AXON GUIDANCE

Endocannabinoids steer developing axons

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Since the discovery of the cannabinoid receptors and their endogenous ligands — the primary endocannabinoids anandamide and 2-arachidonoylglycerol — multiple roles for endocannabinoid signalling in CNS function have emerged, leading to questions about the potential effects of cannabis on brain function and in particular on foetal brain development. Providing fresh insights into this issue, Harkany and colleagues now reveal that endocannabinoid signalling is crucial for establishing connectivity in the developing cortex.

To investigate the effects of cannabinoids on brain development, the authors examined the expression patterns of the neuronal cannabinoid receptor, CB_1R, and enzymes involved in endocannabinoid synthesis. They showed that in developing GABA (γ-aminobutyric acid)-containing interneurons, CB_1Rs are expressed on axons and axonal growth cones during developmental periods in which the interneurons migrate to their final cortical positions while simultaneously forming accurate synaptic connections. Furthermore, CB_1R expression in these interneurons was coordinated with the production of endocannabinoid-synthesizing enzymes in the dendrites of glutamatergic pyramidal cells, with which the interneurons preferentially form synaptic connections.

The authors examined the role of endocannabinoids in the formation of these connections in cultured GABA-containing interneurons. Application of anandamide caused internalization of CB_1Rs and triggered downstream signalling, including phosphorylation of ERK1/2. Stimulation of CB_1Rs with a synthetic CB_1R agonist, WIN55,212-2, induced growth cone repulsion and collapse, and neurite retraction.

To examine the molecular changes underlying this chemorepulsion, the authors examined the effects of CB_1R activation on RhoA, which mediates the cytoskeletal alterations associated with growth cone motility. WIN55,212-2 treatment increased RhoA activity in primary cortical cultures. The authors also demonstrated the involvement of Rho kinase, which is activated by RhoA: when interneuron cultures were pre-treated with a Rho kinase inhibitor, the effects of WIN55,212-2 on neurite retraction and repulsion were reversed, indicating that CB_1R-mediated chemorepulsion uses the same pathways as many other axon guidance molecules.

To determine whether CB_1Rs are involved in axon guidance *in vivo*, the authors examined adult transgenic mice in which CB_1R was specifically deleted from GABA-containing interneurons. They showed that GABA-containing interneurons in these mice were impaired in their ability to select synaptic targets, as they formed connections with many more pyramidal neurons than usual. This indicated a crucial role of endocannabinoid signalling in target selection and synaptogenesis.

This study indicates an important role for endocannabinoid signalling in the formation of accurate synaptic connections by GABA-containing interneurons. It is likely that CB_1R signalling will have a similar role in the many other neuronal subtypes in which the receptor is expressed. The study also provides a potential mechanism by which cannabis exposure in the womb might have detrimental effects on brain development by disrupting synaptic connectivity.

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