On Morpho-Physiological Features, Circuit, and Behavioral Functions of Cholecystokinin-Expressing Interneurons in the Mouse Dentate Gyrus

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The hippocampal dentate gyrus (DG) is a critical structure for learning, memory, and emotional regulation, receiving sensory inputs from multiple brain areas. Inhibitory interneurons (INs) in the DG, including those expressing cholecystokinin (CCK), play important roles in regulating hippocampal circuits and behavior. However, the subtype diversity of CCK-INs and their precise contributions to circuit function and behavior are not well understood.

Using an intersectional genetic approach, we characterized the morphology and axonal projections of CCK-INs in the DG of mice, identifying nine distinct subpopulations based on their projection targets. These CCK-IN subtypes collectively cover the entire axo-somato-dendritic axis of granule cells (GCs), the main type of excitatory neuron in the DG. CCK-INs express cannabinoid type 1 receptors (CB1Rs), which downregulate GABA release in response to endocannabinoid stimulation. At the circuit level, we found that activation of CB1Rs with a specific agonist reduced GC population spikes (pSpikes) in response to sensory input, and this effect was dependent on both GABA and CCK-INs. Moreover, chemogenetic inactivation of CCK-INs in the ventral DG decreased anxiety-like behaviors and increased sociability in mice, suggesting that these neurons play specific roles in regulating emotional behaviors. Our findings reveal the diversity of CCK-IN subtypes and their importance in regulating hippocampal circuit function and behavior, providing new insights into the cellular and molecular mechanisms underlying the DG's role in learning, memory, and emotional regulation.