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Developmental refinement of vesicle cycling at Schaffer collateral synapses
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ABSTRACT: At synapses formed between dissociated neurons, about half of all synaptic vesicles are refractory to evoked release, forming the so-called ‘‘resting pool.’’ Here, we use optical measurements of vesicular pH to study developmental changes in pool partitioning and vesicle cycling in cultured hippocampal slices. Two-photon imaging of a genetically encoded two-color release sensor (ratio-sypHy) allowed us to perform calibrated measurements at individual Schaffer collateral boutons. Mature boutons released a large fraction of their vesicles during simulated place field activity, and vesicle retrieval rates were 7-fold higher compared to immature boutons. Saturating stimulation mobilized essentially all vesicles at mature synapses. Resting pool formation and a concomitant reduction in evoked release was induced by chronic depolarization but not by acute inhibition of the protein phosphatase calcineurin. We conclude that synapses in CA1 undergo a prominent refinement of vesicle use during early postnatal development that is not recapitulated in dissociated neuronal culture.

STATEMENT*: Our work challenges the textbook view that small excitatory synapses in the brain use only a small fraction of their total vesicle reserve. This idea was originally based on experiments on dissociated neurons grown on glass cover slips and found support by recent in-vivo studies that used dye uptake as a proxy for neurotransmitter release. In hippocampal tissue, we found evidence for a resting pool of vesicles only in very young neurons, but not after 2-3 weeks of maturation. We show that normal exploratory activity of an adult rat is accompanied by activity patterns in the hippocampus that trigger the release and rapid recycling of most transmitter vesicles. Our findings demonstrate that excitatory synapses dramatically improve their speed and efficiency during early postnatal development.*

BACKGROUND: Imaging experiments were performed by Tobias Rose at the Friedrich Miescher Institute in Basel and at the Institute for Synaptic Physiology, Center for Molecular Neurobiology Hamburg. Activity of slice cultures was characterized by Philipp Schoenenberger in the Oertner lab. *In vivo* recordings from rat hippocampus were performed by Karel Jezek at the Kavli Institute for Systems Neuroscience in Trondheim, Norway. The work was funded by the Novartis Research Foundation, SystemsX.ch, the Kavli Foundation, and the University Medical Center Hamburg-Eppendorf.