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Signalling networks in focus

Endocannabinoid signalling in neuronal migration☆

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ABSTRACT

The endocannabinoid (eCB) system consists of several endogenous lipids, their target CB1 and CB2 receptors and enzymes responsible for their synthesis and degradation. The most abundant eCB in the central nervous system (CNS), 2-arachidonoyl glycerol (2-AG), triggers a broad range of signalling events by acting on CB1, the most abundant G protein-coupled receptor in the CNS. The eCB system regulates many physiological processes including neurogenesis, axon guidance and synaptic plasticity. Recent studies have highlighted an additional important role for eCB signalling in neuronal migration, which is crucial to achieve the complex architecture and efficient wiring of the CNS. Indeed, eCB signalling controls migration both pre- and post-natally, regulating interneuron positioning in the developing cortex and hippocampus and the polarised motility of stem cell-derived neuroblasts. While these effects may contribute to cognitive deficits associated with cannabis consumption, they also provide potential opportunities for endogenous stem cell-based neuroregenerative strategies.

Signalling network facts

- CB1 and CB2 are G-protein coupled receptors (GPCRs) sharing 48% sequence similarity. They are expressed in the developing and adult brain including neural progenitors and their progeny. CB1 is the most abundant GPCR in the brain and is activated by endogenous lipids, predominantly 2-arachidonoyl glycerol (2-AG) that can be synthesised on demand by enzymes-diacylglycerol lipases (DAGLs).
- eCB signalling can cross-talk with FGF, BDNF, NCAM, N-cadherin-triggered signalling pathways.
- eCB signalling triggers a large number of downstream events, including regulation of the PI3K and MAPK pathways, cAMP and intracellular calcium levels, small GTPase-dependent cytoskeletal rearrangement.
- Aberrant eCB signalling is associated with a large number of neuropsychiatric disorders and neurodegenerative diseases. Components of eCB signalling system are considered potential therapeutic targets for many conditions such as anxiety, depression, schizophrenia, Alzheimer's and Parkinson's diseases.

1. Introduction

Although the therapeutic applications of *Cannabis sativa* have been known in medicine for almost 5000 years, the identification of Δ^9-tetrahydrocannabinol (Δ^9-THC) as its main psychoactive component occurred only in the twentieth century and triggered a cascade of crucial discoveries leading to the characterisation of the endocannabinoid (eCB) signalling system (Compagnucci et al., 2013). The identification of the specific binding site of Δ^9-THC in the brain was followed by the cloning of the first endocannabinoid receptor, CB1 (Matsuda et al., 1990). Subsequently, 2-arachidonoylglycerol (2-AG), the most abundant eCB in the brain, was identified (Mechoulam et al., 1995, Sugiura et al., 1995). This was followed by the cloning of monoacylglycerol lipase (MAGL), the enzyme required for 2-AG degradation (Saario and Laitinen, 2007), and of two *sn*-1-selective diacylglycerol lipases (DAGLα and β), the enzymes responsible for 2-AG synthesis (Bisogno et al., 2003). These discoveries greatly contributed to the development of new therapeutic strategies targeting components of endocannabinoid system. Besides 2-AG, several other endogenous lipids have been proposed to function as eCBs. These include derivatives of arachidonic acid conjugated with ethanolamine or glycerol such as arachidonoylethanolamide (AEA), also known as anandamide (CB1/CB2 agonist), noladin ether (CB1 agonist), virodhamine (CB1 antagonist/CB2 agonist) (Bisogno et al., 2005). 2-AG and anandamide, the two main eCBs found in the brain, are the best-characterised eCBs. By acting on the two $G_{i/o}$ protein-coupled cannabinoid receptors (CB1 and CB2), they trigger downstream signalling cascades regulating key events in brain development like

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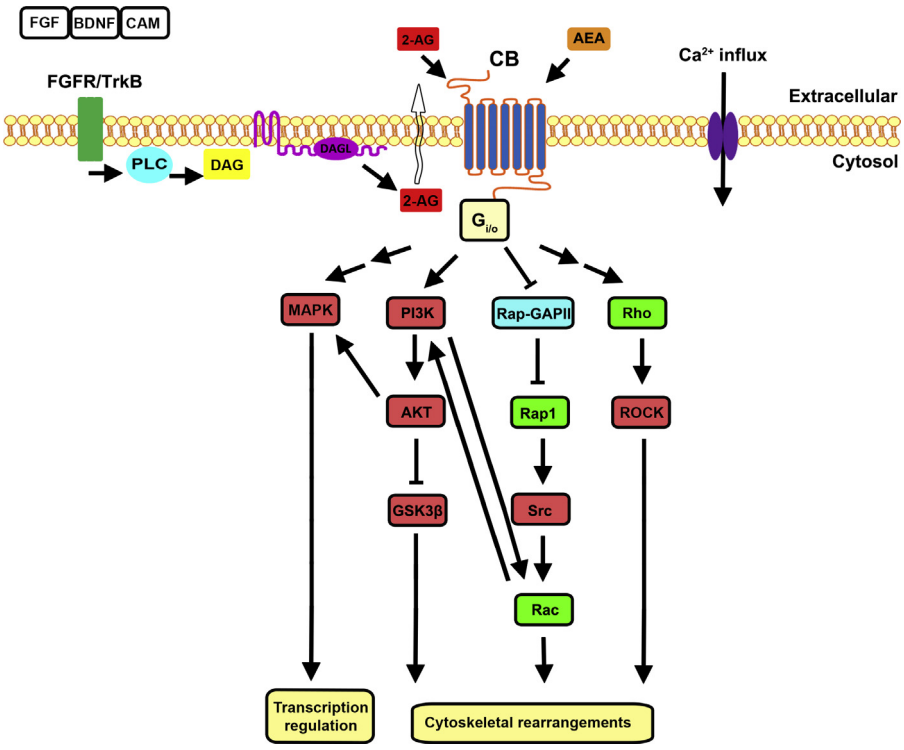

Fig. 1. An overview of the eCB signalling system in neuronal migration. DAGL-dependent local synthesis of 2-AG, the main eCB in the brain, can occur downstream of tyrosine kinase receptors (such as FGF and TrkB). Cell adhesion molecules (N-cadherin/NCAM) can also cross-talk with the FGF receptor. Following release of 2-AG (or after binding of other eCBs like anandamide), CB receptor activation can trigger stimulation of PI3K and MAPK pathways and activation of small GTPases such as Rap1, Rac and Rho, potentially regulating migration by affecting translation, adhesion and cytoskeletal rearrangement. Please see the text for further details.

axon growth and guidance, neurogenesis, and retrograde signalling at synapses (Oudin et al., 2011b). Besides these important roles, recent data have involved eCB signalling in the migration of neurons and neural progenitors of the developing and postnatal brain. Here we will provide an overview on eCB signalling focussing on the molecular pathways implicated in neuronal migration (Fig. 1) (for general reviews of eCB signalling in other systems please see (Piomelli, 2003; Bisogno et al., 2005; Ben Amar, 2006)) and describe potential therapeutic approaches targeting the eCB system in neurological disorders and brain injury.

2. Functions of eCB signalling

CB1, the cannabinoid receptor responsible for mediating the neurobehavioural effects of Δ^9-THC, is the most abundant G-protein coupled receptor in the CNS. However, it can also be found in peripheral organs such as liver and skeletal muscle (Matias and Di Marzo, 2007). CB2 is instead mainly expressed in immune system cells, however lower levels are believed to be present in some restricted areas of the CNS (Howlett et al., 2002; Duff et al., 2013). The distribution pattern of CB1 and CB2 receptors in the developing and adult brain is highly correlated with the expression of the DAGLα/β enzymes, the enzymes responsible for 2-AG synthesis (Bisogno et al., 2003; Yoshida et al., 2006; Oudin et al., 2011b), suggesting that locally synthesised 2-AG is able to trigger signalling *via* closely located CB receptors. For example, 2-AG synthesised by DAGL activates CB1 in the same presynaptic growth cone of developing axons, ensuring proper growth and guidance in the developing brain (Williams et al., 2003). Consistent with this local signalling concept, in the adult brain DAGL expression is restricted to dendritic postsynaptic compartments to release newly synthesised eCBs acting as retrograde messengers on presynaptic CB1, suppressing further transmitter release in excitatory and inhibitory synapses (Bisogno et al., 2003; Gao et al., 2010; Oudin et al., 2011b). Recent studies have also highlighted an important role of DAGL-dependent eCB signalling in adult neurogenesis, a highly adaptive form of cellular plasticity crucial for learning and memory (Gao et al., 2010; Zhao et al., 2008). Indeed, the eCB system contributes to the control of neural stem cell proliferation in the dentate gyrus of the hippocampus and the subventricular zone (SVZ), the two main neurogenic niches in the postnatal brain (Oudin et al., 2011b). For more information about cannabinoid and neurogenesis, please refer to relevant recent reviews (Mechoulam and Parker, 2013; Galve-Roperh et al., 2009; Oudin et al., 2011b).

Like proliferation, the migration of neural progenitors and newborn neurons represents a fundamental process for brain development. Remarkably, the migration of niche-derived neural progenitors persists after birth, and is essential for proper maturation and integration of newborn neurons into the pre-existing synaptic circuit (Belvindrah et al., 2011, Valiente and Marin, 2010). Two classical types of migration have been identified: radial and tangential (perpendicular and parallel to the pial surface, respectively). During brain development, an endogenous cannabinoid tone in the ventricular/subventricular zone controls neural progenitor proliferation and radial migration of immature pyramidal cells to their appropriate location in the cortical layers. Both 2-AG and anandamide could be involved in mediating these events (Mulder et al., 2008) (Fig. 2). Moreover, eCB signalling may regulate the radial migration of cortical neuron precursors derived from ganglionic eminences in the developing brain. This process ensures the targeting of neural precursors to their final location in the neocortex and hippocampus, where they differentiate into GABAergic interneurons (Berghuis et al., 2005). Interestingly, CB1 is highly expressed in a subpopulation of cholecystokinin (CCK)-containing inhibitory interneurons, which follow a complex radial and tangential migratory pattern across the telencephalon, ultimately reaching the hippocampus. This long migratory journey could entail an interaction between CB1 and reelin, another key