The role of the circadian clock in the pathogenesis of psychiatric disease Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract: Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent psychiatric disorders in children and adults. While ADHD patients often display circadian abnormalities, the mechanisms underlying circadian regulation of the pathogenesis of ADHD are unclear. Here we found zebrafish mutants for circadian gene \textit{period1b} (\textit{per1b}) display hyperactive-, impulsive-, attention deficit-like behaviors and low levels of dopamine, reminiscent of human ADHD patients. We found that the circadian clock directly regulates the dopamine catabolism genes \textit{dopamine beta hydroxylase} (\textit{dbh}) and \textit{monoamine oxidase} (\textit{mao}), and likely acts through genes important for the development or maintenance of dopaminergic neurons to regulate their number and organization in the ventral diencephalic posterior tuberculum (PT). We then found that \textit{Per1} knockout mice also display ADHD symptoms and reduced levels of dopamine, thereby implicating circadian roles in ADHD are highly conserved. Our studies demonstrate that disruption of a circadian clock gene elicits ADHD-like syndrome. The circadian model for ADHD sheds light on ADHD pathogenesis and opens avenues for exploring novel targets for diagnosis and therapy for this common psychiatric disorder.

Keywords: Circadian rhythms, Dopamine, Hyperactivity, Period, Zebrafish