Glutamate and Gaba Co-transmission at the Supramammillary-dentate Gyrus Synapses Promotes Spike-timing Precision and Long-term Potentiation

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The dentate gyrus (DG) is the first relay station of the hippocampus and composed of glutamatergic principal neurons and GABAergic inhibitory interneurons (INs). The granule cells (GCs), which are the majority of principal cells, receive inputs from the cortex and multiple subcortical regions and transfer information to the hippocampal proper. Cortico-GC pathways are known to be crucial to declarative memory and spatial navigation. However, the functional relevance of subcortical inputs to information processing at cortico-GC pathways has not been widely explored. The supramammillary nucleus (SuM) is a hypothalamic structure, in which a subset of neurons co-expressing VGLUT2 and VGAT project substantially to the DG. Although VGLUT2 and VGAT are anatomically segregated into distinct synaptic vesicles at SuM terminals, it remains unclear whether the co-transmission is target cell specific. Furthermore, the functional relevance of co-transmission onto GCs remains unclear. By combining optogenetic, electrophysiological and pharmacological approaches, we show that SuM terminals activation elicits monosynaptic composite glutamate/GABA responses onto both GCs and INs but exclusively excites dendrite-targeting GABAergic INs. Consistently, SuM-GC and SuM-soma-targeting IN synapses are dominated by the GABAergic conductance with excitation (E)/ inhibition (I) ratio <1, whereas SuM-dendrite-targeting INs synapses are largely mediated by the glutamatergic conductance (E/I>1). SuM terminals activation not only enhances GC responses but also bolsters GC spike-timing precision. Furthermore, pairing the cortical input with the SuM input at a precise time interval induces long-term enhancement of GC excitability. Taken together, these findings highlight the significance of SuM-mediated glutamate and GABA co-transmission in synaptic and network functions.

Keywords: dentate gyrus, co-transmission, optogenetics, plasticity, supramammillary nucleus

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