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MEETING ABSTRACT

A17.1
Impact of dopamine transporter-mediated, non-vesicular DA release on ADHD traits as studied in the DAT Val559 mouse model
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Genetic, pharmacological and imaging studies support a role for dopamine (DA) signaling dysfunction in establishing risk for attention-deficit hyperactivity disorder (ADHD). In this regard, the presynaptic DA transporter (DAT, SLC6A3) has been of particular interest, given that the most commonly prescribed ADHD medications, methylphenidate and amphetamine derivatives, target DAT, either by blocking DAT-mediated DA clearance, or the induction of transporter reversal or non-vesicular DA release. In an effort to establish a causal link between DAT dysfunction and ADHD risk, we pursued a search for rare, but functionally penetrant, DAT coding variants in ADHD subjects [1, 2]. One of these variants, DAT Val559, a variant previously reported in a female subject with bipolar disorder [3] and recently linked syndromes. Two unrelated males with autism spectrum disorder [4], when expressed in HEK 293 cells, established an anomalous DA efflux (ADE) indicative of spontaneous DAT reversal. Furthermore, the ADE of DAT Val559-transfected cells could be blocked either by methylphenidate or amphetamine, suggesting that the actions of these therapeutic psychostimulants in some ADHD subjects could arise from ADE. To test the hypothesis that DAT Val559 could induce ADE in vivo and provoke ADHD-associated behavioral traits, we generated knock-in mice expressing the Val559 variant from the endogenous Slc6a3 locus [5, 6], with studies supporting the institution of tonically elevated extracellular DA, constitutive activation of DA autoreceptors, and altered spontaneous and amphetamine/methylphenidate-induced locomotor behavior. In more recent studies with these mice, to be discussed in the presentation, we have obtained evidence for disturbances in cognitive and reward behaviors, as well as anomalous behavioral responses to cocaine. These studies support the in vivo functional status of the DAT Val559 variant and the DAT Val559 knock-in mouse as a construct-valid model of perturbations in DA homeostasis underlying ADHD risk, changes that may be shared with other DA-linked syndromes.

References
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