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Na^+/Ca^{2+} exchanger (NCX)-2, a temporal factor in regulation of synaptic plasticity and cognition

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The role of a postsynaptic rise of $[Ca^{2+}]_i$ in the induction of LTP and LTD has been well established. Both the levels and the duration of elevated $[Ca^{2+}]_i$ are important in synaptic plasticity. LTP and LTD could be selectively induced according to intracellular Ca^{2+} concentration. Although the specificity of Ca^{2+} signaling can be achieved not only by amplitude but also by the frequency and duration of the calcium transient, the effects of changing amplitudes of Ca^{2+} transients on synaptic plasticity have been extensively documented, but not so the effects of temporal changes. Although many studies have concentrated on Ca^{2+} influx through membrane channels or Ca^{2+} release from internal Ca^{2+} stores, contributions of Ca^{2+} clearance in the plasma membrane have often been overlooked in studies of synaptic plasticity. To address this question, we have generated knock-out mice for Na^+/Ca^{2+} exchanger (NCX)-2, a major isoform in the brain. The plasma membrane Na^+/Ca^{2+} exchanger (NCX) plays a role in regulation of intracellular Ca^{2+} concentration via the forward mode (Ca^{2+} efflux) or the reverse mode (Ca^{2+} influx). Mutant hippocampal neurons exhibited a significantly delayed clearance of elevated Ca^{2+} following depolarization. The frequency threshold for LTP and LTD in the hippocampal CA1 region was shifted to a lowered frequency in the mutant mice thereby favoring LTP. Behaviorally, the mutant mice exhibited enhanced performance in several hippocampus-dependent learning and memory tasks. These results demonstrate that NCX2 can be a temporal regulator of Ca^{2+} homeostasis and as such is essential for the control of synaptic plasticity and cognition.