Endogenous 24S-hydroxycholesterol modulates NMDAR-mediated function in hippocampal slices

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N-methyl-D-aspartate receptors (NMDARs), a major subtype of glutamate receptors mediating excitatory transmission throughout the CNS, play critical roles in governing brain function and cognition. Because NMDAR dysfunction contributes to the etiology of neurological and psychiatric disorders including stroke and schizophrenia, NMDAR modulators are potential drug candidates. Our group recently demonstrated that the major brain cholesterol metabolite, 24S-hydroxycholesterol (24S-HC), positively modulates NMDARs when exogenously administered. Here, we studied whether endogenous 24S-HC regulates NMDAR activity in hippocampal slices. In *CYP46A1*$^{-/-}$ (knockout; KO) slices where endogenous 24S-HC is greatly reduced, NMDAR tone, measured as NMDAR to AMPAR EPSC ratio, was reduced. This difference translated into more NMDAR-driven spiking in wild-type (WT) slices compared with KO slices. Application of SGE-301, a 24S-HC analogue, had comparable potentiating effects on NMDAR EPSCs in both WT and KO slices, suggesting that endogenous 24S-HC does not saturate its NMDAR modulatory site in *ex vivo* slices. KO slices did not differ from WT slices in either spontaneous neurotransmission or in neuronal intrinsic excitability, and exhibited LTP indistinguishable from WT slices. However, KO slices exhibited higher resistance to persistent NMDAR-dependent depression of synaptic transmission induced by oxygen-glucose deprivation (OGD), an effect restored by SGE-301. Together, our results suggest that loss of positive NMDAR tone does not elicit compensatory changes in excitability or transmission, but it protects transmission against NMDAR-mediated dysfunction. We expect that manipulating this endogenous NMDAR modulator may offer new treatment strategies for neuropsychiatric dysfunction.