Lack of Cdk5 activity is involved on Dopamine Transporter expression and function: Evidences from an animal model of Attention-Deficit Hyperactivity Disorder

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Abstract
Attention deficit/Hyperactivity disorder (ADHD) is one of the most diagnosed psychiatric disorders nowadays. The core symptoms of the condition include hyperactivity, impulsiveness and inattention. The main pharmacological treatment consists of psychostimulant drugs affecting Dopamine Transporter (DAT) function. We have previously shown that genetically modified mice lacking p35 protein (p35KO), which have reduced Cdk5 activity, present key hallmarks resembling those described in animal models useful for studying ADHD. The p35KO mouse displays spontaneous hyperactivity and shows a calming effect of methylphenidate or amphetamine treatment. Interestingly, dopaminergic neurotransmission is altered in these mice as they have an increased Dopamine (DA) content together with a low DA turnover. This led us to hypothesize that the lack of Cdk5 activity affects DAT expression and/or function in this animal model. In this study, we performed biochemical assays, cell-based approaches, quantitative fluorescence analysis and functional studies that allowed us to demonstrate that p35KO mice exhibit decreased DA uptake and reduced cell surface DAT expression levels in the striatum (STR). These findings are supported by in vitro observations in which the inhibition of Cdk5 activity in N2a cells induced a significant increase in constitutive DAT endocytosis with a concomitant increase in DAT localization to recycling endosomes. Taken together, these data provide evidences regarding the role of Cdk5/p35 in DAT expression and function, thus contributing to the knowledge of DA neurotransmission physiology and also providing therapeutic options for the treatment of DA pathologies such as ADHD.

Keywords: Amphetamine; Cdk5/p35; Dopamine; Endocytosis; Endosomes, ADHD.