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Regulation of calcium signal pathway in fear-related memory

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Na^+/Ca^{2+}exchangers (NCXs) are mainly expressed in the plasma membrane and exchange one $Ca^{2+}$for three Na^+, depending on the electrochemical gradients across the plasma membrane. NCXs have three isoforms, NCX1–3, encoded by distinct genes in mammals. Here, we report that heterozygous mice lacking NCX1 ($NCX1^{+/-}$) exhibit impaired amygdala-dependent cued fear memory. $NCX1^{+/-}$mice showed significant impairment in fear-related behaviors measured with the elevated-plus maze, light-dark, open-field, and marble-burying tasks. In addition, $NCX1^{+/-}$mice showed abnormality in cued fear memory but not in contextual fear memory in a fear-conditioning task. In immunohistochemical analyses, $NCX1^{+/-}$mice had significantly increased number of c-Fos positive cells in the lateral amygdala (LA) but not in the central amygdala following fear-related tone stimuli. c-Fos expression peaked at 1 h. In concordance with the aberrant fear-related behaviors in $NCX1^{+/-}$mice, enhanced long-term potentiation was also observed in the LA of these mice. Furthermore, enhancement of CaMKII or CaMKIV activity in the LA was observed in $NCX1^{+/-}$mice by immunoblot analyses. In contrast, $CaMKII^{+/-}$but not $CaMKIV^{-/-}$mice insufficiently exhibited tone-induced cued fear memory and there was no increase in the number of c-Fos positive cells in the LA. Altogether, the increased CaMKII activity and consequent c-Fos expression likely account for the dysregulation of amygdala-dependent cued fear memory in $NCX1^{+/-}$mice.