

Role of N-Methyl-D-Aspartate Receptor (NMDAR) in Co-morbid Schizophrenia and Substance Abuse

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Both schizophrenia (SZ) and substance abuse (SA) exhibit significant heritability. Moreover, N-methyl-D-aspartate receptors (NMDARs) have been implicated in the pathophysiology of both SZ and SA. We hypothesize that the high prevalence of co-morbid SA in SZ is due to dysfunction of NMDARs caused by shared risk genes. We used transgenic mice with a null mutation of the gene encoding serine racemase (SR), the enzyme that synthesizes the NMDAR co-agonist D-serine, to mimic an established genetic risk factor for SZ. We determined the effect of NMDAR hypofunction resulting from the absence of D-serine on motivated behavior using intracranial self-stimulation (ICSS) and neurotransmitter release in the nucleus accumbens using *in vivo* microdialysis. Compared to wild-type mice (WT), SR^{-/-} mice exhibited similar baseline ICSS thresholds but were less sensitive to the threshold-lowering (rewarding) and the performance-elevating (stimulant) effects of cocaine. While basal dopamine (DA) and glutamate release were elevated in the nucleus accumbens of SR^{-/-} mice, cocaine-induced increases in DA and glutamate release were blunted. γ -Amino-butyric acid (GABA) efflux was unaffected in the SR^{-/-} mice. Together, these findings suggest that the impaired NMDAR function and a consequent decrease in sensitivity to cocaine effects on behavior are mediated by blunted DA and glutamate responses normally triggered by the drug. Preliminary data from ongoing behavioral studies in SR^{-/-} and WT mice also show a decreased sensitivity to nicotine's behavioral effects. Projected to humans, NMDAR hypofunction due to mutations in SR or other genes impacting glutamatergic function in SZ may render abused substances less potent and effective, thus requiring higher doses to achieve a hedonic response, resulting in elevated drug exposure and increased dependence/addiction.