Neuroadaptations underlying relapse to heroin seeking

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Drug addiction is a major burden for society through its impact on healthcare and crime-rate. Due to a lack of understanding of the neurobiological mechanisms underlying addiction, existing medication is still relatively ineffective, exemplified by high rates of relapse to drug use. Learned associations between otherwise neutral stimuli and rewarding properties of the drug play a critical role in persistence of drug addiction, as re-exposure to drug-conditioned cues after long periods of drug abstinence can elicit drug craving and subsequent relapse to drug use (1).

Using animal models (e.g. reinstatement model) that mimic relapse to drug seeking, significant progress has been made towards understanding of the neural circuitry underlying this long-lived behavioral abnormality. Although mediated by overlapping, yet distinct neural circuits, a comprehensive number of studies point to a role of a final common pathway of glutamatergic projections from the medial prefrontal cortex (mPFC) to the nucleus accumbens underlying drug-, stress and cue-induced reinstatement of drug seeking (2). Hence, the mPFC is thought to act as a critical relay station between memory retrieval and initiation of drug seeking behavior upon re-exposure to the previously abused drug or drug-conditioned cues.

In recent years, great progress has been made towards elucidation of cellular and molecular adaptations in animal models of relapse to drug seeking. Many of the identified drug-induced neuroadaptations share striking similarities with mechanisms of synaptic plasticity underlying traditional models of learning and memory (3, 4), arguing for a thorough analysis of molecular adaptations that occur at the synaptic level. The critical role of the mPFC in relapse to drug seeking suggests it may act as a substrate for long-lasting drug-induced neuroadaptations, however, supporting evidence at the level of the synapse was lacking. In this thesis, I studied molecular and cellular mechanisms that are at the basis of (i) long-term neuroadaptations after self-administration of heroin, and (ii) synaptic plasticity that occurs during reinstatement of heroin seeking.

As a first step, I investigated neuroadaptations that underlie natural reward learning, as these might eventually enhance our understanding of the neurobiological underpinnings of drug addiction. In chapter 2, I specifically
examined long-term changes in total protein expression in the mPFC during abstinence from sucrose SA, a natural reward. Although sucrose SA is often used as a direct control for drug-induced molecular changes, it was not known whether sucrose SA results in long-term adaptations in the mesocorticolimbic dopamine system. I set out to measure total protein changes in the mPFC 21 days after cessation of sucrose SA using two-dimensional gel electrophoresis (2D-PAGE) combined with mass-spectrometry and demonstrate that natural reward learning is indeed associated with long-term adaptations in the mPFC. This data indicates that apart from sucrose SA, additional control groups (e.g. saline SA) should be studied to distinguish neuroadaptations underlying natural reward learning from adaptations specifically associated with drug SA.

In a second series of experiments (chapter 3), I tested the hypothesis that heroin SA induces long-lasting alterations in the mPFC synaptic proteome. To this end, a highly novel iTRAQ-based proteomics approach was used together with immunohistochemical and neurophysiological techniques that showed that heroin SA altered the abundance of several extracellular matrix (ECM) proteins surrounding GABAergic interneurons in the mPFC, an effect that may underlie enhanced firing of GABAergic interneurons upon re-exposure to heroin-conditioned cues. Normalization of levels of ECM constituents attenuates cue-induced heroin seeking.

Cue-induced relapse to heroin seeking, but not sucrose seeking, is associated with enhanced neuronal activation in the mPFC (5, 6), pointing to altered synaptic transmission in this brain region upon re-exposure to drug-conditioned cues. I hypothesized that cue-induced relapse to heroin seeking is associated with rapid changes in the synaptic proteome of the mPFC (chapter 4). Using a combination of iTRAQ-proteomics, neurophysiology and molecular intervention, we provide evidence that cue-induced relapse to heroin seeking critically depends on acute AMPA-receptor mediated synaptic depression of pyramidal neuron synapses in the ventral mPFC.

Finally, these findings are discussed in the context of previous observations and I propose a model in which a combination of heroin-induced long-term neuroadaptations and acute cue-induced neuroplasticity results in reduced excitability of pyramidal neurons in the ventral mPFC,
likely diminishing excitatory output from the ventral mPFC and leading to a loss of inhibitory control over responding to heroin-conditioned cues. Identification of these long-term neuroadaptations and synaptic plasticity events in the rat reinstatement model provides new targets for the development of pharmaceutical agents that may reduce the risk of relapse to heroin use in humans.

References

1. A. Wikler, Arch Gen Psychiatry 28, 611 (May, 1973).