Differential Glutamate and GABA Release onto Hippocampal Dentate Cells by Supramammillary Nucleus Neurons

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The hippocampus is a key brain structure for cognitive and emotional behaviors. Among hippocampal subregions, the dentate gyrus (DG) is the first information processor, which receives sensory inputs from the entorhinal cortex (EC) through the perforant path (PP). Cortico-hippocampal pathways are known to be crucial for memory processing and spatial navigation. However, little is known about the functional relevance of subcortical inputs to the hippocampus. The supramammillary nucleus (SuM) is a hypothalamic structure, in which a subset of neurons project substantially to the DG and CA2/CA3a areas. Despite that the SuM-DG pathway is known to regulate hippocampal theta oscillations, learning, REM sleep and explorative locomotor activities, its neurotransmitter signaling and synaptic properties remain elusive.

By combining optogenetic tools, electrophysiological and pharmacological approaches, we found that DG-projecting SuM neurons preferentially innervate the DG granule cell layer, and form functional connections with granule cells (GCs), mossy cells (MCs) and GABAergic interneurons (INs). Optogenetic activation of channelrhodopsin2 (ChR2)-expressing SuM-DG terminals elicits monosynaptic responses of both glutamate and GABA onto single GCs and INs. Short-term plasticity of these two components are almost identical, suggesting co-release of two transmitters. Further analysis of individual connections revealed that SuM-GC and SuM-fast spiking IN synapses are dominated by GABAergic transmission (inhibition (I)/excitation (E) ratio 4.4, n = 23) whereas SuM-non-fast spiking INs synapses are largely mediated by glutamatergic transmission (I/E ratio 0.45, n = 5). Our findings suggest differential co-release of glutamate and GABA onto DG neurons by SuM neurons or differential innervation of DG neurons by distinct glutamatergic and GABAergic neurons within the SuM.