

EPIGENETIC REGULATION OF COCAINE ADDICTION

Arturo Martínez Martínez



Degree in Genetics. Universitat Autònoma de Barcelona. 2014-2015.
Tutor: Antonio Armario García

Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences. The addictive phenotype can persist for the length of an individual's life, suggesting that drugs of abuse may induce long-lasting changes in the brain.

NEUROBIOLOGY OF ADDICTION

The activation of the mesolimbic dopaminergic system produces a reward signal, related with learning mechanisms to beneficial actions. Drugs of abuse can activate this circuit far more intensively than natural rewards, being able to hijack these learning mechanisms. Besides, they can induce molecular adaptations, that translate into neuroplastic changes in the mesolimbic system.

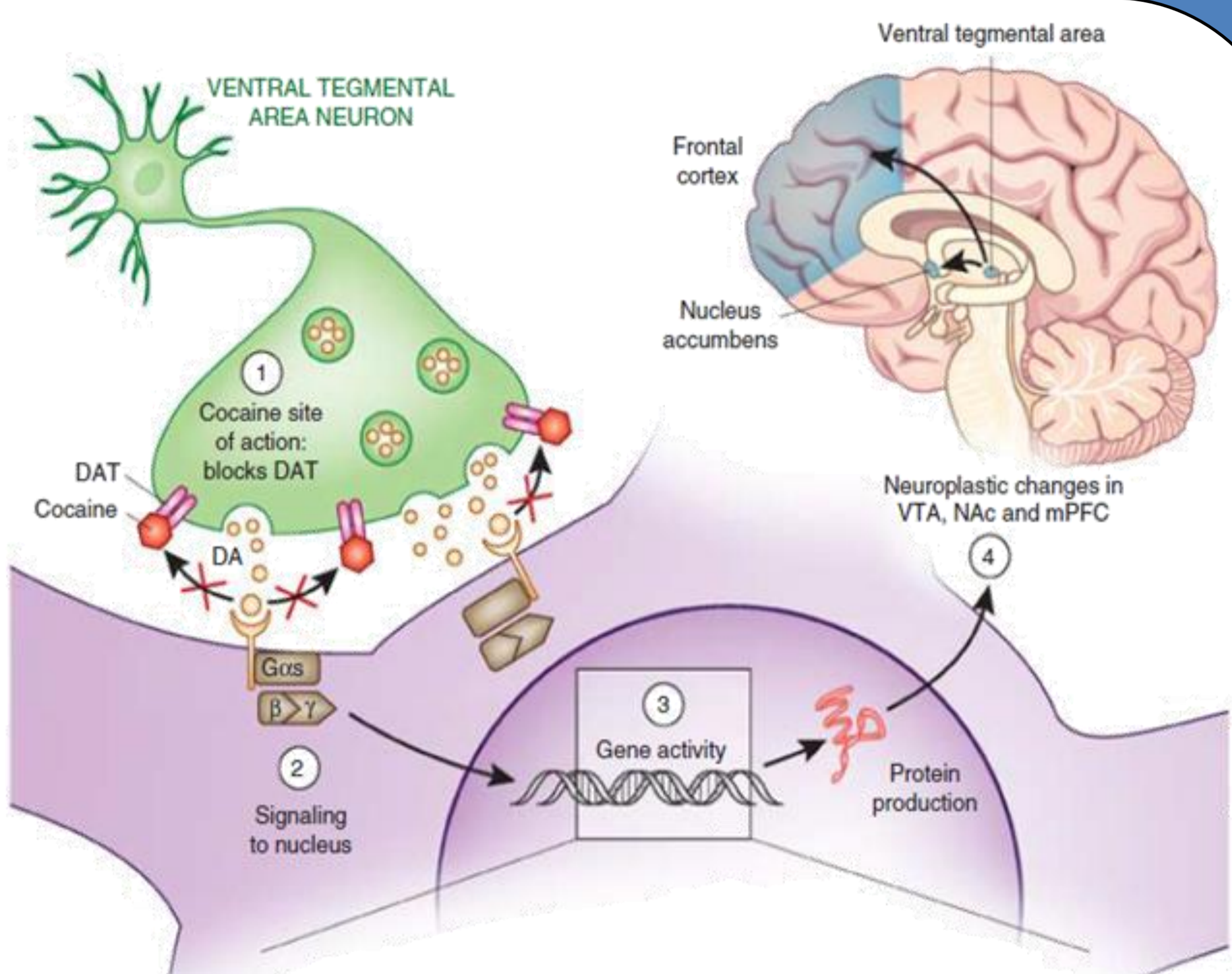


Figure 1. Cocaine induces molecular adaptations in the mesolimbic dopaminergic system. Extracted from Rogge & Wood, 2013.

EPIGENETIC MECHANISMS

Histone acetylation

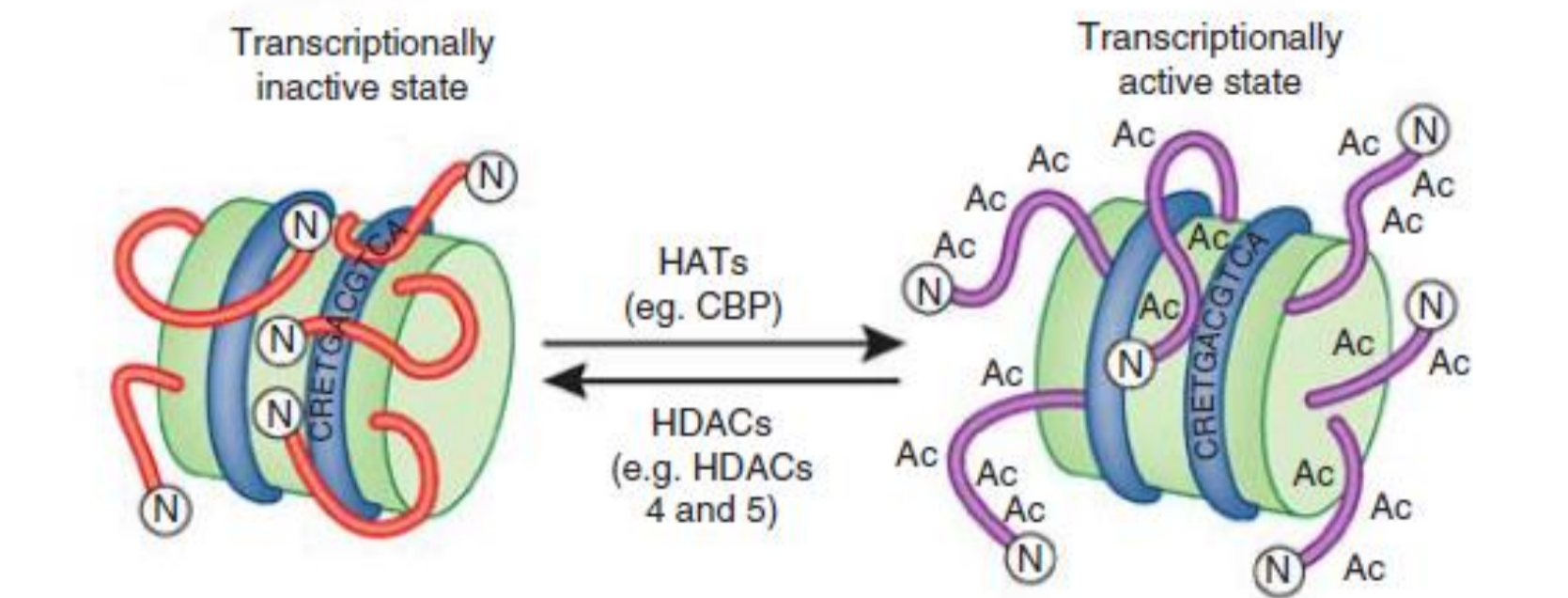


Figure 2. Histone acetylation, mediated by HATs and HDACs, can alter chromatin conformation. Extracted from Rogge & Wood, 2013.

Histone methylation

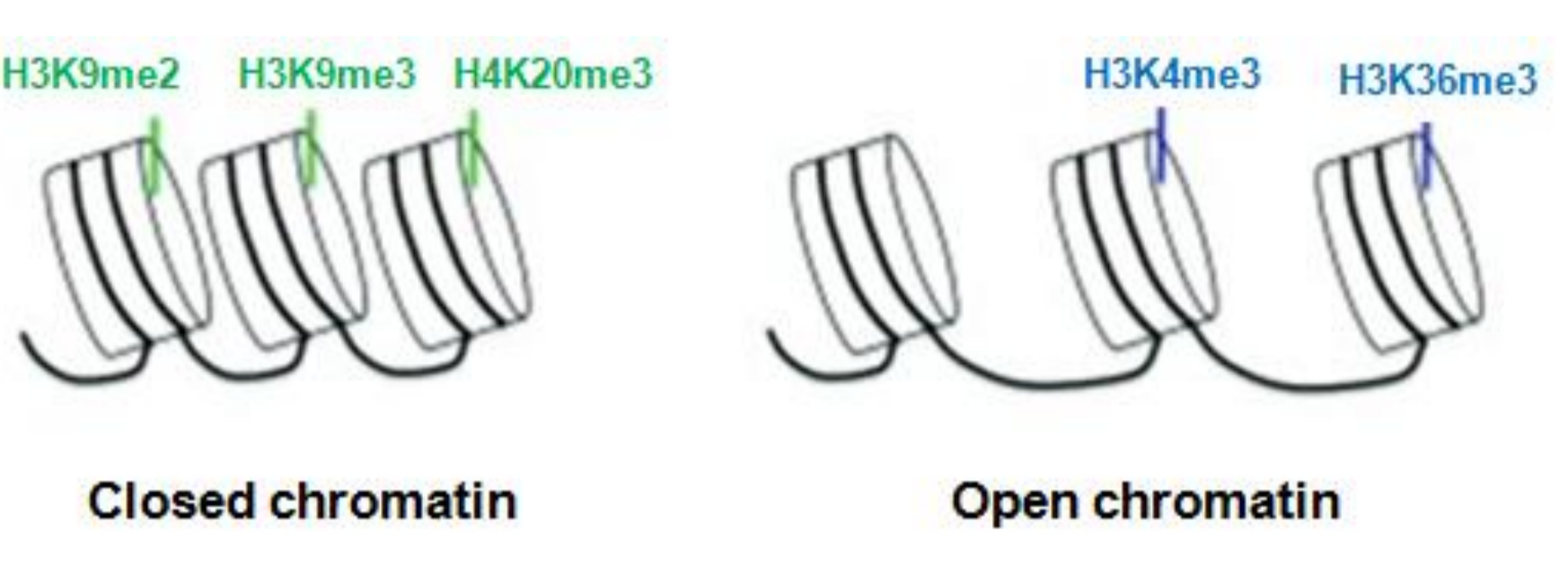


Figure 3. Histone methylation. Some modifications are marks of heterochromatin whereas others produce euchromatin. Adapted from Han & Brunet, 2012.

DNA methylation

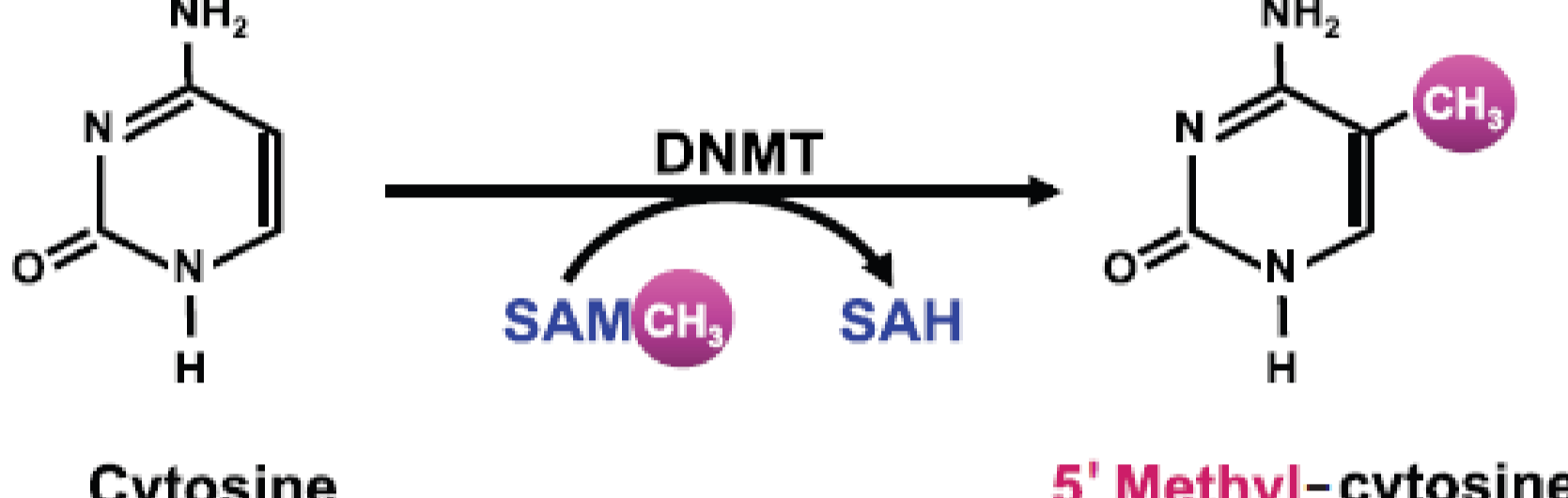


Figure 4. Schematic representation of cytosine methylation. Extracted from Zakhari, 2013.

miRNAs

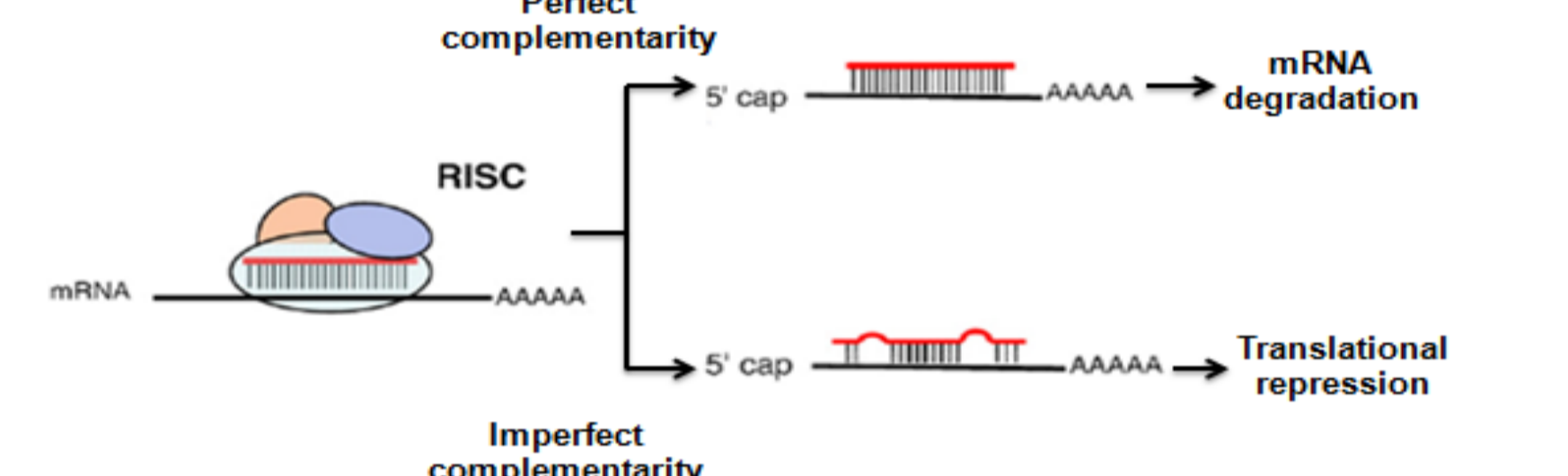
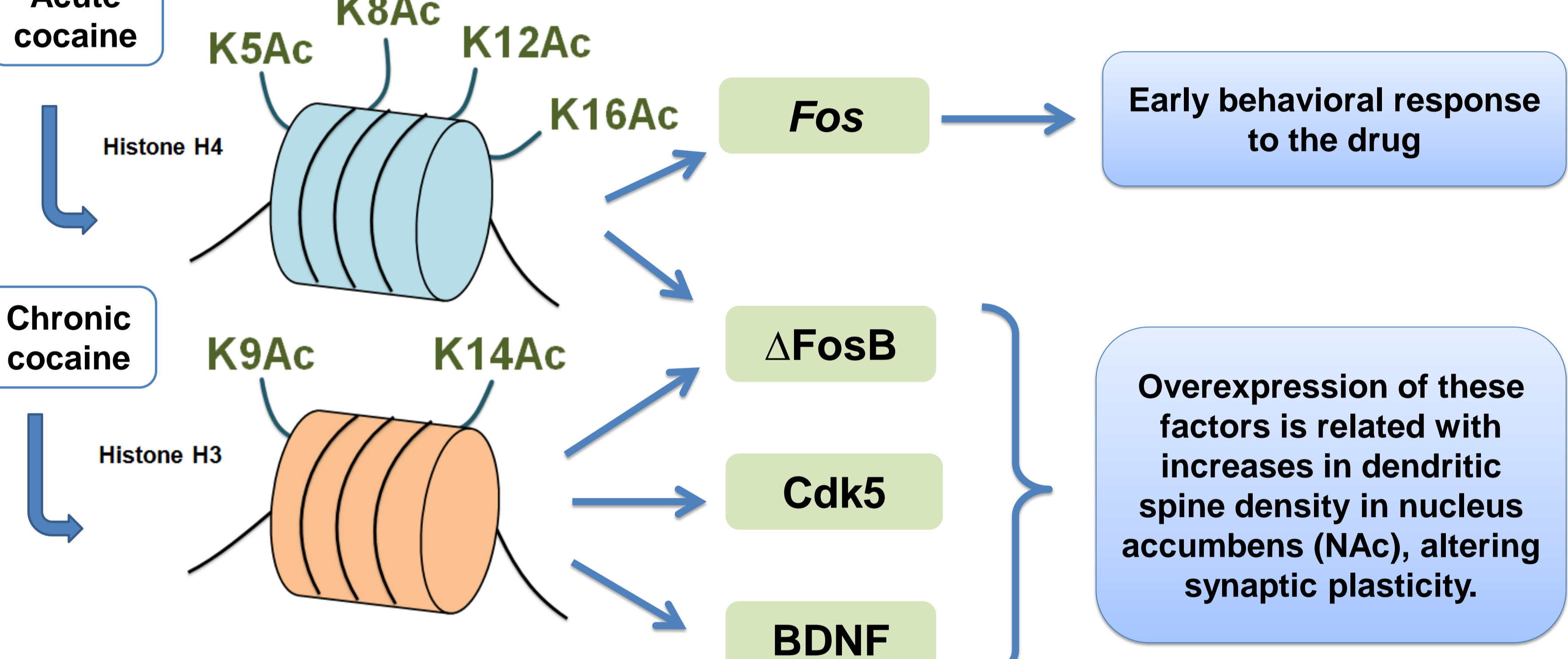


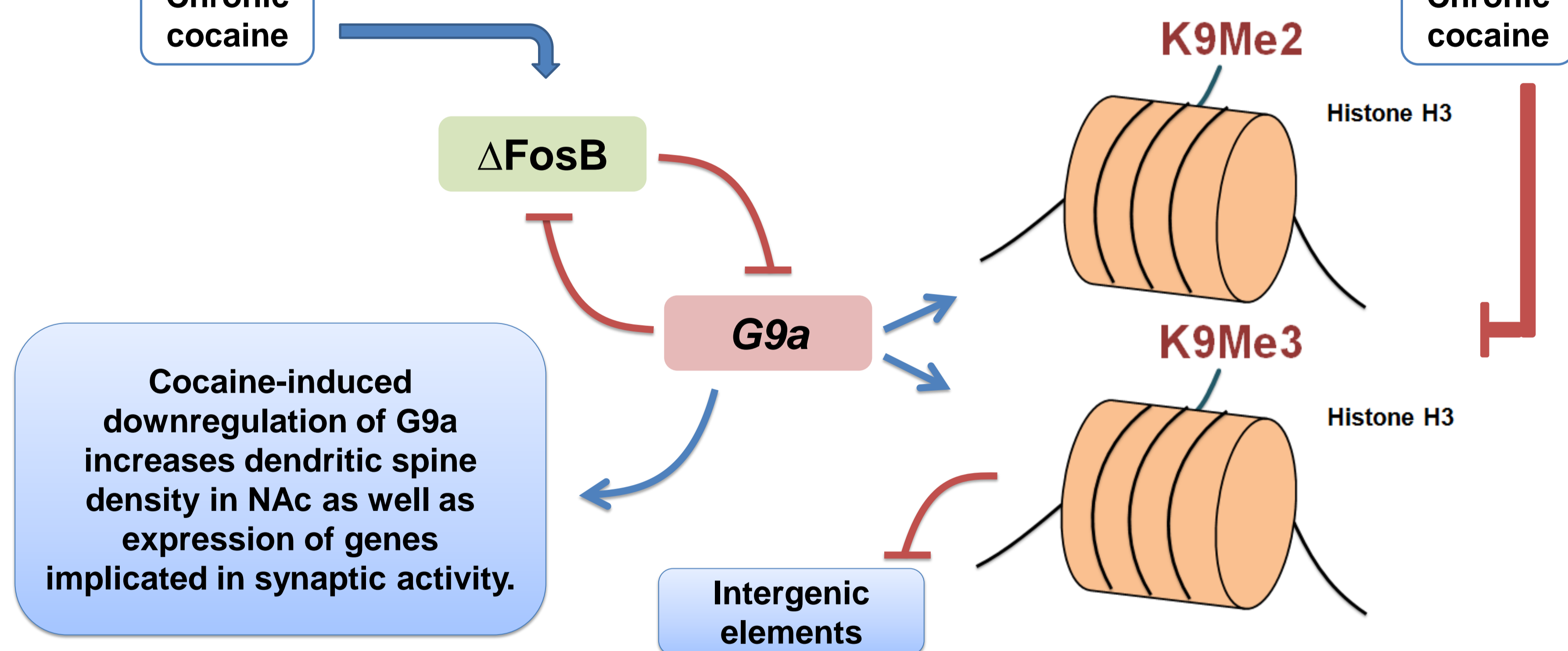
Figure 5. miRNAs form a protein complex (RISC) that can inhibit the expression of target mRNAs. Adapted from Faraoni et al., 2009.

EPIGENETIC REGULATION OF COCAINE ADDICTION

Histone acetylation

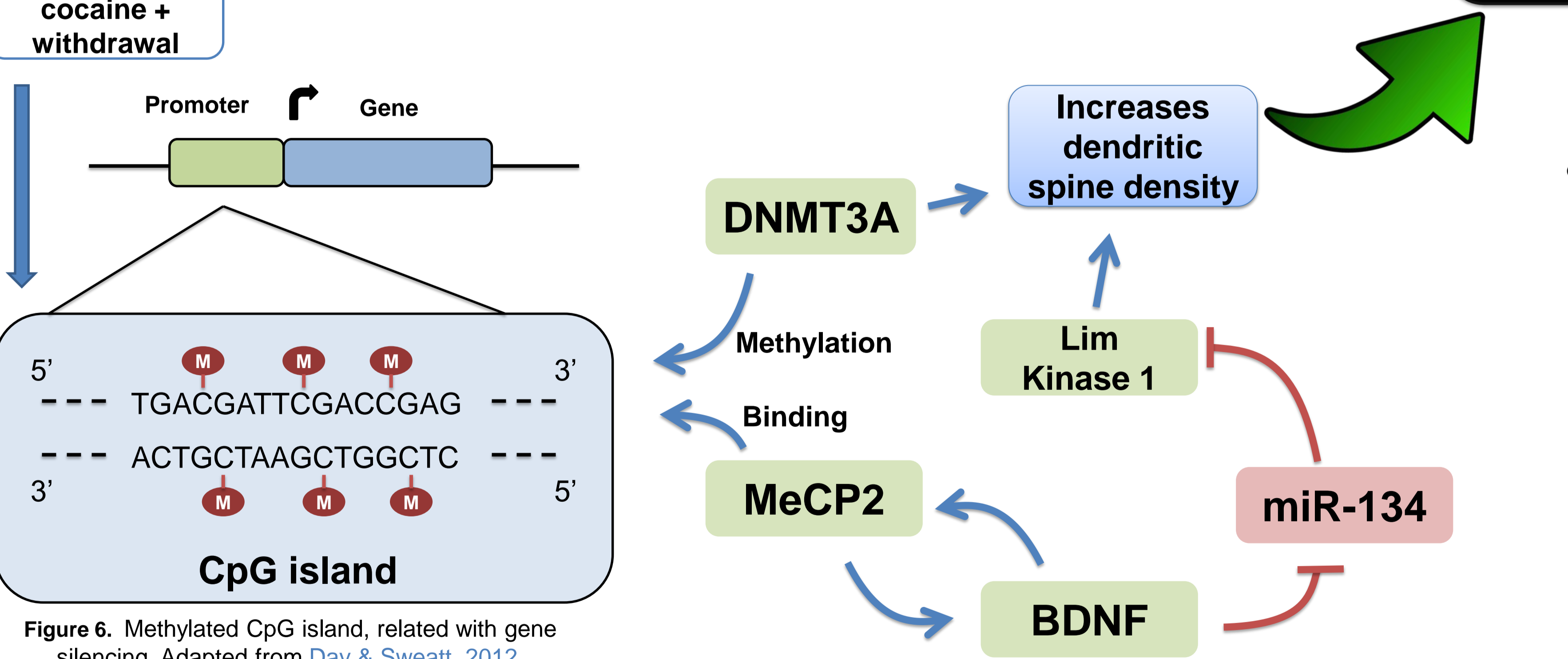


Histone methylation

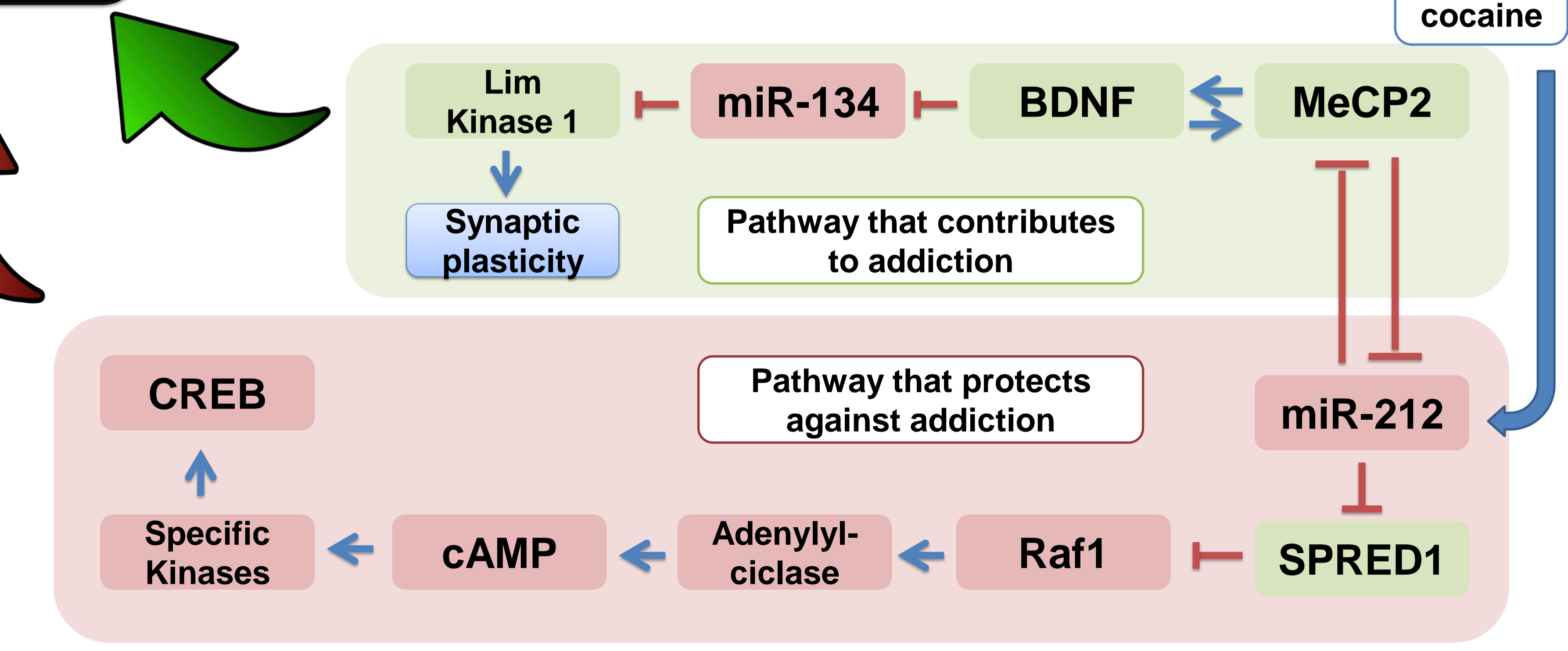


Escalating cocaine intake

DNA methylation



miRNAs



CONCLUSIONS

- The exposition to cocaine triggers mechanisms of epigenetic regulation involved in the modulation of synaptic plasticity and physiological adaptation in the mesolimbic dopaminergic system. These alterations correlate with escalating cocaine intake.
- Structural plasticity in NAc plays an important role in voluntary decision making towards drug intake.
- Chronic cocaine exposure causes molecular adaptations with contrary consequences, establishing a balance that can contribute more or less strongly to addiction. This effect may depend on several individual factors, such as genetic predisposition.
- Therapeutic implications: HDAC inhibition allows a faster extinction of drug-seeking behavior, also attenuating the probability of relapse.

REFERENCES

Day, J. J. & Sweatt, J. D. Epigenetic Treatments for Cognitive Impairments. *Neuropsychopharmacology* 37, 247–260 (2012).

Faraoni, I., Antonetti, F. R., Cardone, J. & Bonmassar, E. miR-155 gene: a typical multifunctional microRNA. *Biochim. Biophys. Acta* 1792, 497–505 (2009).

Han, S. & Brunet, A. Histone methylation makes its mark on longevity. *Trends Cell Biol.* 22, 42–49 (2012).

Rogge, G. A. & Wood, M. A. The Role of Histone Acetylation in Cocaine-Induced Neural Plasticity and Behavior. *Neuropsychopharmacology* 38, 94–110 (2012).

Zakhari, S. Alcohol metabolism and epigenetics changes. *Alcohol Res.* 35, 6–16 (2013).