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Invited review

Synaptic functions of endocannabinoid signaling in health and disease

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ABSTRACT

Endocannabinoids (eCBs) are a family of lipid molecules that act as key regulators of synaptic transmission and plasticity. They are synthetized "on demand" following physiological and/or pathological stimuli. Once released from postsynaptic neurons, eCBs typically act as retrograde messengers to activate presynaptic type 1 cannabinoid receptors (CB_1) and induce short- or long-term depression of neurotransmitter release. Besides this canonical mechanism of action, recent findings have revealed a number of less conventional mechanisms by which eCBs regulate neural activity and synaptic function, suggesting that eCB-mediated plasticity is mechanistically more diverse than anticipated. These mechanisms include non-retrograde signaling, signaling via astrocytes, participation in long-term potentiation, and the involvement of mitochondrial CB_1. Focusing on paradigmatic brain areas, such as hippocampus, striatum, and neocortex, we review typical and novel signaling mechanisms, and discuss the functional implications in normal brain function and brain diseases. In summary, eCB signaling may lead to different forms of synaptic plasticity through activation of a plethora of mechanisms, which provide further complexity to the functional consequences of eCB signaling.

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Contents

1. Introduction

Synaptic plasticity is critical to experience-dependent adaptations of neural circuits and normal brain function. From early

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development to adulthood, changes of synaptic function in response to environmental stimuli and individual experiences are necessary to learn new abilities, form new memories and generate new adaptive behaviors. Key mediators of synaptic plasticity, the endocannabinoids (eCBs) constitute a family of lipid molecules that are typically synthetized "on demand", following either physiological and/or pathological stimuli (Castillo et al., 2012; Kano et al., 2009; Katona and Freund, 2012) (Fig. 1). The eCB signaling system comprises (1) two G protein-coupled receptors (GPCRs), known as the cannabinoid type 1 and type 2 receptors (CB_1 and CB_2); (2) one receptor channel, the transient receptor potential vanilloid type 1 (TRPV1); (3) the endogenous ligands (eCBs), of which 2-arachidonoylglycerol (2-AG) and anandamide (AEA) are the best characterized; and (4) synthetic and degradative enzymes and transporters that regulate eCB levels (Piomelli, 2003). 2-AG originates from the metabolism of triacylglycerols by the activity of diacylglycerol (DAG) lipase in response to activation of metabotropic receptors coupled to the PLCβ (e.g. group I metabotropic glutamate receptor-mGluR1/5, muscarinic acetylcoline-mAChtypes M1/M3). The biosynthesis of AEA from the precursor *N*-arachidonoyl-phosphatidylethanolamine (NAPE) requires intracellular Ca^{2+} elevations upon depolarization and/or activation of ionotropic receptors, and the activity of the enzyme NAPE-PLD. Once released from the postsynaptic neurons, eCBs act primarily as retrograde messengers by activating presynaptic CB_1 receptors, one of the most abundant $G_{i/o}$ protein-coupled receptor in the brain. CB_1 activation decreases the probability of neurotransmitter release by diverse mechanisms, including presynaptic inhibition of Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs), activation of presynaptic K^+ channels and cAMP/PKA signaling (Castillo et al., 2012; Kano et al., 2009). Termination of synaptic eCB signaling is initiated by re-uptake followed by intracellular degradation. 2AG is degraded by the presynaptic enzyme monoacylglycerol lipase (MAGL) and α/β-Hydrolase domain-containing 6 (ABHD6) (Dinh et al., 2002; Marrs et al., 2010), whereas AEA from the fatty acid amide hydrolase (FAAH) (Ahn et al., 2008; Di Marzo, 2009). There is also evidence that both 2-AG and AEA can act in a non-retrograde manner (Castillo et al., 2012), 2-AG by activating postsynaptic CB_1 or CB_2, and AEA by activating TRPV1.

Furthermore, eCBs released by neurons can modulate presynaptic and postsynaptic circuit elements through the activation of CB_1 expressed on astrocytes (Metna-Laurent and Marsicano, 2015; Navarrete et al., 2014). Regulation of synaptic transmission that follows eCB mobilization occurs both on a short and long timescale. eCB-mediated short-term changes in synaptic transmission (tens of seconds) encompass depolarization-induced suppression of excitation (DSE) and inhibition (DSI) depending on whether eCBs target glutamatergic or GABAergic terminals (Castillo et al., 2012; Kano et al., 2009). Long-term synaptic changes (minute to hour) that depend upon eCB signaling can occur in response to diverse patterns of presynaptic and/or postsynaptic activity. Thus, eCBs are powerful regulators of synaptic function through the brain. By modulating both excitatory and inhibitory synaptic strength, eCBs can regulate a number of brain functions, including cognition,

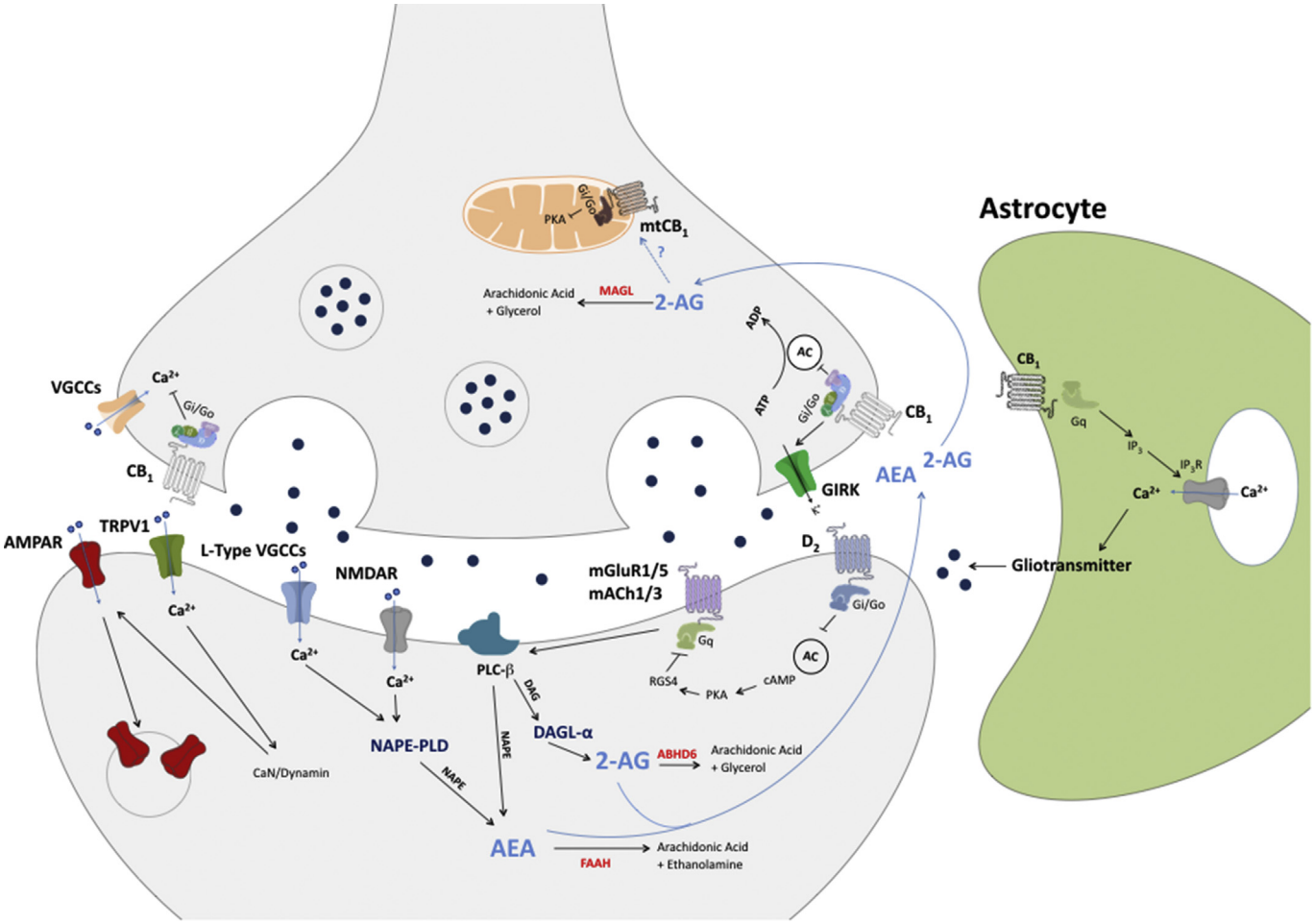

Fig. 1. Schematic of eCB signaling at the synapse.