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A transcriptional control pathway for behavioral plasticity induced by ethanol

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Our goal is to uncover causal mechanisms for behavioral plasticity that are initiated by the first exposure to ethanol. Individuals nearly always require repeated exposures to ethanol to elicit alcohol use disorder (AUD). How do the early molecular events relate to AUD? A current hypothesis is that drug induced changes in gene expression alter the molecular landscape for the next drug exposure: each repeat exposure will act on neurons with changed properties and changed gene expression responses. Defining which gene expression changes are critical to the progression of AUD is a major challenge. We identify the genes that are regulated by the first ethanol exposure and determine their role in ethanol-induced behavioral plasticity. A network of evolutionarily conserved transcriptional regulators is affected by the first ethanol exposure and are critical for forms of plasticity, including tolerance, preference, and reward in Drosophila. The network is defined by the Mef2 transcription factor, the Hr38/Nr4a1-3 immediate early gene (IEG), and the Sirt1 histone deacetylase. Mef2 induces Hr38 and Sirt1 terminates Hr38 induction. We showed that each regulatory interaction is required for behavioral plasticity induced by the first ethanol exposure. Further, the three genes function in the same neurons, the mushroom body α/β neurons, to promote ethanol tolerance, preference, and reward. Hr38 is a transcriptional repressor. Therefore, our finding suggest that ethanol uses a rapid and transient repression of the expression of specific genes to allow a coherent molecular program to drive behavioral plasticity. Which genes must remain repressed and which genes are the effectors of plasticity, and how these specific changes alter the cellular responses to chronic and repeated drug exposure are important to determine.