Epigenetics of Methamphetamine-Induced Changes in Glutamate Function

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Rolling the Dice: The Importance of Mesolimbic Dopamine Signaling in Risky Decision Making

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To maximize resources, organisms must learn to predict the outcome of various options and choose the most valuable alternative. Behavioral choices such as 'playing it safe' *vs* 'taking a risk' engage a complex circuit that includes the mesolimbic dopamine (DA) system. A seminal study by Schultz *et al* (1997) showed that mesolimbic DA neurons function as a 'teaching signal' and encode cues that predict rewards and errors in those predictions. DA release in the nucleus accumbens (NAc) reflects this learning signal, and also processes information about reward value as animals are actively making decisions. For example, DA release in the NAc core is higher for cues that predict more valuable rewards, and signals the most valuable available option (Day *et al*, 2010).

Organisms rarely encounter situations in which simple stimulus-outcome associations are in effect, and thus must rely on multiple factors to make appropriate decisions including the representations of internal needs and external states, possible courses of action, and the consequences of those actions (Rangel *et al*, 2008). Risky decision making involves this type of complex evaluation and is of particular interest because it is implicated in several psychiatric disorders, including gambling and drug addiction. Risk-taking behavior has been modeled in rats using a task where subjects are allowed to choose between larger more uncertain rewards or smaller certain rewards. Importantly, in this task, it is not more advantageous to make one response over the other, and as such it is possible to evaluate intrinsic subjective value and individual risk attitudes. We have found that DA release in the NAc encodes the subjective value of future outcomes and, when given a free choice, may bias animals toward a risk or safe preference (Sugam *et al*, 2012).

However, the mesolimbic DA-NAc system does not function in isolation. Disruptions of the basolateral amygdala (BLA), prefrontal cortex (PFC) and NAc circuitry have resulted in differential effects on risk-taking. The BLA-NAc circuit appears critical for encoding reward probabilities, thus biasing animals to more valuable options when risks are lower. The PFC appears critical for tracking reward omissions and is important for shifting behavior as rewards become more uncertain and less valuable (St Onge *et al*, 2012). These findings suggest that each discrete region in this larger circuit has different roles in mediating appropriate decision making, and signaling from these structures likely modulate the value signaling of the mesolimbic DA system in risky decision making.

Recent advances in optogenetic techniques allow for the probing of individual portions of the reward circuit in mediating risk-taking behavior. For example, using a genetic line of rats, researchers were able to selectively activate DA fibers arising from the ventral tegmental area and showed that this manipulation is sufficient to drive motivated behaviors (Witten *et al*, 2011). Thus, future studies can apply optogenetic tools to selectively manipulate DA signaling while rats are deciding to engage in risk-taking behavior, and examine the causal relationship between rapid DA signaling in each discrete region of the mesolimbic circuit and risky behaviors. Determining the mechanisms that underlie appropriate risk-taking behavior will not only enhance our understanding of the role of this circuitry in normal decision making, but will also provide insight into what goes wrong during maladaptive risk taking. This approach may help identify optimal targets for therapeutic treatments of maladaptive decision making that occur, for example, in drug or gambling addiction or in eating disorders.

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DISCLOSURE
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Day JJ, Jones JL, Wightman RM, Carelli RM (2010). Phasic nucleus accumbens dopamine release encodes effort- and delay-related costs. *Biol Psychiatry* **68**: 306–309.
Rangel A, Camerer C, Montague PR (2008). A framework for studying the neurobiology of value-based decision making. *Nat Rev* **9**: 545–556.
Schultz W, Dayan P, Montague PR (1997). A neural substrate of prediction and reward. *Science* **275**: 1593–1599.
St. Onge JR, Stopper CM, Zahm DS, Floresco SB (2012). Separate prefrontal-subcortical circuits mediate different components of risk-based decision making. *J Neurosci* **32**: 2886–2899.
Sugam JA, Day JJ, Wightman RM, Carelli RM (2012). Phasic nucleus accumbens dopamine encodes risk-based decision-making behavior. *Biol Psychiatry* **71**: 199–205.
Witten IB, Steinberg EE, Lee SY, Davidson TJ, Zalocusky KA, Brodsky M *et al* (2011). Recombinase-driver rat lines: tools, techniques, and optogenetic application to dopamine-mediated reinforcement. *Neuron* **72**: 721–733.

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Epigenetics of Methamphetamine-Induced Changes in Glutamate Function

Addiction to methamphetamine (METH) is a relapsing neuropsychiatric disorder that is secondary, in part, to functional changes in limbic and striatal brain regions (reviewed in Krasnova and Cadet (2009)). Stimulant-induced plastic changes within the striatum are dependent on a series of events that include modifications in the number and subtypes of glutamate receptors (Wolf and Ferrario, 2010). Elucidating the basic mechanisms that maintain METH addiction is important because such an understanding will probably lead to the development of efficacious treatments. The accumulated evidence supports the notion that illicit drugs exert substantial transcriptional and epigenetic changes in the brain (Robison and Nestler, 2011).

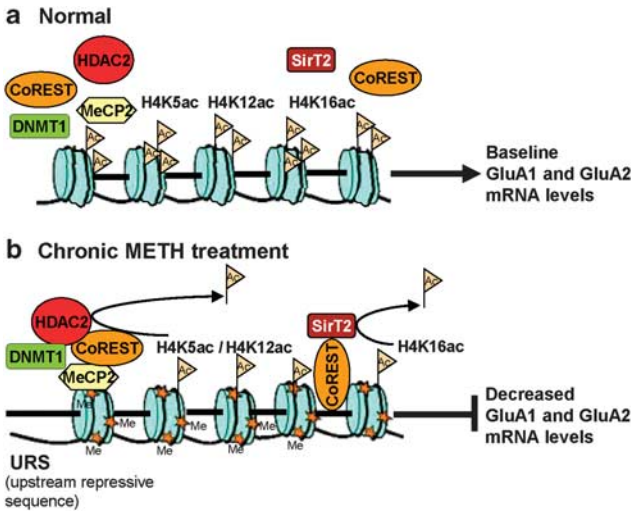

Figure 1. Models illustrating METH-induced epigenetic modifications in the dorsal striatum. Under normal conditions, a balance exists between histone acetyltransferases (HATs) and histone deacetylases (HDACs) that regulate the histone acetylation/deacetylation status that control the mRNA expression of AMPA receptor subunits (a). Chronic METH exposure (b) increases the expression of HDAC2, SIRT2, CoREST, and MeCP2. This is followed by the formation of protein repressor complexes that cause histone H4 hypoacetylation. Histone H4 hypoacetylation then produces decreased expression of GluA1 and GuA2 in the dorsal striatum of chronically METH-exposed rats.

Gene transcription is regulated by complex epigenetic changes that include post-translational histone modifications and DNA methylation (Mehler, 2008). There is evidence that epigenetic phenomena are intimately involved in the development and the clinical course of complex neuropsychiatric diseases including addiction (Robison and Nestler, 2011). Therefore, we thought it likely that METH might engender transcriptional and epigenetic alterations that are unique to this clinically devastating drug.

As a first step toward clarifying the effects of METH on glutamatergic function, we treated rats with an escalating METH dose paradigm that started at METH (0.5 mg/kg twice/day) and ended with METH (3 mg/kg four times per day) over a period of 2 weeks (McCoy *et al*, 2011). We found that chronic METH caused significant decreases in mRNA and protein levels of both GluA1 and GluA2 AMPA receptor subunits. We also found that METH caused significant decreases in acetylation of histone H4 at lysine 5 (H4K5), lysine 12 (H4K12), and lysine 16 (H4K16). Using chromatin immunoprecipitation-PCR assay, we found that repeated METH injections produced decreased binding of acetylated H4K5, H4K12, and H4K16 on GluA1 and GluA2 DNA sequences. In addition, chronic METH administration enhanced the recruitment of corepressor of RE1 silencing transcription (CoREST) factor onto GluA1 and GluA2 DNA sequences. METH also caused CoREST co-immunoprecipitation with histone deacetylase 2 (HDAC2) and sirtuin 2 (SIRT2). Moreover, METH increased enrichment of methyl CpG binding protein 2 (MeCP2) on the promoters of both GluA1 and GluA2, with co-immunoprecipitation studies revealing METH-induced MeCP2 interactions with HDAC2. Finally, we demonstrated that the FDA-approved HDAC inhibitor, valproic acid, prevented METH-induced downregulation of GluA1 and GluA2 mRNA levels.

In summary, the present study provides direct evidence for epigenetic regulation of chronic transcriptional effects of METH in the dorsal striatum. Figure 1 provides a scheme that describes a potential role of CoREST, HDAC2, MeCP2, and SIRT2 in the mediation of METH-induced downregulation of GluA1 and GluA2 mRNA levels. Specifically, CoREST might recruit SIRT2 onto the chromatin, with resulting H4K16ac hypoacetylation and decreased H4K16ac binding onto GluA1 and GluA2 DNA sequences. In addition, a METH-induced MeCP2-CoREST-HDAC2 complex might preferentially be involved in the hypoacetylation of histone H4 at lysines 5 and 12. The present observations add to the accumulating evidence that psychostimulants can cause substantial transcriptional and epigenetic changes in the brain. These results also suggest that therapeutic approaches that involved the use of epigenetic agents might be important areas for future investigations.

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Krasnova IN, Cadet JL (2009). Methamphetamine toxicity and messengers of death. *Brain Res Rev* **60**: 379–407.

Mehler MF (2008). Epigenetic principles and mechanisms underlying nervous system functions in health and disease. *Prog Neurobiol* **86**: 305–341.

McCoy MT, Jayanthi S, Wulu JA, Beauvais G, Ladenheim B, Martin TA *et al* (2011). Chronic methamphetamine exposure suppresses the striatal expression of members of multiple families of immediate early genes (IEGs) in the rat: normalization by an acute methamphetamine injection. *Psychopharmacology* **215**: 353–365.

Robison AJ, Nestler EJ (2011). Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci* **12**: 623–637.

Wolf ME, Ferrario CR (2010). AMPA receptor plasticity in the nucleus accumbens after repeated exposure to cocaine. *Neurosci Biobehav Rev* **35**: 185–211.

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Preclinical Studies Shed Light on Individual Variation in Addiction Vulnerability

Cues associated with drug use attract the attention of addicts, draw them to locations where drugs are located, and motivate drug-seeking—often leading