) prolongs DSE in Purkinje neurons in cerebellar slices and in autaptic hippocampal neurons, and DSI in CA1 pyramidal neurons in hippocampal slices (Pan et al., 2009; Straiker et al., 2009). Studies have also shown that retrograde endocannabinoid signaling to suppress GABA-mediated transmission at inhibitory synapses, a phenomenon known as depolarization induced suppression of inhibition (DSI), is absent in DAGL α but not DAGL β -deficient mouse brain, indicating that DAGL α is the more relevant enzyme for 2-AG function in the brain (Gao et al., 2010; Tanimura et al., 2010).

Blocking MAGL, much like blocking the anandamide-degrading enzyme fatty acid amide hydrolase (FAAH), does not cause full-blown cannabinoid-behaviors observed with direct cannabinoid agonists such as catalepsy and hypothermia (Long et al., 2009b; Long et al., 2009c). However, acute MAGL blockade by JZL184 does produce modest cannabinoid-mediated hypomotility in open-field (Long et al., 2009b). Chronic pharmacological blockade or genetic deletion of MAGL, unlike FAAH inhibition, leads to functional antagonism and loss of cannabinoid-mediated effects and produces cross-tolerance to CB1 agonists in mice. Chronic MAGL blockade also causes physical dependence, impaired endocannabinoid-dependent synaptic plasticity, and desensitized brain CB1 receptors (Schlosburg et al., 2010). Interestingly, dual blockade of MAGL and FAAH by either the dual inhibitor JZL195 or by JZL184-treatment in FAAH $-/-$ mice, exerts synergistic CB1-dependent analgesic and

cataleptic behavior not observed with blocking either MAGL or FAAH alone, indicating potential behavioral processes regulated by crosstalk of both 2-AG and anandamide signaling (Long et al., 2009c). In contrast, FAAH blockade raises the levels of the endocannabinoid anandamide to provide continued CB1-dependent antinociceptive effects (Cravatt et al., 2001). It is therefore of future interest to determine whether partial MAGL blockade may maintain the endocannabinoid signaling under chronic MAGL inhibition.

The Role of MAGL in Pain and Inflammation

Cannabinoid receptor agonists are currently clinically used to treat pain, spasticity, emesis, and anorexia (Di Marzo, 2006; Di Marzo et al., 2004; Ligresti et al., 2009). In addition to these clinical avenues, both CB1 and CB2 agonists have also been shown to exert antinociceptive and anti-inflammatory action in various rodent models of neuropathic pain and inflammation (Bridges et al., 2001; Costa et al., 2004; Fox et al., 2001; Ibrahim et al., 2003; Kinsey et al., 2011a; Quartilho et al., 2003; Valenzano et al., 2005). NSAIDs such as aspirin and ibuprofen are widely used to treat pain, fever, and inflammation through blockade of cyclooxygenases (COX 1/2) and subsequent lowering of pro-inflammatory prostaglandins and thromboxanes (Rouzer and Marnett, 2011). NSAIDs are also used as an anti-platelet therapy for prevention of heart attacks, stroke, and blood clot formation and clinically used to treat inflammatory disorders such as rheumatoid arthritis (Dinarello, 2010; Patrono et al., 2005; Rouzer and Marnett, 2011).

Consistent with the role of MAGL in modulating 2-AG-mediated endocannabinoid signaling, acute pharmacological blockade of MAGL exerts CB1-dependent antinociceptive effects in mouse models of noxious chemical, inflammatory, thermal, and neuropathic pain (Guindon et al., 2011; Kinsey et al., 2009; Long et al., 2009a). MAGL blockade reduces mechanical and acetone-induced cold allodynia in mice subjected to chronic constriction injury of the sciatic nerve (Kinsey et al., 2009). Recent studies have also shown that MAGL blockade is protective in a mouse model of inflammatory bowel disease. MAGL blockade by JZL184 reduces macroscopic and histological colon alterations and pro-inflammatory cytokines in a trinitrobenzene sulfonic acid-induced colitis model, and restores integrity of the intestinal barrier function resulting in reduced endotoxemia and peripheral and brain inflammation in a CB1 or CB2-dependent manner (Alhouayek et al., 2011).

The Role of MAGL in Neurodegenerative Diseases

Beyond pain, neuroinflammation is now widely considered to be a hallmark of multiple neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease (AD), multiple sclerosis and stroke (Glass et al., 2010). Both cannabinoid receptor agonists and COX inhibitors have shown protective or palliative benefit against neurodegenerative diseases (Aid and Bosetti, 2011; Ligresti et al., 2009; Sanchez-Pernaute et al., 2004; Scotter et al., 2010). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Parkinson's disease models, both nonselective CB1/CB2 agonists and CB2-selective agonists exhibit increased survival of dopaminergic neurons and fibers, an attenuation of dopamine depletion in the substantia nigra, and improved motor function in a CB1 or CB2-dependent manner through reductions in NADPH oxidase, reactive oxidative stress, and pro-inflammatory cytokine release from activated microglia (Chung et al., 2011; Fox et al., 2002; Garcia-Arencibia et al., 2007; Price et al., 2009). In an AD mouse model, cannabinoid receptor agonists WIN55,212-2 and JWH-133 reduced microglial activation, tumor necrosis factor α (TNF α) levels, COX2 expression, and amyloid β plaque levels in transgenic amyloid precursor protein (*App*⁺) mice (Ramirez et al., 2005). Intracerebroventricular administration of the synthetic cannabinoid WIN55,212-2 to rats prevents amyloid β induced microglial activation, cognitive impairment, and loss of neuronal markers (Ramirez et al., 2005).

Ablation of COX1 or COX2 with inhibitors or in COX1 or COX2 knockout mice has also been shown to be protective in neurodegenerative diseases (Aid and Bosetti, 2011). In Parkinson's disease mouse models, COX inactivation has been shown to protect against dopaminergic neurodegeneration through attenuating neuroinflammation and oxidative stress, and improving motor function (Reksidler et al., 2007; Sanchez-Pernaute et al., 2004; Teismann et al., 2003). In AD mouse models, COX inhibitors and COX1 $-/-$ mice have been shown to exhibit attenuated neuroinflammation, concordant with significant improvements in cognitive, behavioral and memory impairments and reductions in A β plaques and hyperphosphorylated tau (Choi and Bosetti, 2009; Kotilinek et al., 2008; McKee et al., 2008). Retrospective human epidemiological studies have also demonstrated protective effects or delayed onset against AD upon prolonged NSAID treatment initiated early and before disease initiation (Rogers et al., 1993; Szekely et al., 2008).

Consistent with the beneficial roles previously observed with direct cannabinoid agonists and COX inhibitors in neuroinflammation and neurodegenerative disease models, both genetic and pharmacological blockade of MAGL also exhibit anti-inflammatory effects in the brain and neuroprotective effects in mouse models of Parkinson's disease and Alzheimer's disease (Nomura et al., 2011b). Genetic and pharmacological inactivation of MAGL suppresses LPS-induced pro-inflammatory cytokine release and microglial activation not through CB1 or CB2-dependent mechanisms, but rather through lowering neuroinflammatory eicosanoid production (Nomura et al., 2011b). Consistent with this anti-inflammatory effect, we found that MAGL blockade with JZL184 or MAGL deficiency significantly protects against dopaminergic neurodegeneration and dopamine loss in an MPTP model of Parkinson's disease, concordant with suppression in pro-inflammatory eicosanoids. These effects were once again not driven through CB1 or CB2-dependent pathways, but rather presumably through lowering eicosanoids (Nomura et al., 2011b). Metabolomic profiling efforts have also uncovered elevated levels of endocannabinoids and eicosanoids in the brains of a presenilin/amyloid precursor protein (*PS1/APP*⁺) mouse model of AD. MAGL inactivation lowers the pro-inflammatory eicosanoid levels in the AD mouse model, concordant with suppression of astrocyte and microglial activation and attenuation of pro-inflammatory cytokines, leading to a substantial reduction in amyloid plaques. The eicosanoid and cytokine-lowering effects in this AD mouse model were not reversed upon CB1 and CB2 antagonist treatment, likely indicating that the neuroprotective effects observed were through eicosanoid lowering effects (Piro et al., 2012).

Collectively, MAGL inhibitors exhibit antinociceptive and anti-inflammatory effects through simultaneously enhancing endocannabinoid and suppressing eicosanoid levels in the brain. The lack of a cannabinoid component in the protective response observed with MAGL inhibitors in the Parkinson's disease or AD mouse models may be due to the functional desensitization of the cannabinoid system upon chronic MAGL blockade (Schlosburg et al., 2010).

The Role of MAGL in Anxiety

Both cannabinoid receptor agonists and FAAH-selective inhibitors that enhance anandamide or CB1 signaling provide anti-anxiety effects in rodents (Zanettini et al., 2011). Multiple studies have shown that MAGL blockade by JZL184 also exert anxiolytic responses. In a marble burying model of repetitive and compulsive behavior inherent to anxiety disorders, MAGL blockade reduced marble burying at doses that did not affect motility, on-par with the activity observed with FAAH inhibitor or tetrahydrocannabinol administration, in a CB1-dependent manner (Kinsey et al., 2011c). MAGL blockade also exerts anxiolytic effects in an elevated plus maze paradigm for anxiety, showing increased percentage open arm time and number of open arm entries under high, but not low, levels of environmental

aversiveness (Sciolino et al., 2011). Sumislawski et al showed that chronic MAGL blockade prevented chronic stress-induced anxiety-like behavior and emergence of long-term depression of GABAergic transmission, indicating that enhanced endocannabinoid signaling prevents behavioral and synaptic adaptations to chronic stress that underlies the development and worsening of affective disorders (Sumislawski et al., 2011). Collectively, MAGL inhibitors show promise, much like FAAH inhibitors or direct cannabinoid agonists, in reducing anxiety.

MAGL in Cancer and Cancer-Related Symptoms

Beyond their anti-nociceptive, analgesic, and anxiolytic effects, cannabinoid receptor agonists also exhibit anti-cancer effects through inducing apoptosis *in vitro* and angiogenesis and metastasis *in vivo* (Guzman, 2003). In addition to direct effects upon cancer, cannabinoids have been clinically used to relieve chemotherapy side effects like nausea, pain, and lack of appetite (Guzman, 2003). COX2-mediated prostaglandin production has been implicated in cancer progression and genetic or pharmacologic inactivation of COX has been shown to curb cancer malignancy (Bos et al., 2009; Cathcart et al., 2011; Schneider and Pozzi, 2011).

Previous studies have shown that 2-AG or derivatives such as nolandin ether, as well as inhibitors of 2-AG hydrolysis exert anti-proliferative activity and reduction in prostate cancer cell invasiveness (Nithipatikom et al., 2004; Nithipatikom et al., 2005; Nithipatikom et al., 2011). MAGL is upregulated in aggressive human cancer cells and primary tumors where it has a unique role of providing lipolytic sources of free fatty acids (FFAs) for synthesis of oncogenic signaling lipids that promote cancer aggressiveness. We have shown that MAGL blockade in aggressive breast, ovarian, and melanoma cancer cells impairs cell migration, invasiveness, and tumorigenicity through lowering FFAs and protumorigenic signaling lipids, which include lysophosphatidic acid and prostaglandins (Kopp et al., 2010), rather than enhancing endocannabinoid signaling. In contrast, we showed that in prostate cancer, MAGL inhibitors impair prostate cancer pathogenicity through simultaneously enhancing anti-tumorigenic cannabinoid pathways while lowering FFA-derived protumorigenic lipid signals (Nomura et al., 2011a). Other studies have shown that MAGL inhibitors impair colorectal cancer tumorigenesis (Ye et al., 2011).

Consistent with clinical utility of direct cannabinoid agonists towards relieving physical symptoms associated with cancer and chemotherapy, MAGL blockade or 2-AG administration by intraplantar injection peripherally enhances 2-AG levels and exerts anti-hyperalgesic effects in a CB2-dependent mechanism in a mouse model of mechanical hyperalgesia evoked by the growth of a fibrosarcoma tumor in and around the calcaneus bone (Khasabova et al., 2011). MAGL blockade also shows anti-emetic and anti-nausea effects in a lithium chloride model of vomiting in shrews (Sticht et al., 2012).

Thus, beyond the physiological roles of MAGL in mediated endocannabinoid signaling, MAGL in cancer plays a distinct role in modulating the fatty acid precursor pools for synthesis of protumorigenic signaling lipids in malignant human cancer cells. MAGL inhibitors therefore show promise in curbing the malignancy of aggressive human cancer cells as well as alleviating cancer-associated symptoms such as pain and nausea.

MAGL Inhibitors in Addiction

The endocannabinoid system has been shown to modulate drug addiction (Parolaro and Rubino, 2008). MAGL blockade, through enhancing endocannabinoid levels, has also been shown to reduce precipitated withdrawal responses in certain paradigms. Both the cannabinoid receptor agonist Δ^9 -tetrahydrocannabinol and MAGL blockade reduces the

intensity of naloxone-precipitated morphine withdrawal symptoms in mice, in a CB1-dependent manner. MAGL blockade also attenuated spontaneous withdrawal signs as well as ilea contractions in morphine-dependent mice (Ramesh et al., 2011). Acute administration of MAGL or FAAH with JZL184 or URB597, respectively, also significantly attenuates rimonabant-precipitated withdrawal signs in THC-dependent mice (Schlosburg et al., 2009). Many motivated and addiction-related behaviors are sustained by activity of both dopamine D1 and D2-type receptors as well as CB1 receptors in the nucleus accumbens. Seif et al showed that MAGL blockade allowed subthreshold levels of D1 and D2 receptor agonists to enhance receptor firing indicating that nucleus accumbens core 2-AG signaling mediates dopamine receptor enhancement of firing, which provides a potential cellular mechanism underlying the interconnectivity between cannabinoid, dopaminergic, and glutamatergic pathways in drug-seeking behaviors (Seif et al., 2011). Collectively, MAGL inhibitors may have utility in modulating drug dependence of opiates and THC.

Advantages and Potential Liabilities of MAGL Inhibitors

So far, this review has discussed the many potential benefits of blocking MAGL and modulating multiple lipid signaling pathways to modulate disease etiology. However, studies have also shown that chronic MAGL ablation produces functional antagonism of the endocannabinoid system and mild physical dependence, and impaired endocannabinoid-dependent synaptic plasticity (Schlosburg et al., 2010). This is in contrast to fatty acid amide hydrolase (FAAH) inhibitors that block the hydrolysis of the other endocannabinoid anandamide, to produce sustained CB1-dependent analgesia without receptor desensitization. These results are of potential concern since CB1 receptor antagonists, such as rimonabant were withdrawn from clinical use towards treating obesity, due to increased anxiety, depression, and suicidal tendencies (Moreira et al., 2009). However, recent studies provide evidence that this functional antagonism associated with chronic MAGL blockade may be avoided by partially blocking MAGL. Busquets-Garcia et al show that partial blockade of MAGL by administering low dose of JZL184 exerts antinociceptive and anxiolytic responses that are maintained under chronic treatment (Busquets-Garcia et al., 2011).

Furthermore, MAGL inhibitors provide the added benefit of lowering pro-inflammatory eicosanoids to produce anti-inflammatory and neuroprotective responses and modulating a fatty acid network in malignant cancer cells to curb cancer cell pathogenicity. Because MAGL inhibitors do not exert control over AA and prostaglandin pathways in the gastrointestinal system, they also do not exhibit the gastrointestinal toxicity commonly associated with COX1/COX2 inhibitors (Nomura et al., 2011b). In fact, Kinsey et al showed that MAGL blockade protects against gastrointestinal bleeding caused by diclofenac, a dual COX1/COX2 inhibitor, through CB1-dependent mechanisms (Kinsey et al., 2011b).

Future Therapeutic Potential of MAGL Inhibitors

MAGL inhibitors provide many of the beneficial effects observed with direct cannabinoid receptor agonists or COX inhibitors without exerting their respective unwanted side-effects. Here, we review how MAGL blockade, through coordinately enhancing endocannabinoid signaling or suppressing eicosanoid production, attenuates pain, anxiety, nausea, inflammation, neurodegeneration, precipitated opioid or cannabis withdrawal responses, and cancer pathogenicity. Since inflammation underlies a host of pathologies for which both cannabinoid agonists and COX inhibitors have shown neuroprotective roles, we anticipate that future studies will likely show that MAGL inhibitors may also provide protective and therapeutic benefit towards multiple diseases having an inflammatory component such as multiple sclerosis, stroke, ischemia/reperfusion injuries, and fibrosis.

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References

- Ahn K, McKinney MK, Cravatt BF. Enzymatic pathways that regulate endocannabinoid signaling in the nervous system. *Chemical reviews*. 2008; 108:1687–1707. [PubMed: 18429637]
- Aid S, Bosetti F. Targeting cyclooxygenases-1 and -2 in neuroinflammation: Therapeutic implications. *Biochimie*. 2011; 93:46–51. [PubMed: 20868723]
- Alhouayek M, Lambert DM, Delzenne NM, Cani PD, Muccioli GG. Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2011; 25:2711–2721. [PubMed: 21551239]
- Batkai S, Osei-Hyiaman D, Pan H, El-Assal O, Rajesh M, Mukhopadhyay P, Hong F, Harvey-White J, Jafri A, Hasko G, et al. Cannabinoid-2 receptor mediates protection against hepatic ischemia/reperfusion injury. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2007; 21:1788–1800. [PubMed: 17327359]
- Blankman JL, Simon GM, Cravatt BF. A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. *Chem Biol*. 2007; 14:1347–1356. [PubMed: 18096503]
- Bonventre JV, Huang Z, Taheri MR, O'Leary E, Li E, Moskowitz MA, Sapirstein A. Reduced fertility and postischemic brain injury in mice deficient in cytosolic phospholipase A2. *Nature*. 1997; 390:622–625. [PubMed: 9403693]
- Bos PD, Zhang XHF, Nadal C, Shu WP, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA, et al. Genes that mediate breast cancer metastasis to the brain. *Nature*. 2009; 459:1005–U1137. [PubMed: 19421193]
- Bridges D, Ahmad K, Rice AS. The synthetic cannabinoid WIN55, 212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. *British journal of pharmacology*. 2001; 133:586–594. [PubMed: 11399676]
- Buczynski MW, Dumlao DS, Dennis EA. An integrated omics analysis of eicosanoid biology (vol 50, pg 1015, 2009). *Journal of lipid research*. 2009; 50:1505–1505.
- Busquets-Garcia A, Puighermanal E, Pastor A, de la Torre R, Maldonado R, Ozaita A. Differential role of anandamide and 2-arachidonoylglycerol in memory and anxiety-like responses. *Biological psychiatry*. 2011; 70:479–486. [PubMed: 21684528]
- Cathcart MC, Lysaght J, Pidgeon GP. Eicosanoid signalling pathways in the development and progression of colorectal cancer: novel approaches for prevention/intervention. *Cancer metastasis reviews*. 2011; 30:363–385. [PubMed: 22134655]
- Chanda PK, Gao Y, Mark L, Btesh J, Strassle BW, Lu PM, Piesla MJ, Zhang MY, Bingham B, Uveges A, et al. Monoacylglycerol Lipase Activity Is a Critical Modulator of the Tone and Integrity of the Endocannabinoid System. *Molecular pharmacology*. 2010; 78:996–1003. [PubMed: 20855465]
- Choi SH, Bosetti F. Cyclooxygenase-1 null mice show reduced neuroinflammation in response to beta-amyloid. *Aging-Us*. 2009; 1:234–244.
- Chung YC, Bok E, Huh SH, Park JY, Yoon SH, Kim SR, Kim YS, Maeng S, Park SH, Jin BK. Cannabinoid receptor type 1 protects nigrostriatal dopaminergic neurons against MPTP neurotoxicity by inhibiting microglial activation. *J Immunol*. 2011; 187:6508–6517. [PubMed: 22079984]
- Costa B, Colleoni M, Conti S, Trovato AE, Bianchi M, Sotgiu ML, Giagnoni G. Repeated treatment with the synthetic cannabinoid WIN 55,212-2 reduces both hyperalgesia and production of pronociceptive mediators in a rat model of neuropathic pain. *British journal of pharmacology*. 2004; 141:4–8. [PubMed: 14662732]
- Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, Lichtman AH. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking

- fatty acid amide hydrolase. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98:9371–9376. [PubMed: 11470906]
- Di Marzo V. A brief history of cannabinoid and endocannabinoid pharmacology as inspired by the work of British scientists. *Trends Pharmacol Sci*. 2006; 27:134–140. [PubMed: 16476494]
- Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. *Nature reviews Drug discovery*. 2004; 3:771–784.
- Dinarello CA. Anti-inflammatory Agents: Present and Future. *Cell*. 2010; 140:935–950. [PubMed: 20303881]
- Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, Kathuria S, Piomelli D. Brain monoglyceride lipase participating in endocannabinoid inactivation. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99:10819–10824. [PubMed: 12136125]
- Dinh TP, Kathuria S, Piomelli D. RNA interference suggests a primary role for monoacylglycerol lipase in the degradation of the endocannabinoid 2-arachidonoylglycerol. *Molecular pharmacology*. 2004; 66:1260–1264. [PubMed: 15272052]
- Fox A, Kessingland A, Gentry C, McNair K, Patel S, Urban L, James I. The role of central and peripheral Cannabinoid1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. *Pain*. 2001; 92:91–100. [PubMed: 11323130]
- Fox SH, Henry B, Hill M, Crossman A, Brotchie J. Stimulation of cannabinoid receptors reduces levodopa-induced dyskinesia in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*. 2002; 17:1180–1187. [PubMed: 12465055]
- Gao Y, Vasilyev DV, Goncalves MB, Howell FV, Hobbs C, Reisenberg M, Shen R, Zhang MY, Strassle BW, Lu P, et al. Loss of retrograde endocannabinoid signaling and reduced adult neurogenesis in diacylglycerol lipase knock-out mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2010; 30:2017–2024. [PubMed: 20147530]
- Garcia-Arencibia M, Gonzalez S, de Lago E, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. *Brain research*. 2007; 1134:162–170. [PubMed: 17196181]
- Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell*. 2010; 140:918–934. [PubMed: 20303880]
- Guindon J, Guijarro A, Piomelli D, Hohmann AG. Peripheral antinociceptive effects of inhibitors of monoacylglycerol lipase in a rat model of inflammatory pain. *British journal of pharmacology*. 2011; 163:1464–1478. [PubMed: 21198549]
- Guzman M. Cannabinoids: potential anticancer agents. *Nature reviews Cancer*. 2003; 3:745–755.
- Ibrahim MM, Deng H, Zvonok A, Cockayne DA, Kwan J, Mata HP, Vanderah TW, Lai J, Porreca F, Makriyannis A, et al. Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100:10529–10533. [PubMed: 12917492]
- Jaworski K, Ahmadian M, Duncan RE, Sarkadi-Nagy E, Varady KA, Hellerstein MK, Lee HY, Samuel VT, Shulman GI, Kim KH, et al. AdPLA ablation increases lipolysis and prevents obesity induced by high-fat feeding or leptin deficiency. *Nature medicine*. 2009; 15:159–168.
- Khasabova IA, Chandiramani A, Harding-Rose C, Simone DA, Seybold VS. Increasing 2-arachidonoyl glycerol signaling in the periphery attenuates mechanical hyperalgesia in a model of bone cancer pain. *Pharmacological research : the official journal of the Italian Pharmacological Society*. 2011; 64:60–67. [PubMed: 21440630]
- Kinsey SG, Long JZ, O'Neal ST, Abdullah RA, Poklis JL, Boger DL, Cravatt BF, Lichtman AH. Blockade of endocannabinoid-degrading enzymes attenuates neuropathic pain. *The Journal of pharmacology and experimental therapeutics*. 2009; 330:902–910. [PubMed: 19502530]
- Kinsey SG, Mahadevan A, Zhao BJ, Sun H, Naidu PS, Razdan RK, Selley DE, Damaj MI, Lichtman AH. The CB(2) cannabinoid receptor-selective agonist O-3223 reduces pain and inflammation

without apparent cannabinoid behavioral effects. *Neuropharmacology*. 2011a; 60:244–251. [PubMed: 20849866]

- Kinsey SG, Nomura DK, O'Neal ST, Long JZ, Mahadevan A, Cravatt BF, Grider JR, Lichtman AH. Inhibition of monoacylglycerol lipase attenuates nonsteroidal anti-inflammatory drug-induced gastric hemorrhages in mice. *The Journal of pharmacology and experimental therapeutics*. 2011b; 338:795–802. [PubMed: 21659471]
- Kinsey SG, O'Neal ST, Long JZ, Cravatt BF, Lichtman AH. Inhibition of endocannabinoid catabolic enzymes elicits anxiolytic-like effects in the marble burying assay. *Pharmacology, biochemistry, and behavior*. 2011c; 98:21–27.
- Kopp F, Komatsu T, Nomura DK, Trauger SA, Thomas JR, Siuzdak G, Simon GM, Cravatt BF. The glycerophospho metabolome and its influence on amino acid homeostasis revealed by brain metabolomics of GDE1(–/–) mice. *Chemistry & biology*. 2010; 17:831–840. [PubMed: 20797612]
- Kotilinek LA, Westerman MA, Wang Q, Panizzon K, Lim GP, Simonyi A, Lesne S, Falinska A, Younkin LH, Younkin SG, et al. Cyclooxygenase-2 inhibition improves amyloid-beta-mediated suppression of memory and synaptic plasticity. *Brain : a journal of neurology*. 2008; 131:651–664. [PubMed: 18292081]
- Ligresti A, Petrosino S, Di Marzo V. From endocannabinoid profiling to 'endocannabinoid therapeutics'. *Current opinion in chemical biology*. 2009; 13:321–331. [PubMed: 19497779]
- Long JZ, Cravatt BF. The Metabolic Serine Hydrolases and Their Functions in Mammalian Physiology and Disease. *Chemical reviews*. 2011; 111:6022–6063. [PubMed: 21696217]
- Long JZ, Li W, Booker L, Burston JJ, Kinsey SG, Schlosburg JE, Pavon FJ, Serrano AM, Selley DE, Parsons LH, et al. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. *Nature chemical biology*. 2009a; 5:37–44.
- Long JZ, Nomura DK, Cravatt BF. Characterization of monoacylglycerol lipase inhibition reveals differences in central and peripheral endocannabinoid metabolism. *Chem Biol*. 2009b; 16:744–753. [PubMed: 19635411]
- Long JZ, Nomura DK, Vann RE, Walentiny DM, Booker L, Jin X, Burston JJ, Sim-Selley LJ, Lichtman AH, Wiley JL, et al. Dual blockade of FAAH and MAGL identifies behavioral processes regulated by endocannabinoid crosstalk in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2009c; 106:20270–20275. [PubMed: 19918051]
- McKee AC, Carreras I, Hossain L, Ryu H, Klein WL, Oddo S, LaFerla FM, Jenkins BG, Kowall NW, Dedeoglu A. Ibuprofen reduces Abeta, hyperphosphorylated tau and memory deficits in Alzheimer mice. *Brain Res*. 2008; 1207:225–236. [PubMed: 18374906]
- Mechoulam R, Benshabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR, et al. Identification of an Endogenous 2-Monoglyceride, Present in Canine Gut, That Binds to Cannabinoid Receptors. *Biochem Pharmacol*. 1995; 50:83–90. [PubMed: 7605349]
- Miner J, Hoffhines A. The discovery of aspirin's antithrombotic effects. *Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital*. 2007; 34:179–186.
- Mitchell JA, Warner TD. COX isoforms in the cardiovascular system: understanding the activities of non-steroidal anti-inflammatory drugs. *Nature reviews Drug discovery*. 2006; 5:75–86.
- Moreira FA, Grieb M, Lutz B. Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression. *Best practice & research Clinical endocrinology & metabolism*. 2009; 23:133–144. [PubMed: 19285266]
- Nithipatikom K, Endsley MP, Isbell MA, Falck JR, Iwamoto Y, Hillard CJ, Campbell WB. 2-arachidonoylglycerol: A novel inhibitor of androgen-independent prostate cancer cell invasion. *Cancer Res*. 2004; 64:8826–8830. [PubMed: 15604240]
- Nithipatikom K, Endsley MP, Isbell MA, Wheelock CE, Hammock BD, Campbell WB. A new class of inhibitors of 2-arachidonoylglycerol hydrolysis and invasion of prostate cancer cells. *Biochem Bioph Res Co*. 2005; 332:1028–1033.
- Nithipatikom K, Isbell MA, Endsley MP, Woodliff JE, Campbell WB. Anti-proliferative effect of a putative endocannabinoid, 2-arachidonoylglycerol ether in prostate carcinoma cells. *Prostaglandins & other lipid mediators*. 2011; 94:34–43. [PubMed: 21167293]

- Nomura DK, Lombardi DP, Chang JW, Niessen S, Ward AM, Long JZ, Hoover HH, Cravatt BF. Monoacylglycerol Lipase Exerts Dual Control over Endocannabinoid and Fatty Acid Pathways to Support Prostate Cancer. *Chem Biol.* 2011a; 18:846–856. [PubMed: 21802006]
- Nomura DK, Morrison BE, Blankman JL, Long JZ, Kinsey SG, Marcondes MC, Ward AM, Hahn YK, Lichtman AH, Conti B, et al. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. *Science.* 2011b; 334:809–813. [PubMed: 22021672]
- Pan B, Wang W, Long JZ, Sun DL, Hillard CJ, Cravatt BF, Liu QS. Blockade of 2-Arachidonoylglycerol Hydrolysis by Selective Monoacylglycerol Lipase Inhibitor 4-Nitrophenyl 4-(Dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate (JZL184) Enhances Retrograde Endocannabinoid Signaling. *Journal of Pharmacology and Experimental Therapeutics.* 2009; 331:591–597. [PubMed: 19666749]
- Parolaro D, Rubino T. The role of the endogenous cannabinoid system in drug addiction. *Drug news & perspectives.* 2008; 21:149–157. [PubMed: 18560613]
- Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *The New England journal of medicine.* 2005; 353:2373–2383. [PubMed: 16319386]
- Piro JR, Benjamin DI, Duerr JM, Pi Y, Gonzales C, Wood KM, Schwartz JW, Nomura DK, Samad TA. A dysregulated endocannabinoid-eicosanoid network supports pathogenesis in a mouse model of Alzheimer's disease. *Cell Reports.* 2012 in press.
- Price DA, Martinez AA, Seillier A, Koek W, Acosta Y, Fernandez E, Strong R, Lutz B, Marsicano G, Roberts JL, et al. WIN55,212-2, a cannabinoid receptor agonist, protects against nigrostriatal cell loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *The European journal of neuroscience.* 2009; 29:2177–2186. [PubMed: 19490092]
- Quartilho A, Mata HP, Ibrahim MM, Vanderah TW, Porreca F, Makriyannis A, Malan TP. Inhibition of inflammatory hyperalgesia by activation of peripheral CB2 cannabinoid receptors. *Anesthesiology.* 2003; 99:955–960. [PubMed: 14508331]
- Ramesh D, Ross GR, Schlosburg JE, Owens RA, Abdullah RA, Kinsey SG, Long JZ, Nomura DK, Sim-Selley LJ, Cravatt BF, et al. Blockade of endocannabinoid hydrolytic enzymes attenuates precipitated opioid withdrawal symptoms in mice. *The Journal of pharmacology and experimental therapeutics.* 2011; 339:173–185. [PubMed: 21719468]
- Ramirez BG, Blazquez C, Gomez del Pulgar T, Guzman M, de Ceballos ML. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2005; 25:1904–1913. [PubMed: 15728830]
- Reksidler AB, Lima MM, Zanata SM, Machado HB, da Cunha C, Andreatini R, Tufik S, Vital MA. The COX-2 inhibitor parecoxib produces neuroprotective effects in MPTP-lesioned rats. *European journal of pharmacology.* 2007; 560:163–175. [PubMed: 17320073]
- Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, Zaluski J, Cofield M, Mansukhani L, Willson P, et al. Clinical trial of indomethacin in Alzheimer's disease. *Neurology.* 1993; 43:1609–1611. [PubMed: 8351023]
- Romero J, Orgado JM. Cannabinoids and neurodegenerative diseases. *CNS & neurological disorders drug targets.* 2009; 8:440–450. [PubMed: 19839933]
- Rouzer CA, Marnett LJ. Endocannabinoid Oxygenation by Cyclooxygenases, Lipoxygenases, and Cytochromes P450: Cross-Talk between the Eicosanoid and Endocannabinoid Signaling Pathways. *Chemical reviews.* 2011; 111:5899–5921. [PubMed: 21923193]
- Sanchez-Pernaute R, Ferree A, Cooper O, Yu M, Brownell AL, Isacson O. Selective COX-2 inhibition prevents progressive dopamine neuron degeneration in a rat model of Parkinson's disease. *Journal of neuroinflammation.* 2004; 1:6. [PubMed: 15285796]
- Schlosburg JE, Blankman JL, Long JZ, Nomura DK, Pan B, Kinsey SG, Nguyen PT, Ramesh D, Booker L, Burston JJ, et al. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. *Nature neuroscience.* 2010; 13:1113–1119.
- Schlosburg JE, Carlson BL, Ramesh D, Abdullah RA, Long JZ, Cravatt BF, Lichtman AH. Inhibitors of endocannabinoid-metabolizing enzymes reduce precipitated withdrawal responses in THC-dependent mice. *The AAPS journal.* 2009; 11:342–352. [PubMed: 19430909]

- Schneider C, Pozzi A. Cyclooxygenases and lipoxygenases in cancer. *Cancer Metast Rev.* 2011; 30:277–294.
- Sciolino NR, Zhou W, Hohmann AG. Enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-arachidonoylglycerol hydrolyzing enzyme monoacylglycerol lipase, produces anxiolytic effects under conditions of high environmental aversiveness in rats. *Pharmacological research : the official journal of the Italian Pharmacological Society.* 2011; 64:226–234. [PubMed: 21600985]
- Scotter EL, Abood ME, Glass M. The endocannabinoid system as a target for the treatment of neurodegenerative disease. *British journal of pharmacology.* 2010; 160:480–498. [PubMed: 20590559]
- Seif T, Makriyannis A, Kunos G, Bonci A, Hopf FW. The endocannabinoid 2-arachidonoylglycerol mediates D1 and D2 receptor cooperative enhancement of rat nucleus accumbens core neuron firing. *Neuroscience.* 2011; 193:21–33. [PubMed: 21821098]
- Sticht MA, Long JZ, Rock EM, Limebeer CL, Mechoulam R, Cravatt BF, Parker LA. Inhibition of monoacylglycerol lipase attenuates vomiting in *Suncus murinus* and 2-arachidonoyl glycerol attenuates nausea in rats. *British journal of pharmacology.* 2012; 165:2425–2435. [PubMed: 21470205]
- Straiker A, Hu SSJ, Long JZ, Arnold A, Wager-Miller J, Cravatt BF, Mackie K. Monoacylglycerol Lipase Limits the Duration of Endocannabinoid-Mediated Depolarization-Induced Suppression of Excitation in Autaptic Hippocampal Neurons. *Molecular pharmacology.* 2009; 76:1220–1227. [PubMed: 19767452]
- Straiker A, Mackie K. Cannabinoid Signaling in Inhibitory Autaptic Hippocampal Neurons. *Neuroscience.* 2009; 163:190–201. [PubMed: 19501632]
- Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun.* 1995; 215:89–97. [PubMed: 7575630]
- Sumislowski JJ, Ramikie TS, Patel S. Reversible gating of endocannabinoid plasticity in the amygdala by chronic stress: a potential role for monoacylglycerol lipase inhibition in the prevention of stress-induced behavioral adaptation. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2011; 36:2750–2761. [PubMed: 21849983]
- Szabo B, Urbanski MJ, Bisogno T, Di Marzo V, Mendiguren A, Baer WU, Freiman I. Depolarization-induced retrograde synaptic inhibition in the mouse cerebellar cortex is mediated by 2-arachidonoylglycerol. *J Physiol-London.* 2006; 577:263–280. [PubMed: 16973696]
- Szekely CA, Breitner JCS, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, Zandi PP. NSAID use and dementia risk in the cardiovascular health study - Role of APOE and NSAID type. *Neurology.* 2008; 70:17–24. [PubMed: 18003940]
- Tanimura A, Yamazaki M, Hashimoto Y, Uchigashima M, Kawata S, Abe M, Kita Y, Hashimoto K, Shimizu T, Watanabe M, et al. The endocannabinoid 2-arachidonoylglycerol produced by diacylglycerol lipase α mediates retrograde suppression of synaptic transmission. *Neuron.* 2010; 65:320–327. [PubMed: 20159446]
- Teismann P, Tieu K, Choi DK, Wu DC, Naini A, Hunot S, Vila M, Jackson-Lewis V, Przedborski S. Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. *Proceedings of the National Academy of Sciences of the United States of America.* 2003; 100:5473–5478. [PubMed: 12702778]
- Tuma RF, Steffens S. Targeting the endocannabinoid system to limit myocardial and cerebral ischemic and reperfusion injury. *Current pharmaceutical biotechnology.* 2012; 13:46–58. [PubMed: 21470162]
- Valenzano KJ, Tafesse L, Lee G, Harrison JE, Boulet JM, Gottshall SL, Mark L, Pearson MS, Miller W, Shan S, et al. Pharmacological and pharmacokinetic characterization of the cannabinoid receptor 2 agonist, GW405833, utilizing rodent models of acute and chronic pain, anxiety, ataxia and catalepsy. *Neuropharmacology.* 2005; 48:658–672. [PubMed: 15814101]
- Ye L, Zhang B, Seviour EG, Tao KX, Liu XH, Ling Y, Chen JY, Wang GB. Monoacylglycerol lipase (MAGL) knockdown inhibits tumor cells growth in colorectal cancer. *Cancer Lett.* 2011; 307:6–17. [PubMed: 21543155]

Zanettini C, Panlilio LV, Alicki M, Goldberg SR, Haller J, Yasar S. Effects of endocannabinoid system modulation on cognitive and emotional behavior. *Frontiers in behavioral neuroscience*. 2011; 5:57. [PubMed: 21949506]

Figure 1. MAGL coordinately regulates multiple lipid signaling pathways

MAGL blockade leads to an accumulation of the endocannabinoid 2-AG to enhance signaling upon cannabinoid receptors CB1 and CB2. In certain tissues, such as brain, liver, and lung, MAGL controls the primary AA precursor pool for pro-inflammatory prostaglandin production. Blocking MAGL thus leads to a variety of beneficial effects through either enhancing endocannabinoid signaling or suppressing eicosanoid production. In cancer, MAGL plays a distinct role in controlling global FFAs levels that serve as the building blocks for synthesis of pro-tumorigenic signaling lipids such as PGE2 and lysophosphatidic acid (LPA). Blocking MAGL in aggressive cancer cells leads to a reduction in FFAs and attenuated cancer cell pathogenicity.