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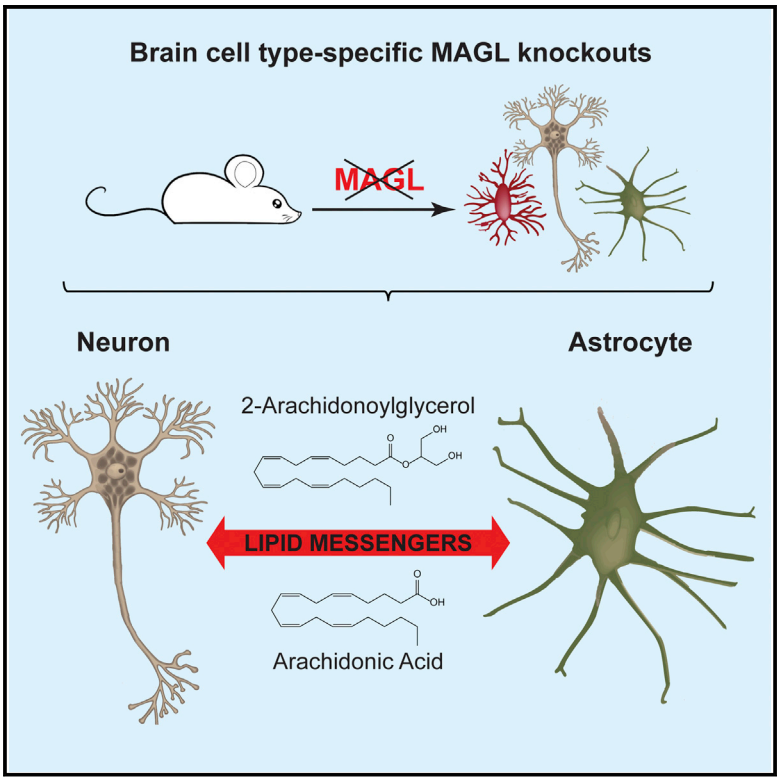
Metabolic Interplay between Astrocytes and Neurons Regulates Endocannabinoid Action

Graphical Abstract



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In Brief

The endocannabinoid 2-arachidonoylglycerol (2-AG) is a retrograde lipid messenger that broadly modulates brain synapses, neurophysiology, and behavior. Viader et al. show that endocannabinoid signaling is regulated by the cooperative, transcellular metabolism of 2-AG, which is shuttled between neurons and astrocytes.

Highlights

- Genetic mouse models reveal cellular specificity of 2-AG metabolism
- Astrocytes and neurons collaborate to terminate endocannabinoid signaling
- Coordinated astrocytic-neuronal metabolism protects against CB_1R desensitization
- Astrocytes couple 2-AG hydrolysis to neuroinflammatory prostaglandin production

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Metabolic Interplay between Astrocytes and Neurons Regulates Endocannabinoid Action

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SUMMARY

The endocannabinoid 2-arachidonoylglycerol (2-AG) is a retrograde lipid messenger that modulates synaptic function, neurophysiology, and behavior. 2-AG signaling is terminated by enzymatic hydrolysis—a reaction that is principally performed by monoacylglycerol lipase (MAGL). MAGL is broadly expressed throughout the nervous system, and the contributions of different brain cell types to the regulation of 2-AG activity in vivo remain poorly understood. Here, we genetically dissect the cellular anatomy of MAGL-mediated 2-AG metabolism in the brain and show that neurons and astrocytes coordinately regulate 2-AG content and endocannabinoid-dependent forms of synaptic plasticity and behavior. We also find that astrocytic MAGL is mainly responsible for converting 2-AG to neuroinflammatory prostaglandins via a mechanism that may involve transcellular shuttling of lipid substrates. Astrocytic-neuronal interplay thus provides distributed oversight of 2-AG metabolism and function and, through doing so, protects the nervous system from excessive CB_1 receptor activation and promotes endocannabinoid crosstalk with other lipid transmitter systems.

INTRODUCTION

Historical neuron-centric conceptualizations of brain function have given way to a deeper appreciation of the important roles played by additional brain cell types in regulating chemical transmission throughout the nervous system (McIver et al., 2013). Astrocytes are now recognized as integral components of synapses and central regulators of neurotransmission and interneuronal communication (Halassa and Haydon, 2010). Astroglial transporters clear neurotransmitters, such as glutamate and γ-amino butyric acid (GABA), from synaptic clefts to modulate the signaling activities of these chemical messengers and limit their toxic accumulation in the extracellular space (Danbolt, 2001). Metabolic pathways in astrocytes are also essential for the recycling and resupply of neurotransmitters needed to maintain sustained rounds of synaptic activity (Coulter and Eid, 2012). Moreover, defects in astrocytic functions that lead to alterations in the homeostasis of major neurotransmitters have been linked to a variety of mental and neurodegenerative disorders (Allaman et al., 2011; Halassa and Haydon, 2010). Microglia, which are resident immune cells of the nervous system, also contribute to neurotransmission through activity-dependent remodeling and pruning of synapses (Salter and Beggs, 2014; Schafer et al., 2012). Efforts to elucidate the contributions of glia to the regulation of synaptic function therefore stand to both enrich our mechanistic understanding of intercellular communication in the brain and provide new therapeutic avenues for the treatment of diverse neurological conditions.

The endogenous cannabinoid (endocannabinoid or eCB) 2-arachidonoylglycerol (2-AG) is an arachidonic acid (AA)-derived retrograde lipid messenger that broadly modulates synaptic function throughout the nervous system (Fowler et al., 2005; Kano et al., 2009; Pacher et al., 2006). 2-AG is synthesized by diacylglycerol lipases (DAGLs) (Reisenberg et al., 2012) and released in an activity-dependent manner from postsynaptic neurons to act on presynaptic G-protein-coupled cannabinoid receptors CB_1 (CB_1R) and CB_2, which are also targets of the primary psychoactive component of marijuana (Δ^9-tetrahydrocannabinol) (Mechoulam and Hanus, 2000). Principally through its activity on CB_1Rs, 2-AG inhibits neurotransmitter release and regulates diverse neurophysiological processes, including mood, nociception, appetite, and memory (Pacher et al., 2006). Enzymatic hydrolysis of 2-AG, which is primarily mediated by monoacylglycerol lipase (MAGL) in the nervous system (Dinh et al., 2002; Ueda et al., 2013), terminates CB_1R-dependent signaling (Chanda et al., 2010; Schlosburg et al., 2010; Zhong et al., 2011) and concomitantly provides a major source of AA

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