ABSTRACT - NIDA Genetics Consortium Meeting, Dec 1-2, 2016

CBP mediated control of long-term drug neuroadaptation in *Drosophila*

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Sedative organic solvents such as alcohol are known to trigger homeostatic adaptations in the brain that lead to the development of drug tolerance, dependence and behavioral dysregulation. These adaptations are believed to be of central importance in producing the addictive state. In Drosophila, a single alcohol exposure results in a prolonged increase in alcohol resistance and susceptibility to seizures that extends over several days. The persistent nature of the drug-induced adaptations suggests that the mechanisms behind them involve long-lasting changes in gene expression and include the epigenetic restructuring of chromosomal regions that perpetuate them. Epigenetic histone modifications have recently emerged as important modulators of gene expression and are thought to orchestrate and maintain the expression of multi-gene networks. By altering the structural arrangement of chromatin regions, these modifications regulate the accessibility of transcription factors to the underlying DNA and represent a form of transcriptional memory that is directly imprinted on the chromosome. In Drosophila, tolerance to alcohol and organic solvent anesthetics is mediated in part through the activity of a cohort of interconnected pre-synaptic genes that display a dynamic increase in histone H4 acetylation across their transcriptional control region. However, the molecular mediator of the acetylation process remains unknown. Here we show that the Drosophila *nejire* gene, which encodes the histone-acetyl transferase CBP, mediates the histone H4 acetylation required for gene regulation during the development of drug tolerance. We find that *nejire* is necessary for the initiation of tolerance to alcohol and anesthetics, as a mutation that reduces *nejire* expression reduces an early phase of the tolerance response. We propose that CBP regulates gene expression by the targeted acetylation of specific gene promoters, including the BK channel gene *slo*, a central component of the homeostatic response to alcohol and organic solvent anesthetics.