

THE NUCLEUS INCERTUS SPECIFICALLY TARGETS NEURONS RESPONSIBLE FOR THE FORMATION OF CONTEXTUAL MEMORY

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The hippocampus plays an essential role in declarative memory formation by encoding episodic memories, and establishing associations between their features. A well-known example of this hippocampal function is contextual fear conditioning (CFC), in which the subject has to associate a context (conditioned stimulus, CS) with an aversive event (unconditioned stimulus, US).

The encoding of CFC is mediated by the pyramidal cells (PC) of the hippocampal CA1 region. CA1 PCs receive the contextual information (CS) from the CA3 and the primary sensory information (US) from the entorhinal cortex, which inputs target different parts of their dendritic tree. The very delicate timing of these inputs is essential for the CA1 PCs for being able to forge an associative link between them. The GABAergic somatostatin (SOM)-positive interneurons located in the stratum oriens of the hippocampus play an essential role in the temporal regulation of these inputs. SOM cells receive glutamatergic and cholinergic excitatory inputs from the medial septum (MS). These inputs promote memory encoding and theta-generation and carry information about the state of the animal during US. The permissive role of these SOM cells is so strong that, if they are artificially inhibited directly during US presentation, mice are unable to make CFC memory traces. However, it is unknown, whether there is any natural subcortical inhibitory input targeting the hippocampal SOM cells that could prevent the formation of unnecessary contextual memories of everyday events.

Using retrograde tracing and confocal fluorescent microscopy in vesicular GABA-transporter (vGAT)-reporter mice, we found that the GABAergic cells of the pontine nucleus incertus (NI) send a strong inhibitory input to the hippocampus and MS. Cre-dependent viral anterograde tracing in vGAT-Cre mice showed that NI innervates hippocampal SOM cells very selectively, and also establishes synaptic contacts with glutamatergic and cholinergic MS cells, whereby it can decrease the activity of hippocampal SOM cells indirectly. Our correlated light and electron microscopic investigations showed that NI establishes gephyrin and GABAA receptor containing symmetrical synapses. In addition, optogenetic stimulation of NI fibers showed picrotoxin-sensitive inhibitory postsynaptic currents on hippocampal SOM interneurons and an inhibition of hippocampal sharp-waves in vitro. Post hoc reconstruction of these cells showed that these SOM positive cells are oriens-lacunosum moleculare (O-LM) cells or projection interneurons.

Our results show that inhibitory neurons in the NI of the brain stem are in ideal position for effectively vetoing the activity of hippocampal SOM cells, whereby they could regulate septohippocampal theta-generation and prevent the formation of unnecessary contextual memories. Behavioral data are presentment in a parallel poster.