DYSFUNCTION OF D2 DOPAMINE RECEPTOR NEURONS UNDERLIES SELECT MANIC-LIKE BEHAVIORS IN SHANK3 OVEREXPRESSING MICE

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Background: We have previously described the SHANK3 duplication syndrome and reported that mice modeling this disorder have multiple behavioral abnormalities including hyperactivity and accentuated amphetamine induced hyperactivity (AIH). SHANK3 resides in the post-synaptic density of excitatory synapses where it acts as a scaffolding protein linking neurotransmitter receptors and other transmembrane proteins to the underlying cytoskeleton. SHANK3 is most abundantly expressed in the striatum which is known to be a critical center for control of motor movement.

Materials/Methods: Measurements of synaptic activity were determined by patch-clamp neurophysiology in Shank3 overexpressing mice (Shank3 TG mice). Shank3 TG mice were treated with two novel D2 dopamine receptor (D2dr) antagonists developed as potential anti-psychotics. To further explore the necessity of Shank3 overexpression in these neurons for hyperactivity phenotypes, we created mice with a floxed Shank3 TG allele (conditional rescue mice). These mice were crossed with mice expressing Cre recombinase only in D2 dopamine receptor expressing neurons to normalize Shank3 expression.

Results: Frequency of miniature excitatory post-synaptic currents (mEPSCs) was significantly elevated in medium spiny neurons of the striatum in Shank3 TG mice while amplitude was unchanged. Furthermore, only D2dr positive neurons have elevated mEPSC frequency while the frequency in D1 dopamine receptor neurons is normal. Sub-acute treatment of Shank3 TG mice with D2dr antagonists rescues hyperactivity and accentuated AIH while other abnormal behaviors are unchanged. Similarly, when the conditional overexpression allele was disrupted by Cre recombinase expressed only in the D2 dopamine receptor expressing neurons, the baseline hyperactivity as well as accentuated AIH was rescued without altering other behavioral abnormalities previously observed in these mice.

Conclusions: Together these data demonstrate that dysfunction of D2dr neurons in Shank3 TG mice contributes to their baseline hyperactivity as well as accentuated AIH. These data also suggest a potential personalized therapy for individuals with genomic duplications involving SHANK3.