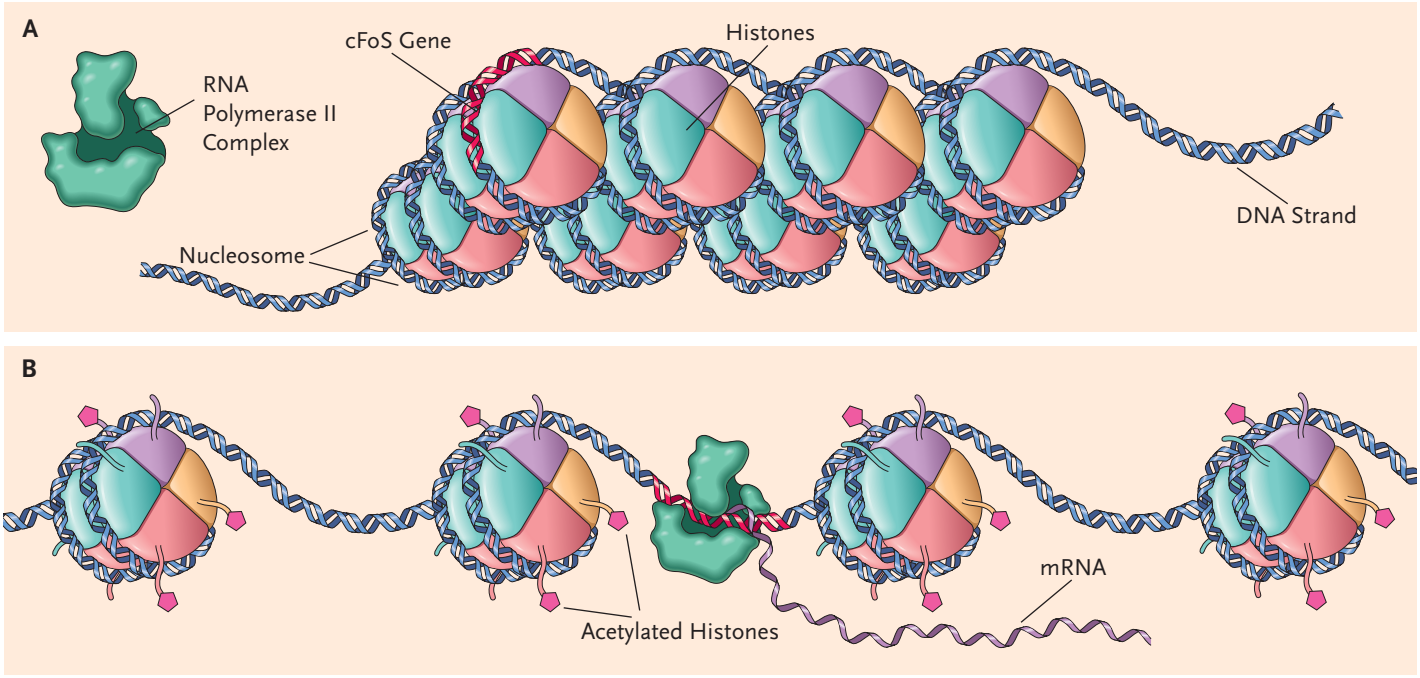
Graphic Evidence

Cocaine Activates Genes Through Chromatin Remodeling



Scientists recently pinpointed a basic mechanism underlying some cocaine-associated brain changes. The drug triggers chromatin remodeling, a common process that alters the rate of gene transcription—the initial step in the process of making new protein molecules.

Chromatin remodeling contributes to healthy adaptations, including learning and memory, and to diseases, including schizophrenia. Dr. Eric Nestler and colleagues at the University of Texas Southwestern Medical Center and Harvard Medical School revealed its role in cocaine pathology. In a series of experiments with rats, they demonstrated that cocaine-induced chromatin remodeling increases the production rates of four proteins that have been implicated in cocaine addiction: cFos, Δ FosB, BDNF, and Cdk5.

Each of the body's roughly 26,000 genes consists of a chain of deoxyribonucleic acid (DNA) molecules interpolated into 1 of 23 long DNA strands called chromosomes. The DNA strand loops around a core structure made up of molecules called histones, which are packed in clusters called nucleosomes. Together, the DNA and core are called chromatin.

Prior to cocaine exposure (Panel A), the nucleosomes in chromosome 14 are closely packed. The DNA strand, which includes the gene for the cFos protein, loops tightly around them. The gene's compact configuration limits the ability of free-floating molecules—including those that transcribe the gene—to access, attach to, and interact with it.

Cocaine remodels (reshapes) the chromatin by causing the nucleosomes to separate and spread out (Panel B). The DNA strand now stretches across open spaces between the nucleosomes, exposing the *cFos* gene broadly to free-floating molecules. One such molecule, the RNA polymerase II complex, attaches to the gene. It will transcribe the gene by working its way along the genetic DNA and constructing a complementary molecular strand of messenger ribonucleic acid (mRNA). After several further steps, this process will culminate in the construction of a new molecule of cFos.

The alteration of histones is the change that starts the chromatin-remodeling process in this example. Cocaine reacts chemically with some histones, converting them to acetylated and phosphoacetylated variants (tagged with pink pentagons in Panel B) that have different molecular shapes, causing the nucleosomes to separate.

Dr. Nestler and colleagues also showed that increased levels of altered histones correspond with drug-seeking behaviors in animals, while blocking histone alteration inhibits such behaviors. Such insights into the neural changes in cocaine addiction, and their behavioral consequences, may be clues to effective new treatments.

Sources: Feinberg, A.P., 2007. Phenotypic plasticity and the epigenetics of human disease. *Nature* 447(7143):433-440.

Kumar, A., et al., 2005. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. *Neuron* 48(2):303-314.

Renthal, W., et al., 2007. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. *Neuron* 56(3):517-529.