Circuit mechanisms underlying CB1R mediated suppression of dentate granule cell recruitment by cortical input

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The neuromodulatory system plays an important role in regulating synaptic plasticity, signaling environmental cues and modulating cognitive functions. The cannabinoid type 1 receptors (CB1Rs) in the dentate gyrus (DG) have been implicated in cognition and emotion, and are highly expressed in GABAergic cholecystokinin-expressing interneurons (CCK-INs) and glutamatergic hilar mossy cells. Endocannabinoids released from the post-synaptic dendrites retrogradely target the pre-synaptic CB1Rs in an activity-dependent manner, and thereby lead to a reduction of neurotransmitter release. The DG, the first station of the hippocampus, receives multimodal inputs from the cortex and processes the information to downstream hippocampal CA regions. However, how the endocannabinoid system (ECS) modulates the DG input-output transformation remains unclear.

Using *ex vivo* electrophysiological recording and pharmacological approaches, we found that activating endocannabinoid signaling by the CB1R agonist WIN 55,212-2 (5 μM) attenuated the perforant path (PP)-mediated granule cell population spikes (GC pSpikes) without affecting synaptic transmission of the PP. Moreover, CCK-INs appear to be essential for CB1R-induced suppression of GC activity because either blockade of $GABA_AR$ or chemogenetic inactivation of CCK-INs abolished the reduction of GC pSpikes after CB1R activation. The neural mechanism by which CB1R activation at CCK-INs contributes to suppression of GC responses to the cortical inputs remains unclear and awaits to be explored in the near future.