NEURAL REGENERATION RESEARCH
www.nrronline.org

Endocannabinoid metabolism and Alzheimer's disease

Chu Chen*

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Unfortunately, there are no effective therapies currently available for prevention and treatment of AD. As it is clear now, the etiology of AD is multifactorial and complex. This means that development of AD is linked to multiple mechanisms or signaling pathways and that a single-target therapy for AD is likely insufficient to achieve therapeutic goals. Therefore, an ideal therapy for AD should be able to modify the disease through multiple signaling pathways. 2-Arachidonoylglycerol (2-AG) is an endogenous cannabinoid (endocannabinoid) displaying anti-inflammatory and neuroprotective properties, while its metabolites are arachidonic acid (AA) and AA-derived prostaglandins and leukotrienes, which are proinflammatory and neurotoxic (**Figure 1**). The results from recent studies show that restraining 2-AG degradation reduces neuroinflammation, Aβ formation and tau phosphorylation, maintains the synaptic integrity, and improves long-term synaptic plasticity and cognitive function in mouse models of AD (Chen et al., 2012; Piro et al., 2012; Zhang et al., 2014; Zhang and Chen, 2018; Hashem et al., 2021). These beneficial effects produced by inhibition of 2-AG metabolism result likely from enhanced 2-AG signaling and concurrently decreased eicosanoid levels as 2-AG and eicosanoids mediate multiple signaling pathways (**Figure 1**), suggesting that limiting 2-AG metabolism in the brain would be an ideal therapy for AD.

Endocannabinoids are naturally occurring lipid mediators involved in a variety of physiological, pharmacological, and pathological processes. Several lines of evidence indicate that endocannabinoids play an important role in maintaining brain homeostasis by modulating synaptic transmission and plasticity, resolving neuroinflammation, and protecting neurons from harmful insults (Chen, 2015). 2-AG is the most abundant endogenous endocannabinoid and a full agonist for cannabinoid receptor 1 and 2 (CB1R and CB2R). 2-AG is predominantly synthesized from diacylglycerol (DAG) by diacylglycerol lipases (DAGLα and β) and hydrolyzed by monoacylglycerol lipase (MAGL), α/β hydrolase domain-containing protein 6 and 12, and oxidatively metabolized by cyclooxygenase-2 when expression and activity of cyclooxygenase-2 are excessively elevated during inflammation (**Figure 1**). While 2-AG is degraded by several enzymes, it has been estimated that 85% of 2-AG in the brain is hydrolyzed by MAGL (Blankman et al., 2007), indicating the important role of MAGL in control of 2-AG levels in the brain. Recent studies provided new insights into synthesis and metabolism of 2-AG in the brain. It has been revealed that 2-AG in neurons and astrocytes is synthesized primarily through DAGLα, while it is formed in microglial cells through DAGLβ (Viader et al., 2015; Viader et al., 2016). On the other hand, MAGL is the primary enzyme hydrolyzing 2-AG in neurons and astrocytes, whereas α/β hydrolase domain-containing protein 12 is the major enzyme degrading 2-AG in microglial cells (Viader et al., 2016). This is further supported by the fact that there are no differences in the 2-AG levels between normal control mice and microglial MAGL knockout mice (Viader et al., 2015). In addition, the amount of 2-AG-generated in microglial cell only contributes a small proportion of 2-AG to the 2-AG pool in the brain (Viader et al., 2015). These results suggest that synthesis and degradation of 2-AG in the brain are cell type-specific.

The immediate metabolite of 2-AG is AA, a precursor of prostaglandins through the enzymes COX-1/2 and leukotrienes (LT4s: A4 to E4) through the enzyme arachidonate 5-lipoxygenase (LOX; **Figure 1**). While 2-AG is capable of resolving neuroinflammation and protecting neurons from harmful insults (Zhang and Chen, 2008; Du et al., 2011), AA-derived prostaglandins and leukotrienes are proinflammatory and neurotoxic. Obviously, "*a dual hit*" occurs when MAGL is inactivated, resulting in augmentation of anti-inflammatory and neuroprotective of 2-AG signaling, while concurrently lowering of proinflammatory and neurotoxic eicosanoids, suggesting that inhibition of 2-AG metabolism by inactivation of MAGL is of therapeutic potential for AD through 2-AG- and eicosanoid-mediated multiple signaling pathways (**Figure 1**). Previous studies have provided evidence supporting this assumption (Chen et al., 2012; Piro et al., 2012; Hashem et al., 2021). For instance, pharmacological inhibition of MAGL robustly reduces neuroinflammation and β-amyloid (Aβ) formation and improves synaptic and cognitive functions in amyloid precursor protein (APP) transgenic mouse models of AD (Chen et al., 2012). Likewise, genetic deletion of MAGL also results in decreases in production of proinflammatory cytokines and Aβ in APP transgenic mice (Piro et al., 2012). Since accumulation and deposition of extracellular Aβ plaques are one of the neuropathological hallmarks of AD, the neuroprotective effects of MAGL inactivation in APP transgenic mice apparently result from reduction of Aβ formation through limiting expression and transcription of β-site amyloid precursor protein cleaving enzyme 1 (Chen et al., 2012; Zhang et al., 2014). Thus, it has been proposed that MAGL is a therapeutic target for AD (Chen et al., 2012; Zhang et al., 2014). However, intracellular accumulation of neurofibrillary tangles consisting primarily of hyperphosphorylated tau proteins is another important neuropathological hallmark of AD. To ascertain generalizability of MAGL as a promising therapeutic target for AD, a recent study provides further evidence that pharmacological inactivation of MAGL mitigates neuroinflammation and tauopathies and prevents deteriorations in synaptic proteins and cognitive decline

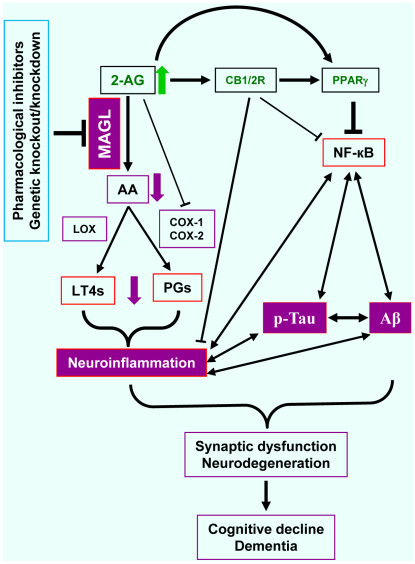

Figure 1 | Cartoon illustrating potential signaling pathways mediating enhanced 2-AG signaling in alleviation of neuropathology and improvement of cognitive function in AD.
2-AG in the brain is primarily metabolized by MAGL to AA. AA is a precursor of PGs through the enzymes COX-1/2 and LT4s through LOX. Inhibition of 2-AG metabolism by inactivation of MAGL augments 2-AG signaling, which is anti-inflammatory and neuroprotective, while concurrently reduces PGs and LT4s, which are proinflammatory and neurotoxic. The neuroprotective effects of MAGL inactivation likely result from reduced 2-AG metabolites and enhanced 2-AG levels through CB1R/CB12R-dependent and independent signaling pathways to limit the inflammatory responses, and decrease Aβ formation and tau phosphorylation, which prevent synaptic dysfunction and cognitive decline in AD. 2-AG: 2-Arachidonoylglycerol; AA: arachidonic acid; AD: Alzheimer's disease; CB1/2R: type 1 and 2 cannabinoid receptor; COX-1/2: cycloxygnase-1/2; LOX: arachidonate 5-lipoxygenase; LT4s: leukotrienes; MAGL: monoacylglycerol lipase; NF-kB: nuclear factor kappa; PGs: prostaglandins; PPARγ: peroxisome proliferator activated receptor γ.

in P301S/PS19 mice, a tau mouse model of AD (Hashem et al., 2021). Alleviation of both Aβ and tau pathologies in APP and tau mouse models of AD by inactivation of MAGL, which augments anti-inflammatory and neuroprotective 2-AG signaling and concurrently curbs proinflammatory and neurotoxic 2-AG metabolites eicosanoids, suggests that inhibition of 2-AG metabolism would be an ideal therapeutic approach for AD. Importantly, there is evidence showing elevated expression of MAGL in the brains of both patients with AD and animal models of AD (Farooqui et al., 1988; Syal et al., 2020) and reduced brain levels of 2-AG in AD mice (Maroof et al., 2014). These results indicate that escalated 2-AG metabolism may lead to the loss of brain homeostasis in AD (Chen, 2015), further supporting MAGL as a promising therapeutic target for AD.

Although the results from studies in APP and tau mouse models of AD showing resolution of neuroinflammation, amelioration of neuropathology, and improvement of cognitive function by inhibition of 2-AG metabolism are promising for MAGL as a therapeutic target for AD, several issues remain to be solved. First, no lead compounds of selective MAGL inhibitors have currently entered human clinical testing for AD therapies. This means that there remains a gap from basic science research to bedsides for MAGL as an AD therapeutic target. Second, our understanding of the mechanisms underlying MAGL inactivation-produced alleviation of neuropathology and improvement of synaptic and cognitive functions in AD animals is still limited. Disruption of MAGL-induced anti-inflammatory and neuroprotective effects are apparently not mediated via CB1R or CB2R as pharmacological inhibition or genetic knockout of CB1R or CB2R does not block the beneficial effects produced by inactivation of MAGL (Nomura et al., 2011; Chen et al., 2012; Piro et al., 2012; Zhang and Chen, 2018). It has been proposed that anti-inflammatory and neuroprotective effects produced by inhibition of 2-AG metabolism are as a result of the decreased 2-AG metabolites (e.g., prostaglandins) (Nomura et al., 2011). Other studies provide evidence that peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor that displays significant anti-inflammatory properties, is likely an important signaling molecule in 2-AG-mediated neuroprotective effects (Du et al., 2011; Zhang et al., 2014). 2-AG functions as an endogenous PPARγ agonist activating activity of PPARγ and promoting expression of PPARγ (Zhang et al., 2014), which in turn interacts with NF-kB, a transcription factor regulating expression of genes involved in neuroinflammation and neurodegeneration (**Figure 1**). However, exact signaling mechanisms responsible for the effects of MAGL inactivation warrant to be further elucidated. Third, as described above, expression of MAGL is elevated in AD (Farooqui et al., 1988; Syal et al., 2020), suggesting that escalated 2-AG metabolism in the brain promotes neuropathology. However, it is still not clear whether increased 2-AG degradation in promoting AD neuropathology is cell type-specific. For instance, 2-AG-derived eicosanoids largely originate from astrocytes, rather than from neurons (Viader et al., 2015). Since neuroinflammation is one of the important neuropathological features in the context of AD, 2-AG metabolism in astrocytes may play a unique role in neuropathogenesis of AD. Thus, deciphering the cell type-specific role of 2-AG metabolism in AD will further our understanding of the mechanisms underlying MAGL inactivation-produced neuroprotective effects in AD and provide a better therapeutic strategy for AD.

This work was supported by National Institutes of Health grants R01NS076815, R01MH113535, and R01AG058621 (to CC).

Chu Chen*
Department of Cellular and Integrative Physiology, School of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
***Correspondence to:** Chu Chen, PhD, chenc7@uthscsa.edu or chen502@gmail.com.
https://orcid.org/0000-0003-1287-8059 (Chu Chen)

Date of submission: June 15, 2021
Date of decision: August 13, 2021
Date of acceptance: September 9, 2021
Date of web publication: February 8, 2022

https://doi.org/10.4103/1673-5374.335153
How to cite this article: *Chen C (2022) Endocannabinoid metabolism and Alzheimer's disease. Neural Regen Res 17(9):1987-1988.*

References

Blankman JL, Simon GM, Cravatt BF (2007) A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. Chem Biol 14:1347-1356.

Chen C (2015) Homeostatic regulation of brain functions by endocannabinoid signaling. Neural Regen Res 10:691-692.

Chen R, Zhang J, Wu Y, Wang D, Feng G, Tang YP, Teng Z, Chen C (2012) Monoacylglycerol lipase is a therapeutic target for Alzheimer's disease. Cell Rep 2:1329-1339.

Du H, Chen X, Zhang J, Chen C (2011) Inhibition of COX-2 expression by endocannabinoid 2-arachidonoylglycerol is mediated via PPAR-gamma. Br J Pharmacol 163:1533-1549.

Farooqui AA, Liss L, Horrocks LA (1988) Stimulation of lipolytic enzymes in Alzheimer's disease. Ann Neurol 23:306-308.

Hashem J, Hu M, Zhang J, Gao F, Chen C (2021) Inhibition of 2-arachidonoylglycerol metabolism alleviates neuropathology and improves cognitive function in a Tau mouse model of Alzheimer's disease. Mol Neurobiol 58:4122-4133.

Maroof N, Ravipati S, Pardon MC, Barrett DA, Kendall DA (2014) Reductions in endocannabinoid levels and enhanced coupling of cannabinoid receptors in the striatum are accompanied by cognitive impairments in the AbetaPPswe/PS1DeltaE9 mouse model of Alzheimer's disease. J Alzheimers Dis 42:227-245.

Nomura DK, Morrison BE, Blankman JL, Long JZ, Kinsey SG, Marcondes MC, Ward AM, Hahn YK, Lichtman AH, Conti B, Cravatt BF (2011) Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science 334:809-813.

Piro JR, Benjamin DI, Duerr JM, Pi Y, Gonzales C, Wood KM, Schwartz JW, Nomura DK, Samad TA (2012) A dysregulated endocannabinoid-eicosanoid network supports pathogenesis in a mouse model of Alzheimer's disease. Cell Rep 1:617-623.

Syal C, Kosaraju J, Hamilton L, Aumont A, Chu A, Sarma SN, Thomas J, Seegobin M, Dilworth FJ, He L, Wondisford FE, Zimmermann R, Parent M, Fernandes K, Wang J (2020) Dysregulated expression of monoacylglycerol lipase is a marker for anti-diabetic drug metformin-targeted therapy to correct impaired neurogenesis and spatial memory in Alzheimer's disease. Theranostics 10:6337-6360.

Viader A, Ogasawara D, Joslyn CM, Sanchez-Alavez M, Mori S, Nguyen W, Conti B, Cravatt BF (2016) A chemical proteomic atlas of brain serine hydrolases identifies cell type-specific pathways regulating neuroinflammation. Elife 5:e12345.

Viader A, Blankman JL, Zhong P, Liu X, Schlosburg JE, Joslyn CM, Liu QS, Tomarchio AJ, Lichtman AH, Selley DE, Sim-Selley LJ, Cravatt BF (2015) Metabolic interplay between astrocytes and neurons regulates endocannabinoid action. Cell Rep 12:798-808.

Zhang J, Chen C (2008) Endocannabinoid 2-arachidonoylglycerol protects neurons by limiting COX-2 elevation. J Biol Chem 283:22601-22611.

Zhang J, Chen C (2018) Alleviation of neuropathology by inhibition of monoacylglycerol lipase in APP transgenic mice lacking CB2 receptors. Mol Neurobiol 55:4802-4810.

Zhang J, Hu M, Teng Z, Tang YP, Chen C (2014) Synaptic and cognitive improvements by inhibition of 2-AG metabolism are through upregulation of microRNA-188-3p in a mouse model of Alzheimer's disease. J Neurosci 34:14919-14933.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y