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Imbalanced post- and extrasynaptic SHANK2A functions during development affect social behavior in SHANK2-mediated neuropsychiatric disorders

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Abstract

Mutations in SHANK genes play an undisputed role in neuropsychiatric disorders. Until now, research has focused on the postsynaptic function of SHANKs, and prominent postsynaptic alterations in glutamatergic signal transmission have been reported in Shank KO mouse models. Recent studies have also suggested a possible presynaptic function of SHANK proteins, but these remain poorly defined. In this study, we examined how SHANK2 can mediate electrophysiological, molecular, and behavioral effects by conditionally overexpressing either wild-type SHANK2A or the extrasynaptic SHANK2A(R462X) variant. SHANK2A overexpression affected pre- and postsynaptic targets and revealed a reversible, development-dependent autism spectrum disorder-like behavior. SHANK2A also mediated redistribution of Ca2+-permeable AMPA receptors between apical and basal hippocampal CA1 dendrites, leading to impaired synaptic plasticity in the basal dendrites. Moreover, SHANK2A overexpression reduced social interaction and increased the excitatory noise in the olfactory cortex during odor processing. In contrast, overexpression of the extrasynaptic SHANK2A(R462X) variant did not impair hippocampal synaptic plasticity, but still altered the expression of presynaptic/axonal signaling proteins. We also observed an attention-deficit/hyperactivity-like behavior and improved social interaction along with enhanced signal-to-noise ratio in cortical odor processing. Our results suggest that the disruption of pre- and postsynaptic SHANK2 functions caused by SHANK2 mutations has a strong impact on social behavior. These findings indicate that pre- and postsynaptic SHANK2 actions cooperate for normal neuronal function, and that an imbalance between these functions may lead to different neuropsychiatric disorders.

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