The Role of Smoking in Cocaine Addiction

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1- The Brain, memory, metaplasticity

The brain is the most complex and less understood organ in our body. It is formed by billions of cells that dynamically interact to control most, if not all, aspects of our life and define who we are. A very dynamic organ, it is not complete at birth, but keeps growing during childhood and fully matures only after adolescence. And continues to evolve throughout life, allowing us to adapt to the environment around us and our experiences. This ability of the brain to dynamically evolve is defined *brain plasticity*.

Although considered a single tissue, the brain is characterized by different, but interconnected, regions that have specific functions (Fig 1).

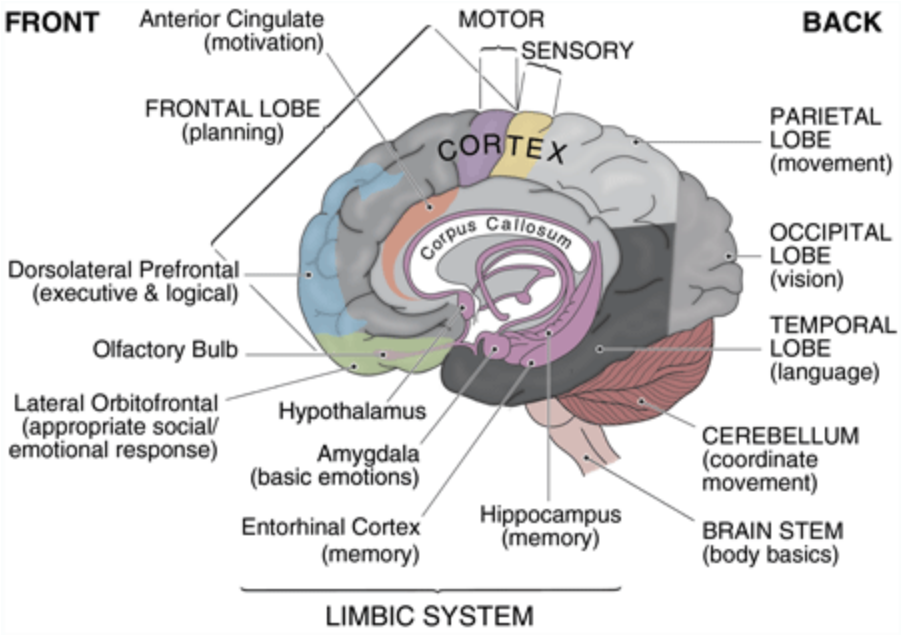


Fig 1 The Brain is characterized by several interconnected regions

For instance, the olfactory bulb is involved in the perception of odors, the amygdala plays a major role in processing emotions, the hippocampus is involved in memory forming and storing while the region responsible for reward, pleasure but also for addictive phenotype is

the striatum (Fig 2).

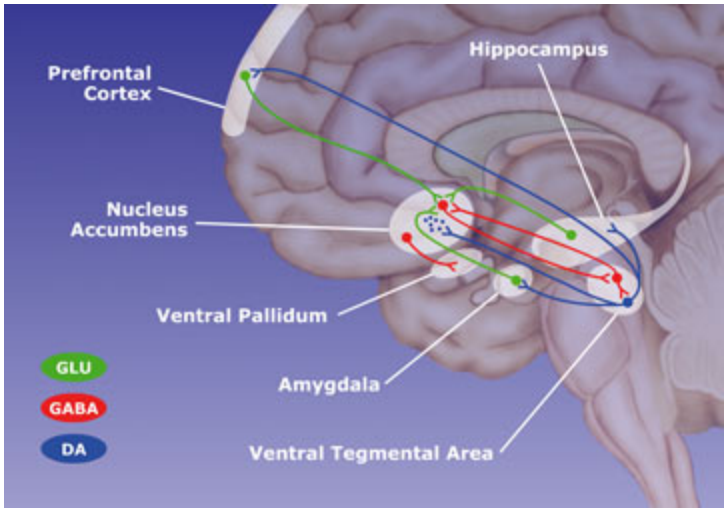


Fig 2 The Striatum is a brain region that regulates reward and addictive phenotypes. The Nucleus Accumbens (N. Acc) and the Ventral Tegmental Area (VTA) are considered the center of addiction.

One of the most remarkable aspects of the brain, and something that has fascinated philosophers, writers and scientists for centuries, is its ability to create memories. An aspect that only now we are starting to understand. The brain encodes for two general types of memories: *short term memory* and *long term memory*. Although the two processes share common mechanisms, they are also profoundly different. *Short term memory*, as the name suggests, is a transient process that does not require expression of new genes or synthesis of new proteins. At any given time all the components required for *short term memory* are present in neurons. However, this memories do not last for a very long time (between minutes to hours) but they can be transformed in *long term memories* when needed. *Long term memories* are thought to be stored in the bioelectrical field generated by networks or circuits

of neurons, and the learning process (meaning how we learn that something has happened) is regulated by the strength of the connections between this neurons. While *short term memories* do not change the strength of synapses, *long term memories do*, allowing the brain to remember specific facts or events.

The transformation of *short term memories* to *long term memories* requires expression of new genes, alterations in the chromatin structure in the nucleus and growth and maintenance of new synaptic connections requiring activation of local protein synthesis at the synapse. This dynamic process is called synaptic plasticity or more in general brain plasticity (Kandel ER 2012).

More recently however, scientists have discovered that the current plasticity state of synapses also depends on their history and they named this phenomenon metaplasticity. Technically, metaplasticity ascertains that certain past experiences change synaptic architecture and neural circuitry in the brain so that when another event comes along it is experienced differently than if the past experience did not occur.

Genes and Proteins Expression

The DNA in the nucleus is organized in a three dimensional structure called chromatin, formed by the DNA itself and specific proteins called histones. The DNA has a high chemical affinity for the histones and it wraps around them (Fig 3).

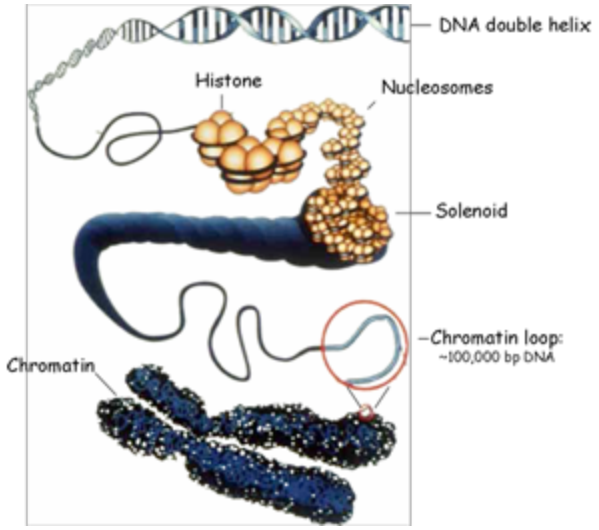


Fig 3 The DNA is organized in a three dimensional structure called chromatin

The role of the histones is not only to organized the DNA but also to regulate the expression of the encoded genes by masking them (Fig 4).

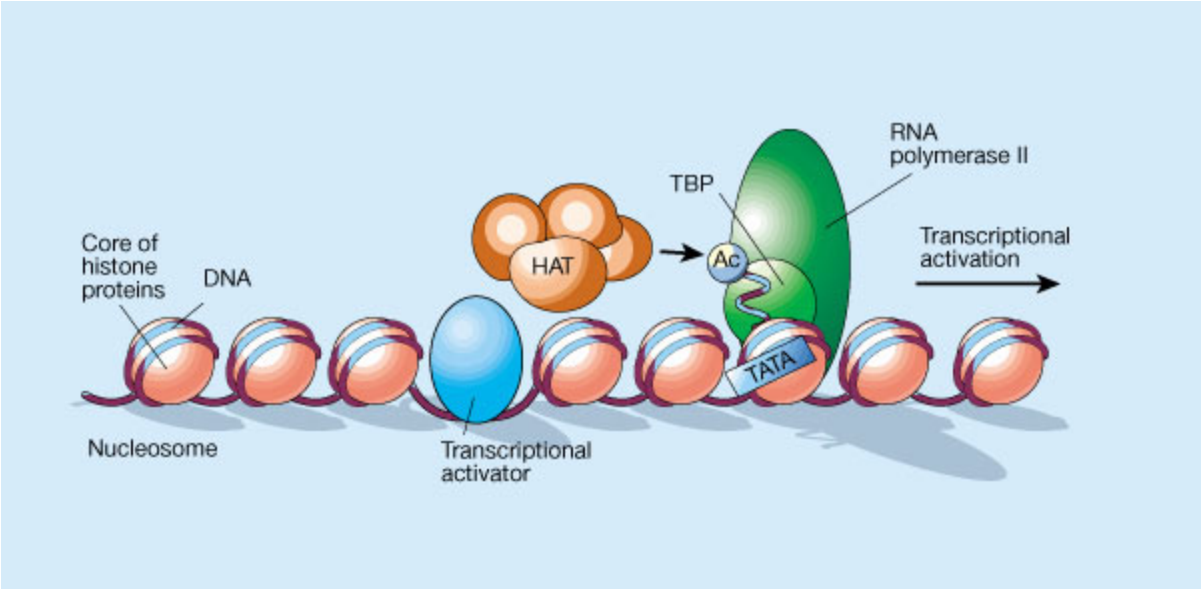
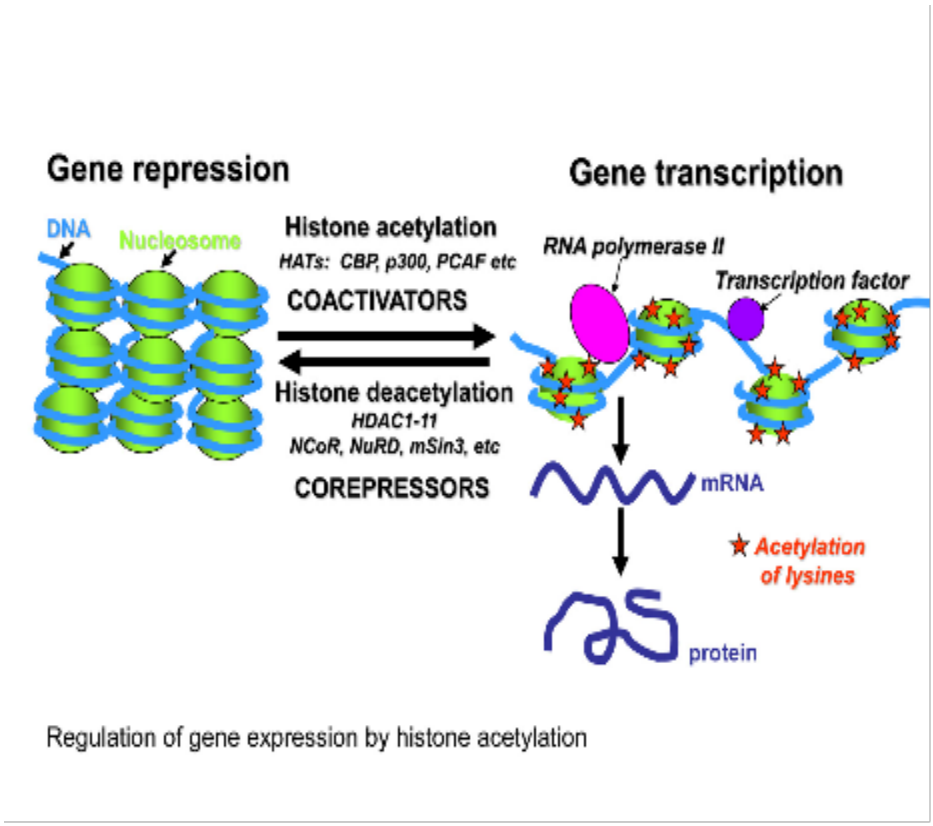


Fig 4 Histones regulate gene expression.

To activate a gene, specific enzymes called histone acetyltransferases bind the histones and

displace them, allowing the DNA to be seen by the transcriptional machinery and the genes to be expressed. Histone deacetylases (HDAC), on the other hand, suppress gene expression by increasing the number of histones bound to the DNA (Fig 5). Gene expression creates mRNA that is next translated into proteins in the cytoplasm.



Regulation of gene expression by histone acetylation

Fig 5 Histone acetyltransferase (HAT) and histone deacetylases (HDACs) regulate histone affinity to DNA and gene expression.

2- Cocaine Addiction

The 2010 National Survey on Drug Use and Health reported that almost 37 million Americans, 12 years of age or older, have tried cocaine in their lifetime, and 5.7 million have used it in the past year – making cocaine the second most commonly used drug of abuse in the United States. The reasons for its popularity are its immediate psychological effects. Snorted or injected cocaine induces self-confidence, euphoria and good feelings, magnifying the intensity of almost all normal pleasures. However, cocaine use also causes medical complications like respiratory failure, cardiovascular and gastrointestinal problems and paranoia. Moreover, after prolonged exposure, individuals become addicted to it, losing control over use of the drug and engaging in destructive behavior related to cocaine procurement. Cocaine addiction is a chronic relapsing condition with high risk of medical complications, cognitive impairment, financial ruin and social issues.

At the cellular level, cocaine increases the available quantity of the neurotransmitter dopamine in the brain, thereby inducing immediate euphoria and pleasure. Dopamine, produced by dopaminergic neurons, controls the activity of dopamine responsive nerve cells, which are particularly abundant in a series of interconnected brain regions that form the mesolimbic dopamine system. In the latter, dopamine stimulates several regions, among them the striatum to produce feelings of reward. Thus, by altering the levels of dopamine in the striatum, cocaine creates intense pleasure and euphoria.

Aside from the striatum, the limbic system contains other regions that are critical substrates for the neural adaptations that underlie addiction. In particular, the amygdala and the hippocampus play a role in memory formation and storage. These regions create long lasting memories of the intense pleasure and the environment associated with drug use, which will

later trigger the desire to repeat the experience and lead to addiction. These memories make cocaine addicts vulnerable to relapse even after years of abstinence. Indeed, re-exposure to cues previously associated with cocaine often provokes cocaine craving that can trigger compulsive drug use. Making cocaine addiction a memory disease.

Cocaine also causes other long-term effects on the brain. Chronic exposure to the drug alters the expression of several genes in the limbic system, which ultimately results in synaptic plasticity changes. A major player in this process seems to be a transcription factor (an enzyme that regulates gene expression) called deltaFosB. Scientists have found that repeated administration of many kinds of drugs of abuse, included cocaine, increase the presence of this protein in the neurons of the striatum. Moreover, genetically engineered mice that overexpress the deltaFosB gene show an enhanced addictive phenotype, linking directly the gene with drug addiction (McClung 2003).

3- The gateway hypothesis

The existence of a developmental sequence of involvement in drugs is one of the best replicated findings in the epidemiology of drug use (Kandel D., 2002). Both in the United States and in other western societies, a regular sequence and stages of progression have been found. In this sequence, the use of cigarettes (nicotine) or alcohol precedes the use of marijuana (cannabis) and, in turn, the use of marijuana precedes the use of other illicit drugs. Very few individuals who have tried cocaine and heroin have not previously used marijuana; and the majority have used alcohol or cigarettes prior to their use of marijuana. Such behavioral regularities have given rise to the “Gateway Hypothesis.” However, in the 30 years

since publication of the original observation (Kandel D. & Faust, 1975), surprisingly little progress has been made in addressing three fundamental questions that derive from the observation that the use of one class of drug is followed by the use of another class. Thus, my laboratory decided to investigate (1) if the use of the first class of drugs, such as nicotine, is a cause of the use of the second class, such as cocaine, or whether the sequence is determined exclusively by availability of the drug or other social factors; (2) what biological mechanisms underlie this progression in drug use; and (3) why early use during adolescence leads to more extensive and chronic use than later onset of drug use post-adolescence.

One reason there has been little progress in the mechanistic understanding of the Gateway Hypothesis is the difficulty of establishing causality in the context of non-experimental epidemiological data. One way to begin to address causality is to use animal models in mice to test epidemiological hypotheses. Mice provide the opportunity for testing directly the causal association between drugs assumed by the Gateway Hypothesis and for identifying underlying biological and behavioral mechanisms. While animal models cannot mimic the variety of cultural, social, and psychological factors that determine drug behavior in human populations (e.g., norms, peer influences, personal meanings, personal traits, etc), animal models can examine one of the fundamental questions that underlies the Gateway Hypothesis: Does prior use of a drug class per se increase the risk of the use of another drug class? In mice, this question can be asked in relation to well-defined prior experiences with specific drugs, independently of questions of access or any other social or legal constraints regulating and defining drug use. Alternate specifications of the sequential order of drug presentation can further help resolve the possibility that the ordered use between any two drugs is determined exclusively by social factors or by the availability of different

substances. In addition, because molecular biology and genetics can readily be used in mice, underlying mechanisms can in principle be identified. Finally, since initial drug involvement in human populations begins most often during adolescence, mouse models also allow one to explore age as a potentially important contributor to the Gateway Hypothesis. Insights from these investigations can in turn feedback and guide future epidemiological studies and even potentially suggest possible new avenues of intervention.

4- Experimental evidence supporting the Gateway Hypothesis

The epidemiological finding that nicotine use (via tobacco smoking) often precedes the use of other drugs may indicate that nicotine has unique biological characteristics which underlie its ability to serve as one of the "gateways" to the use of other addictive drugs. We now have obtained direct evidence to support this component of the Gateway Hypothesis in male mice. We find that pre-exposure to nicotine enhances the subsequent molecular and behavioral response to cocaine, while the reverse does not hold. Pre-exposure to cocaine does not enhance response to nicotine.

More specifically, chronic administration of nicotine causes upregulation of the nicotinic a7* and b2* receptors, and these types of receptors are required for cocaine-induced behavioral sensitization. Blocking these two types of receptors blocks the effects of cocaine. Nicotine also increases the expression of the transcription factor deltaFosB, by altering the chromatin structure in the nucleus. Nicotine inhibits the enzymatic activity of HDACs, thus allowing higher expression of genes, deltaFosB included.

Moreover, nicotine enhances the effects of cocaine increasing locomotion activity in mice

following cocaine exposure and cocaine preference (Levine 2011) (Fig 6).

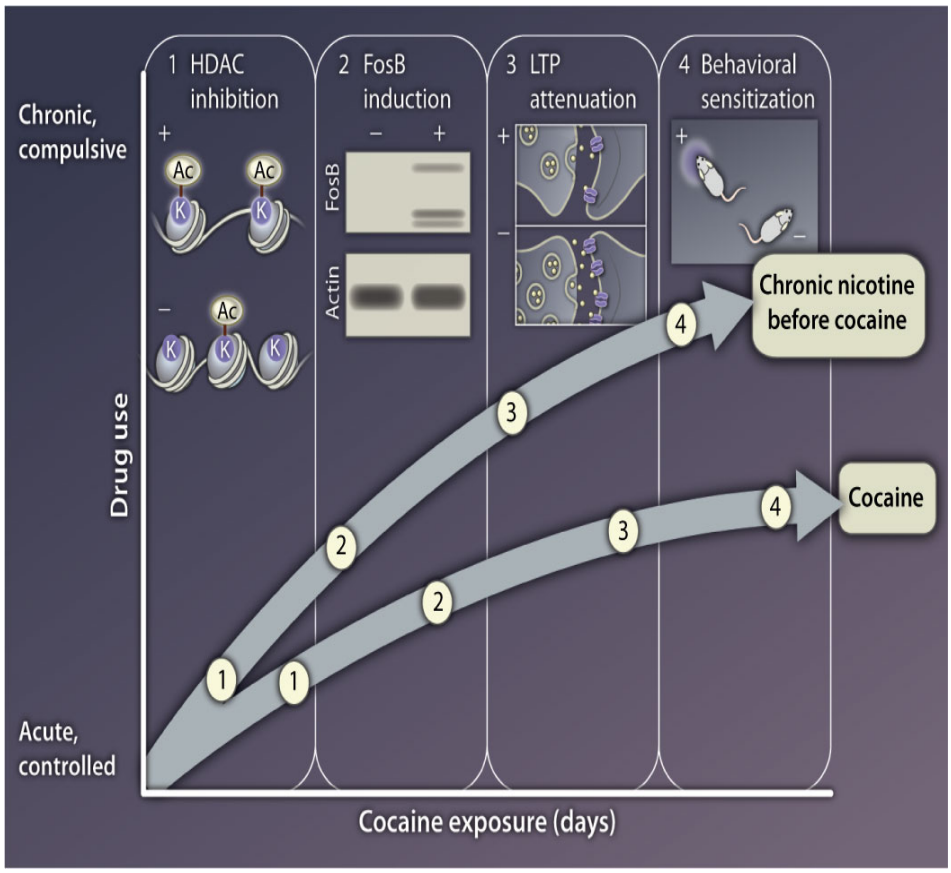


Fig 6 Nicotine pretreatment increases cocaine effects.

These results suggest that nicotine exposure rewires the brain at the molecular and cellular level to enhance the effect of cocaine. Thus, the new findings open a wide range of research and translational opportunities.

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