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INFLUENCE OF THE CIRCADIAN CLOCK ON MOTOR LEARNING PATHWAYS

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Influence of the Circadian Clock on Motor Learning Pathways

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ABSTRACT

The circadian clock is an important regulator of biological processes in living organisms. The canonical mechanism for this cycle is driven through negative feedback loops formed by key transcription factors and their effectors. Recent studies have demonstrated the vast influence of these circadian feedback loops on immunology, metabolism, and even behavioral processes. Thus, the efficacy of therapies that target such proteins under the influence of the circadian clock are especially profound and largely unexplored. Here, we investigated the circadian clock's influence on the ability to learn a motor skill through the utilization of transgenic mice that lack BMAL1 (BMAL1-KO), an essential regulatory component of the circadian clock's transcriptional timing mechanism. In our study, we first designed and built a custom behavior apparatus, commercially known as a rotarod, to quantify motor learning in mice. We then leveraged this technology to uncover that BMAL1-KO exhibited compromised motor ability as well as impaired learning rates at specific time points compared to its wild-type littermate controls. As our studies exemplified impaired motor learning in BMAL1-KO and because dopamine is a critical player in motor behavior, we analyzed levels of key proteins involved in dopamine signal transduction including Gai, Gb, phosphodiesterase 10A (PDE10A), and adenylyl cyclase 5 (AC5). Through Western blot analysis of samples collected over a 24-hour period, we found alterations in the enzymes that maintain homeostasis of the intracellular second messenger cyclic AMP (cAMP) in BMAL1-KO brain samples. Thus, by directly probing cAMP levels in brain lysates, we report downregulation of the cAMP pathway in BMAL1-KO compared with the littermate controls. We expect these observations to be a key starting point in determining molecular mechanisms that link the circadian clock to motor

learning pathways as they feature the unique differences in motor ability and relevant proteins in BMAL1-KO groups and their littermate controls. Moreover, our observations in regard to the timely fluctuations of prominent proteins over a 24 hour period may act as a stepping stone to further discoveries on the impact of the circadian clock. Finally, our findings may provide insight toward the potency and efficacy of neuropharmacological agents that play crucial functions in treating motor-related disorders such as in cases for Parkinson's and Alzheimer's disease.

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