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Short circuit

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Researchers distinguish the roles of two similar neural circuits in the hippocampus.

Like alternate routes to get to work, several neural circuits can connect the same brain structures. Are these pathways redundant, or do they each serve different functions? Nakashiba *et al*. differentiate the functions of two hippocampal circuits in learning and memory in a recent article in *Science*.

Two parallel excitatory pathways relay information from superficial to deep layers of the entorhinal cortex through the hippocampus. In the trisynaptic pathway, information flows from layer II of the entorhinal cortex to the dentate gyrus through the perforant path. Mossy fiber axons from dentate gyrus granule cells synapse on neurons in CA3, which project to CA1 pyramidal cells through the Schaffer collaterals. Finally, CA1 neurons relay information back to layer V of the entorhinal cortex. In the monosynaptic pathway, layer III of the entorhinal cortex relays information to CA1 through the temporoammonic pathway. As in the trisynaptic pathway, projections from CA1 to layer V of the entorhinal cortex complete the monosynaptic pathway.

Tetanus toxin (TeTX) is an endopeptidase that specifically digests VAMP2, which is important in activity-dependent neurotransmitter release. To differentiate hippocampal pathways, the authors silenced synaptic transmission in the trisynaptic pathway by temporally and spatially restricted tetanus toxin expression. They generated CA3-TeTX mice by mating mice expressing the tetracycline transactivator in neurons expressing both the kainate receptor subunit KA1 and the alpha subunit of calcium/calmodulin-dependent kinase II to mice expressing tetanus toxin driven by the tetracycline operator. In the presence of the tetracycline analog doxycycline, CA3-TeTX and control mice showed similar VAMP2 expression. Without doxycycline, the authors found reduced VAMP2 immunoreactivity in Schaffer collaterals and mossy fibers. Extracellular field recordings showed reduced synaptic transmission in Schaffer collaterals but not in the temperoammonic pathway in doxycycline-withdrawn CA3-TeTX relative to control mice, suggesting impairment of the transynaptic but not the monosynaptic pathway in doxycycline-withdrawn CA3-TeTX mice.

The trisynaptic pathway is important for some types of learning. Across trials and probe tests, doxycycline-withdrawn CA3-TeTX and control mice performed similarly in the Morris water maze, suggesting that the monosynaptic pathway is sufficient for incremental spatial learning. When the authors played a shock-associated tone in an unfamiliar environment, in contrast, doxycyline-withdrawn CA3-TeTX mice froze with fear less than did control mice, suggesting deficits in rapid contextual learning. Even when preexposed to the shock chamber before doxycycline withdrawal, doxycycline-withdrawn CA3-TeTX mice showed

reduced context-dependent freezing behavior relative to control mice, suggesting deficits in pattern-completion learning.

The trisynaptic pathway is important in encoding spatial information. The authors recorded ensemble activity of CA1 neurons while mice explored a linear track. On the first and subsequent trials, CA1 neurons showed reduced spatial tuning in doxycycline-withdrawn CA3-TeTX relative to control mice. However, place field size and spatial information increased over time, suggesting that the monosynaptic pathway improves performance with experience.

Therefore, the shorter monosynaptic pathway is sufficient for slower learning completed over many trials, whereas the trisynaptic pathway is important for rapid learning in new environments. These data suggest that similar neural circuits serve distinct, non-redundant functions, which could perhaps be defined by reversible inhibition of neural transmission.

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1. Nakashiba, T., Young, J. Z., McHugh, T. J., Buhl, D. L. & Tonegawa, S. Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. *Science* (2008) doi: 10.1126/science.1151120. | Article |