THE ROLE OF GADD45B IN STRIATAL PHYSIOLOGY AND COCAINE REWARD

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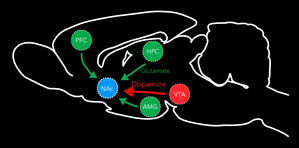
›› Background

› Exposure to drugs of abuse leads to alterations in neuronal activity and synaptic organization, which outlive the direct effects of the drug and may contribute to addiction. The nucleus accumbens (NAc) has a significant role in motivation, reward, and reward-related learning, and it has been identified as a key area in the development and maintenance of addiction.

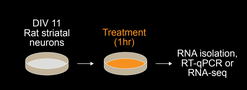
› Furthermore, drug experience alters epigenetic processes in brain reward circuitry, such as DNA methylation, resulting in differential regulation of gene expression. Growth arrest and DNA-damage inducible protein 45 beta (*Gadd45b*) is required for activity-dependent demethylation of DNA, but little is known about how it regulates the activity of brain reward circuits and subsequent behavioral responses to drugs of abuse, such as cocaine.

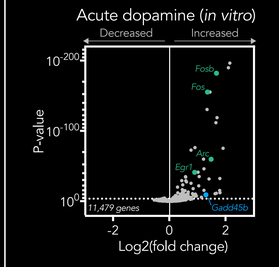


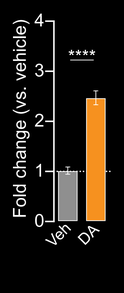
› Our long-term goal is to understand how circuits involving the NAc are altered as a result of drug exposure, and to dissect the epigenetic and molecular mechanisms underlying these long-lasting adaptations at a single-cell resolution. By elucidating the roles of different neurons within the NAc, their circuitry, and their gene expression profiles, we may gain the ability to alter these circuits and attenuate the maladaptive learning in addiction, identifying novel therapeutic targets and approaches.

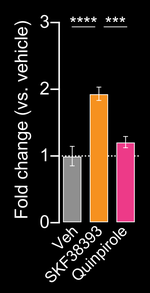
› The present study utilizes unbiased genome-wide transcriptional profiling, pharmacological manipulations, electrophysiological recordings, and CRISPR tools in both *in vitro* and *in vivo* rodent model systems to characterize the imporance of *Gadd45b* in dopamine-dependent epigenetic regulation and cocaine reward.

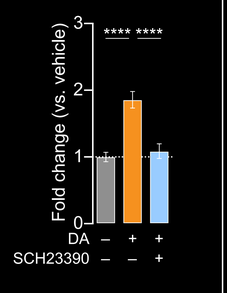
›› Dopamine and Drd1 agonist SKF38393 increase *Gadd45b* in striatal neurons



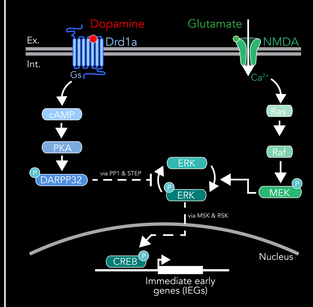


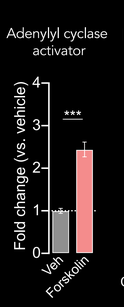


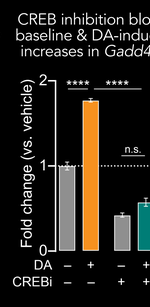


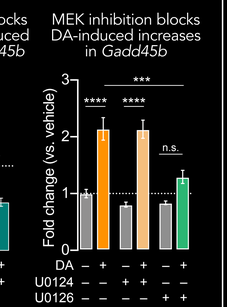


›› Dopamine-induced increases in *Gadd45b* require CREB activation and MEK signaling

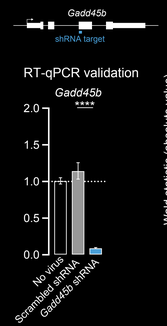


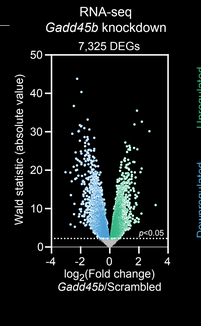


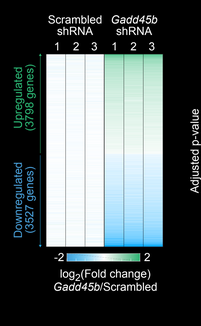


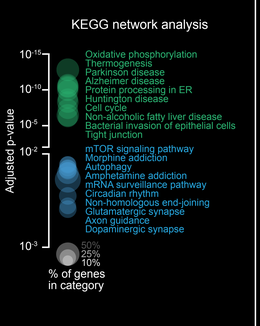


›› RNAi knockdown of *Gadd45b* in striatal neurons decreases expression of genes involved in addiction and dopamine signaling

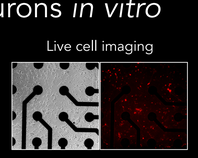


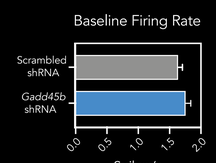


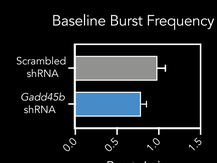


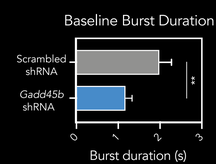


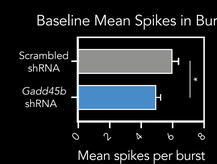
›› RNAi knockdown of *Gadd45b* alters bursting activity of striatal neurons *in vitro*

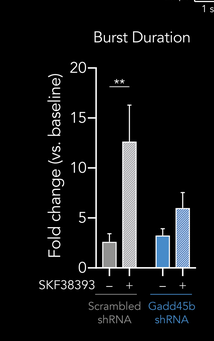




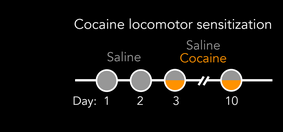


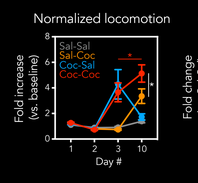


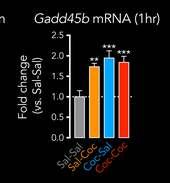


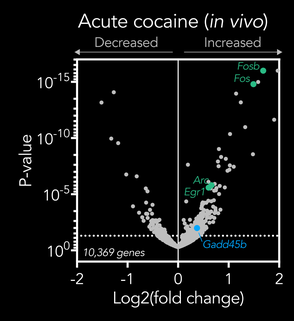


›› Cocaine upregulates *Gadd45b* and immediate early gene expression *in vivo*

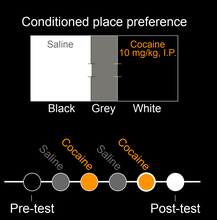


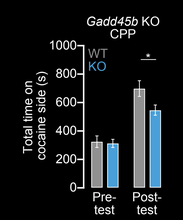




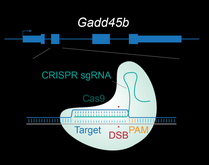


›› *Gadd45b* deletion dampens cocaine place memory in knockout mice

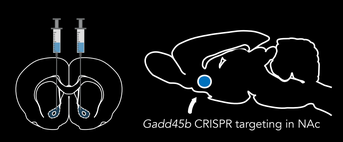


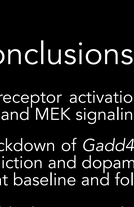


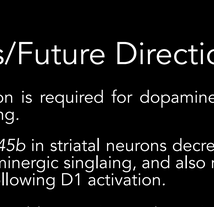
›› CRISPR-driven disruption of *Gadd45b* in neurons

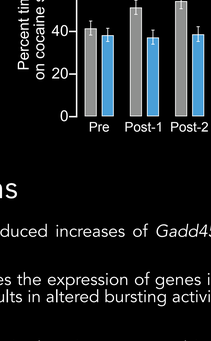


›› *In vivo* Cas9-driven *Gadd45b* disruption attenuates cocaine conditioned place preference memory









›› Conclusions/Future Directions

› D1 receptor activation is required for dopamine-induced increases of *Gadd45b*, as are CREB and MEK signaling.

› Knockdown of *Gadd45b* in striatal neurons decreases the expression of genes implicated in addiction and dopaminergic singlaing, and also results in altered bursting activity *in vitro*, both at baseline and following D1 activation.

› *Gadd45b* is upregulated by cocaine and cocaine-paired environments and is necessary for cocaine-paired place preference memory.

› Currently ongoing studies investigate how bidirectional regulation of *Gadd45b* affects gene expression and neuronal activity *in vitro* using striatal cells cultured on multielectrode arrays.

›› Funding Sources

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
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CMDB
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