This Week in The Journal

Cocaine Sensitization Involves Decreases in DNA Methylation

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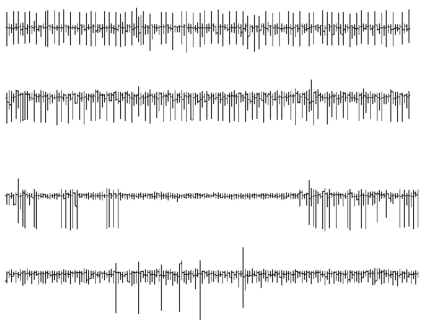
(see pages 8948 – 8958)

Alterations in DNA methylation are thought to contribute to learning, including drug-related learning, and thus may contribute to addiction. Methylation of cytosine residues near transcription start sites typically represses expression of the associated gene. Given the necessity of tightly regulating gene expression, it is remarkable that intravenous delivery of the amino acid L-methionine, a donor of methyl groups, can increase DNA methylation and alter gene expression. Moreover, this treatment has been shown to prevent mice from developing a preference for cocaine-associated chambers (Tian et al., 2012, PloS One 7:e33435).

Wright et al. have further investigated the relationship between DNA methylation and cocaine-related learning by treating rats with methionine, then examining behavioral sensitization and the acquisition, extinction, and reinstatement of cocaine-seeking behaviors. Cocaine increases locomotion in rats, and this behavioral response becomes sensitized—that is, greater increases in locomotion are produced by a given dose—with subsequent injections. This sensitization was blocked by methionine treatment. In contrast, methionine treatment did not alter the rate at which rats self-administered cocaine and it did not affect extinction of cocaine-seeking behaviors. After extinction, cocaine-seeking was reinstated by the presentation of a cocaine-associated cue regardless of whether methionine was administered, but methionine treatment attenuated the reinstatement of cocaine seeking that occurred after a priming dose of cocaine was administered.

To validate the hypothesis that methionine treatment alters responses to cocaine by modifying DNA methylation and gene expression, the authors examined expression of c-Fos. As shown previously, c-Fos expression was induced in the nucleus accumbens—a region involved in reward-seeking behaviors—after cocaine-primed reinstatement. This increase in expression was accompanied by a decrease in methylation of the c-Fos promoter. Importantly, both the reduction in DNA methylation and the increase in c-Fos expression were prevented by methionine treatment.

These data suggest that cocaine causes a reduction in the methylation of some genes in some brain areas, and that such epigenetic modifications make animals more sensitive to the behavioral effects of cocaine. Identification of other genes regulated in this way by cocaine may provide insight into the molecular mechanisms underlying cocaine addiction and may help identify treatments to reduce relapse.



Simple spiking in control Purkinje cells (top two traces) is more regular than in Purkinje cells expressing α1ACT that harbors a polyglutamine expansion (bottom two traces). See Mark et al. for details

Polyglutamine Expansion in P/Q Channel C Terminus Disrupts Cerebellar Plasticity

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(see pages 8882– 8895)

Spinocerebellar ataxia type 6 (SCA6) is characterized by progressive loss of balance and coordination stemming from cerebellar dysfunction. It is caused by expansion of a trinucleotide (CAG) repeat in the gene *CACNA1A*, which results in elongation of a polyglutamine sequence within two encoded proteins: the pore-forming α1A subunit of P/Q-type voltage-sensitive Ca^{2+} channels and a separate peptide comprising the cytoplasmic C terminus of α1A (α1ACT). P/Q channels are an important source of Ca^{2+} for spike-induced neurotransmitter release and they help to ensure regular spiking of Purkinje cells (PCs) by coupling to Ca^{2+}-dependent K^+ channels, but polyglutamine expansion appears to have little, if any, effect on the biophysical properties of P/Q channels. In contrast, expansion of α1ACT, which acts as a transcription factor regulating genes involved in PC development, disrupts α1ACT-mediated transcriptional regulation and causes modest motor impairment and cerebellar atrophy in mice (Du et al., 2013, Cell 154:118).

To further investigate the effects of polyglutamine expansion in α1ACT, Mark et al. expressed peptides including (CT-long) or lacking (CT-short) the sequence in mouse cerebellar neurons. When CT-long was expressed selectively in PCs (CT-long^{PC} mice), the PCs began to degenerate by 4 months of age, and the mice developed signs of progressive ataxia beginning at 8 months. In contrast, CT-short^{PC} mice showed no signs of neurodegeneration or ataxia until 18 months. In addition, eye blink conditioning—a cerebellum-dependent form of associative learning—was impaired in CT-long^{PC}, but not CT-short^{PC}, mice. The behavioral effects of CT-long were accompanied by changes in electrophysiological properties. Specifically, PC firing was more irregular in CT-long^{PC} than in CT-short^{PC} mice, and when virally introduced into mouse cerebellum, CT-long impaired long-term potentiation and depression at parallel-fiber-to-PC synapses.

These data demonstrate that polyglutamine expansion restricted to α1ACT is sufficient to induce PC dysfunction. The molecular mechanisms mediating this dysfunction remain to be elucidated. One possibility is that loss of transcriptional regulation by the expanded α1ACT leads to abnormal firing and impaired synaptic plasticity. Alternatively, the expanded α1ACT may disrupt interactions between the C terminus of P/Q channels and other proteins, such as K^+ channels. Future studies should investigate these mechanisms.

This Week in The Journal is written by Teresa Esch, Ph.D.