The ADHD-linked human dopamine D4 receptor variant D4.7 induces over-suppression of NMDA receptor function in prefrontal cortex.


Abstract

The human dopamine D4 receptor (hD4R) variants with long tandem repeats in the third intracellular loop have been strongly associated with attention deficit hyperactivity disorder (ADHD) and risk taking behaviors. To understand the potential molecular mechanism underlying the connection, we have investigated the synaptic function of human D4R polymorphism by virally expressing the ADHD-linked 7-repeat allele, hD4.7, or its normal counterpart, hD4.4, in the prefrontal cortex (PFC) of D4R knockout mice. We found that hD4R bound to the SH3 domain of PSD-95 in a state-dependent manner. Activation of hD4.7 caused more reduction of NR1/PSD-95 binding and NR1 surface expression than hD4.4 in PFC slices. Moreover, the NMDAR-mediated excitatory postsynaptic currents (NMDAR-EPSC) in PFC pyramidal neurons were suppressed to a larger extent by hD4.7 than hD4.4 activation. Direct stimulation of NMDARs with the partial agonist d-cycloserine prevented the NMDAR hypofunction induced by hD4.7 activation. Moreover, hD4.7-expressing mice exhibited the increased exploratory and novelty seeking behaviors, mimicking the phenotypic hallmark of human ADHD. d-cycloserine administration ameliorated the ADHD-like behaviors in hD4.7-expressing mice. Our results suggest that over-suppression of NMDAR function may underlie the role of hD4.7 in ADHD, and enhancing NMDAR signaling may be a viable therapeutic strategy to ADHD humans carrying the D4.7 allele.