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Role of endocannabinoid signaling in a septohabenular pathway in the regulation of anxiety- and depressive-like behavior

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Abstract

Enhancing endocannabinoid signaling produces anxiolytic- and antidepressant-like effects, but the neural circuits involved remain poorly understood. The medial habenula (MHb) is a phylogenetically-conserved epithalamic structure that is a powerful modulator of anxiety- and depressive-like behavior. Here, we show that a robust endocannabinoid signaling system modulates synaptic transmission between the MHb and its sole identified GABA input, the medial septum and nucleus of the diagonal band (MSDB). With RNAscope in situ hybridization, we demonstrate that key enzymes that synthesize or degrade the endocannabinoids 2-arachidonylglycerol (2-AG) or anandamide are expressed in the MHb and MSDB, and that cannabinoid receptor 1 (CB1) is expressed in the MSDB. Electrophysiological recordings in MHb neurons revealed that endogenously-released 2-AG retrogradely depresses GABA input from the MSDB. This endocannabinoid-mediated depolarization-induced suppression of inhibition (DSI) was limited by monoacylglycerol lipase (MAGL) but not by fatty acid amide hydrolase. Anatomic and optogenetic circuit mapping indicated that MSDB GABA neurons monosynaptically project to cholinergic neurons of the ventral MHb. To test the behavioral significance of this MSDB-MHb endocannabinoid signaling, we induced MSDB-specific knockout of CB1 or MAGL via injection of virally-delivered Cre recombinase into the MSDB of $Cnr1^{loxP/loxP}$ or $Mgll^{loxP/loxP}$ mice. Relative to control mice, MSDB-specific knockout of CB1 or MAGL bidirectionally modulated 2-AG signaling in the ventral MHb and led to opposing effects on anxiety- and depressive-like behavior. Thus, depression of synaptic GABA release in the MSDB-ventral MHb pathway may represent a potential mechanism whereby endocannabinoids exert anxiolytic and antidepressant-like effects.

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