

PUBLIC ABSTRACT

HIPPOCAMPAL EPIGENETIC REGULATION OF THE FOSB GENE IN LEARNING AND ADDICTION

By

Paula Ann Gajewski

The health and financial burden of substance abuse will continue to rise unless specific facets of addiction, particularly relapse, are better treated. Relapse to drug use after prolonged abstinence requires strong associations between the drug and the environment in which it is experienced, and it is essential that we understand the molecular basis of these strong associations if we are to successfully prevent or treat addiction. These associations are mediated by the hippocampus, a brain region critical for memory formation which can drive craving and relapse. The formation of these memories requires long-term changes in hippocampal gene expression, which may occur via the action of stable transcription factors, such as Δ FosB. Δ FosB, a truncated stable product of the *FosB* gene, is uniquely positioned to affect the expression of many genes that play a role in hippocampal synaptic function and plasticity, as it is induced in the hippocampus by many drugs of abuse and is necessary for the formation of drug-environment associations. My data reveal changes in the regulation of the *FosB* gene in the hippocampus after chronic cocaine exposure via an epigenetic mechanism, altered histone methylation. Using novel, locus-specific viral tools to modify histones, I have elucidated how the epigenetic state of the *FosB* promoter drives gene expression and cocaine-related behaviors and memories. These findings identify novel molecular changes in the hippocampus due to cocaine exposure which furthers our understanding of drug-associated memory formation.

Additionally, my work also examined the translation of our research to a clinical setting. Although we have a great deal of evidence that *FosB* gene expression regulates behavior in mouse models of addiction, much less is known about the expression and function of *FosB* in the human brain. To this end, I obtained postmortem samples of human brains from cocaine addicts, depression

patients, and matched controls. I found dysfunction in the regulation of *FosB* gene products in the human hippocampus in response to cocaine and depression, and observed a decrease in Δ FosB protein levels, suggesting hippocampal dysfunction. Taken together, this suggests that Δ FosB in the hippocampus is important for drug-related memories, that cocaine changes how this gene is epigenetically regulated, and that regulation is also disrupted in the hippocampus of cocaine-addicted individuals. Future work will investigate the specific gene targets of Δ FosB, which may reveal new inroads for therapeutic intervention in addiction.

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Drug addiction results in part from maladaptive learning, including the formation of strong associations between the drug, the environment, and circumstances of its use. However, the patterns of gene regulation critical for this learning remain unknown. Consolidation of explicit memories occurs through synaptic plasticity in the hippocampus, and some of the molecular mechanisms of this process are well characterized, but epigenetic regulation underlying changes in hippocampal gene expression and the distribution of altered gene expression is poorly understood. The transcription factor Δ FosB is an important arbitrator of activity-dependent gene expression, and its expression in hippocampus is critical for learning. Previous studies demonstrate that drugs of abuse strongly upregulate Δ FosB in rodent hippocampus, but the mechanism of its induction by cocaine and its role in hippocampus-dependent cocaine responses is unknown. I demonstrate here that Δ FosB induction occurs exclusively within the CA1 subregion of the hippocampus and is facilitated by cocaine-mediated decreases in a repressive histone modification, H3K9me2. Subsequent locus-specific increase of this histone mark in hippocampus is sufficient to impair general learning and memory and cocaine-environment associations. Furthermore, human hippocampus post-mortem samples reveal a decrease in multiple Δ FosB isoforms and some Δ FosB target genes in cocaine-addicted individuals, as well as in depressed individuals, indicating a potential role for this gene in hippocampal pathologies associated with human addiction. These findings collectively suggest that salient stimuli, such as formation of drug-environment associations, induce epigenetic changes in the hippocampal *FosB* gene promoter that regulate Δ FosB induction, which in turn may control the transcription of genes that underlie hippocampal cell function and cocaine-related learning. Moreover, dysregulation of the

FosB gene may contribute to the effects of chronic drug exposure and may underlie cognitive deficits that accompany drug addiction and depression.