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**Modulation of NR2B NMDA receptors and of long-term potentiation via D4 dopamine receptors in stratum oriens of hippocampal CA1**

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The dopaminergic system in the central nervous system is recognized to play an important role in synaptic plasticity and learning, and is involved in the pathogenesis of a variety of neurological and psychiatric disorders. The present study demonstrates in mice, similar to what has earlier been reported in rats, that there is a higher density of dopaminergic fibers in stratum oriens (OR) than in stratum radiatum (RAD) within the CA1 region of the dorsal hippocampus. Furthermore, the effect of the D1/5 agonist SKF38393 on NMDAR-dependent LTP was examined in OR and RAD in four week-old mice. In single CA1 neurons, the presence of SKF38393 strongly and selectively reduced LTP in OR. This compartment-specific effect was caused by dopamine (DA) agonist augmented inactivation of synaptic NMDAR-mediated currents (NMDA EPSCs) during LTP induction through a $Ca^{2+}$-dependent, and G-protein independent mechanism. To analyze NMDAR subtype-specific contributions, two gene-targeted mouse lines were employed. In mice, in which NR2A is constitutively ablated ($NR2A^{-/-}$), the compartment-specific DA agonist mediated effect on NMDA EPSCs and LTP persisted. In contrast, in mice which lack NR2B in principal forebrain neurons ($NR2B^{\Delta Fb-/-}$), the DA agonist-mediated effects were absent. Application of selective D4-agonist PD-168077 reproduced the augmented NMDAR inactivation, which could be completely reversed by selective D4-antagonist L-745,870. In the presence of the D4-agonist PD-168077 LTP was strongly impaired in OR. Taken together, these results indicate that in stratum oriens D4 receptors mediate the dopaminergic modulation of synaptic efficacy via NMDARs containing NR2B subunits. Thus, a DA hyperfunction may result in NMDAR hypofunction in OR that could have an impact on both normal and pathological conditions observed in schizophrenia.