Circadian Rhythms and Opiates: Role of the Circadian Transcription Factor NPAS2 to Regulate Morphine Conditioned Reward

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Sleep and circadian rhythms are involved in the pathophysiology of mood and addiction disorders. However, the mechanisms underlying these relationships remain poorly understood. Almost every cell in the body expresses genes comprising the molecular clock, a series of auto-regulatory transcriptional—translational feedback loops. A primary component of the molecular clock is the gas and metabolic responsive transcription factor, NPAS2, a member of the basic helix-loop-helix (bHLH)-PAS family of transcription factors. The nucleus accumbens (NAc) is a major substrate of mood and reward, composed mostly of medium spiny neurons (MSNs) expressing dopamine 1 or 2 receptors (D1+ or D2+), which exert opposing actions on reward and motivated behaviors. We found NPAS2 is enriched particularly within D1+ MSNs of the NAc. Given these findings, we investigated the role of NPAS2 to regulate cocaine and morphine conditioned place preference (CPP) and self-administration. Both male and female NPAS2-bHLH-deficient (Npas2-ΔbHLH) mice displayed significantly attenuated cocaine and morphine CPP. D1+ specific knockdown of *Npas2* in the NAc recapitulated these findings, suggesting a cell-type specific role of the circadian transcription factor to regulate reward. Currently, we are investigating the whether NPAS2 may directly regulate these receptors as transcriptional targets, or via other mechanisms, and whether NPAS2 may modulate the activity of NAc MSNs during morphine exposure. These findings further demonstrate a link between circadian pathways in the brain and the behavioral response to drugs of abuse, possibly relevant for addiction.