Aberrant regulation of synchronous network activity by the ADHD-associated human dopamine D4 receptor variant D4.7 in prefrontal cortex.

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Abstract
A unique feature of human D4 receptor (hD4 R) gene is the existence of a large number of polymorphisms in exon 3 that codes for the third intracellular loop, which consists of a variable number of tandem repeats. The hD4 R variants with long repeats have been linked to attention-deficit/hyperactivity disorder (ADHD), however the underlying mechanism is unknown. Emerging evidence suggests that selective attention is controlled by the rhythmic synchronization in prefrontal cortex (PFC) and its connected networks, so we examined the role of hD4 R variants in regulating PFC synchronous network activity. D4 R knockout mice with viral infection of hD4.4 or hD4.7 in medial PFC were used. Whole-cell patch-clamp recordings were performed to examine the effects of activating hD4.x on the spontaneous large scale correlated activity in PFC pyramidal neurons. We have found that, compared to the normal 4-repeat variant hD4.4, the ADHD-linked variant hD4.7 induces more suppression of the glutamatergic excitatory network bursts and less suppression of the GABAergic inhibitory network bursts in the PFC circuitry. Methylphenidate, a psychostimulant drug used to treat ADHD, normalized the effects of hD4.7 on synchronous network bursts in PFC pyramidal neurons. These results have revealed the differential effects of hD4 R variants on the integrated excitability of PFC circuits. It suggests that the aberrant regulation of PFC network activity by hD4.7 may underlie its involvement in ADHD. The MPH-induced normalization of synaptic circuitry regulation may contribute to its effectiveness in ADHD treatment.