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Role of the Dopamine System in Motor Skill Learning: Implications for Neurodevelopmental Disorders

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ABSTRACT

Dopamine (DA), released by midbrain neurons, is critical for motor performance, motor skill learning, and corticostriatal synaptic plasticity. Dysregulation of DAergic signaling in corticostriatal circuitry has also been implicated in several highly heritable neurodevelopmental disorders, such as attention/deficit hyperactivity disorder (ADHD), which are often associated with deficits in fine motor skills. However, the cellular and molecular pathways mediating the effects of DA are still poorly understood. In the present thesis, we used a skilled reaching task to investigate potential DAergic mechanisms contributing to the acquisition and performance of fine motor skills (i.e., skilled reaching and grasping).

To explore the influence of natural genetic variation in the DA system in motor skill learning, we took advantage of two inbred strains of mice (i.e., BALB/c and C57BL/6) that differ markedly in the number of midbrain DA neurons. We demonstrate significant variation in skilled reaching behavior in these two strains. Specifically, variations in the rate of motor learning correlated with divergent DA-related gene expression (e.g., DA D1 receptors and DARPP-32) in frontal cortex and striatum. These results implicate genetically driven variation in frontostriatal DAergic neurotransmission as a key contributor to individual differences in fine motor skill.

To identify brain activity patterns associated with different phases of motor skill learning, we studied the induction of the plasticity-related gene Arc (also known as Arg3.1), and also investigated learning-induced changes in the DA system. In the early phase of motor skill learning, Arc mRNA was significantly induced in the corticostriatal circuitry, including the medial prefrontal cortex (mPFC), cingulate cortex, primary motor cortex, and striatum. In the late phase, however, a shift in the expression pattern of Arc was evident–with a significant decrease in Arc mRNA in most regions examined (except in the mPFC and striatum). There were also significant changes in the expression of DA D1 receptors and their intracellular target DARPP-32 in the striatum (but not cortical regions) during the early, but not late, phase of motor skill learning. Analysis of the phosphorylation state of dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa (DARPP-32) and its downstream target cAMP response element-binding protein (CREB) in the striatum indicated increased levels of phospho-Thr34-DARPP-32 and phospho-Ser133-CREB during the early, but not late, phase of motor skill learning. These findings implicate the cAMP/PKA/DARPP-32 signaling pathway in the acquisition of novel motor skills, and also demonstrate a dynamic shift in the contribution of corticostriatal circuitry during different phases of motor skill learning.

Finally, we explored whether spontaneously hypertensive rats (SHRs), the most commonly used genetic animal model of ADHD, is valid for investigating fine motor skill problems displayed by the majority of children with ADHD. Although SHRs could learn the skilled reaching task, their performance is significantly poorer than that of control rats in the most sensitive measure of skilled performance (i.e., success on the first attempt). However, gross motor coordination appears to be normal in SHRs, suggesting that the SHR strain displays specific deficits only in fine motor skills. Moreover, DARPP-32 was significantly higher expressed in corticostriatal circuitry of SHR compared to controls. Our results support the notion that the SHR strain is a useful animal model system to investigate potential molecular mechanisms underlying fine motor skill problems in ADHD.

The present thesis gives evidence supporting the notion that normal genetic variation in the DAergic system might contribute substantially to variability in the acquisition of motor skills in humans. More specifically, the results suggest the involvement of the D1R/cAMP/DARPP-32 signaling pathway in those neurodevelopmental disorders that are associated with fine motor skill deficits.

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