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Drugs, Crime, and the Epigenetics of Hedonic Allostasis

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Abstract

Researchers have found staggering numbers of drug addicts among incarcerated populations and have conceded that drug abuse is an important correlate of deviant behavior, but few included an understanding of the biological process leading to drug addiction. Chronic drug abuse and criminality are housed within a much broader propensity of some individuals to engage in a variety of antisocial behaviors, and this article clarifies the link and proposed shared mechanisms between criminal behavior and drug abuse through a molecular-genetic and neurobiological lens. Multiple genes, enzymes, and transcription factors are involved in drug addiction, with over 100 genes known to be changed with repeated cocaine exposure. The epigenetics of drug addiction, with a specific emphasis on the addiction of cocaine, are brought under examination here. The epigenetic processes of methylation and acetylation are described and their long term effects are illustrated within the processes of allostatic changes to the brain. After the establishment of the rudiments of epigenetic operation and their effects, a discussion is presented on the opponent process and incentive-sensitization models of drug addiction and how all of these factors are impacted by socio-cultural variables.

Drugs and Crime

The Office of Drug Control Policy's Arrestee Drug Abuse Monitoring (ADAM) Program (2010) Found that between 60 and 85% of arrestees in 10 major cities in 2009 tested positive for at least one kind of illicit drug. These data clearly show that illicit drug abuse is strongly associated with criminal behavior, but the link is not necessarily a causal one. Research indicates that drug abuse does not initiate a criminal career, although it does increase the extent and seriousness of one (Menard, Mihalic, & Huizinga, 2001; Quinn & Sneed, 2008). The typical drug addict is not an innocent driven into a criminal career by drugs, although this may occasionally be true. Rather, chronic drug abuse and criminality are part of a broader propensity of some individuals to engage in a variety of antisocial behaviors. A number of studies have shown that traits characterizing antisocial individuals such as ADHD/CD comorbidity, impulsiveness, and high scores on the Psychopathy Checklist also characterize drug addicts (Fishbein, 2003; McDermott et al., 2000). Serious illicit drug use contributes to continuity in a criminal career, however (Menard, Mihalic, & Huizinga, 2001)

This paper explores the alleged common underpinnings of addiction and criminal behavior by examining the epigenetics of drug addiction, with an emphasis on cocaine. A number of criminologists have maintained that criminology is entering a biosocial phase (Cullen, 2009; Walsh, 2009; Wright & Boisvert, 2009). Given this, we believe it to be imperative that criminologists have at least a nodding acquaintance with the processes of how the brain adjusts to chronic drug abuse in order to understand addiction and how difficult it is to beat.

Reward Dominance Theory: The BIS and BAS of Behavior

If social animals are to function normally in their groups they must respond to signals of reward and punishment with socially appropriate approach and avoidance behavior. The major neurobiological theory of behavioral control is *reward dominance theory* (RDT) (Corr, 2004). RDT posits two primary systems of emotional/behavioral regulation located within separate brain circuits that rely on different neurotransmitters: the *behavioral activating (or approach) system* (BAS), and the *behavioral inhibition system* (BIS). The BAS and BIS are part of the limbic system with extension projections into the prefrontal cortex (PFC), the brain's "command and control center." The BAS is sensitive to signals of reward from both conditioned (e.g., alcohol, gambling) and unconditioned (e.g., food, sex) appetitive stimuli. The BIS is sensitive to conditioned (e.g., violations of social rules) and unconditioned (e.g., heights, snarling creatures) threats of punishment (Corr, 2004).

The BAS is primarily associated with dopamine (DA) and with mesolimbic system structures such as the nucleus accumbens, a structure rich in neurons that produce and respond to DA (Day & Carelli, 2007). The BIS is associated with serotonin (5-HT) and with limbic system structures such as the hippocampus and the amygdala that feed their memory circuits into the PFC (Goldsmith & Davidson, 2004). DA and 5-HT are powerful regulators of behavioral and cognitive functions, thus any aspect of reduced and/or enhanced serotonergic or dopaminergic functioning results in emotional, behavioral, and cognitive dysregulation.

The BAS can be likened to an accelerator motivating a person to seek rewarding stimuli; it obeys the pleasure principle driving the organism to acquiring life sustaining necessities and pleasures. The BIS strives for the ideal and represents all the moral and social prescriptions and proscriptions internalized during socialization, and it can be likened to a brake that inhibits a person from going too far in the pursuit pleasure. A normal BAS combined with a faulty BIS or vice versa, may lead to a “craving brain” that can get a person into many physical, social, moral and legal difficulties, such as addiction to gambling, food, sex, alcohol, and drugs (Wand, 2008). Because most of these rewards are natural (unconditioned) they evoke natural responses such as salivation, consumption, and sexual arousal (unconditioned responses) they thus constitute classical (Pavlovian) conditioning, although they become embedded in operant conditioning circumstances as they are actively sought out (Day & Carelli, 2007).

The craving brain concept is common to all craving behaviors, which is why few people are addicted to just one substance or behavior, and why individuals easily addicted are also ripe candidates for criminal behavior (Fishbein, 2001). But addiction is not only about hedonic pleasure because we all receive gratification from the natural pleasures (eating, drinking, sexual activity, bonding) that natural selection has built into us to assure that we like doing things that contribute to our survival and reproduction efforts. Pleasure obtained from unnatural (i.e., evolutionarily novel) sources hijack the brain because they involve much greater DA signaling, thus usurping neural circuits that control responses to natural rewards. As Hyman (2007, p. 10) explains: “unlike natural rewards, addictive drugs always signal ‘better than expected.’ Neural circuits ‘over-learn’ on an excessive and grossly distorted dopamine signal.”

“Better than expected” is a subjective appraisal of bodily states arising from neural firing patterns. Dopaminergic neurons transmit signals by phasic firing (short transient bursts of several signals) or tonic firing (low signaling for a longer period of time). The patterns of phasic/tonic firing are thought to determine the salience of a reward signal (Tsai et al., 2009). A reward that is “better than expected” results in increased DA firing and one that is “worse than expected” results in less firing. Natural rewards that are “just as expected” do not alter the homeostatic rates of neuronal firing. It has been proposed by many addiction researchers that the transition from casual use of drugs to addiction reflects a shift from “better than expected” to “worse than expected” by altering the DA systems natural set points (Wand, 2008).

Epigenetics and Substance Abuse

No other area provides the interesting nuances of the interplay of nature and nurture as epigenetics. The prefix “epi” means *on* or *in addition to*, thus epigenetics means on or in addition to the genes, and includes “any process that alters gene activity without changing the DNA sequence” (Weinhold, 2006, p. 163). Epigenetic modifications affect the ability of the DNA code to be read and translated into proteins by making the code accessible or inaccessible (Gottlieb, 2007). DNA itself only specifies for transcription into messenger RNA (mRNA) which has to be translated by transfer RNA (tRNA) and assembled by ribosomal RNA (rRNA). The genes are switched on and off by signals from the organism’s internal chemical environment and/or by its external environment according to the physical and emotional challenges it faces.

Both the brain and the genome are designed to incorporate environmental information. Neural plasticity allows for novel responses as the brain is physically calibrated to environmental events. Although the genome does not possess the brain’s level of plasticity, epigenetics provides the software by which organisms respond genetically to their environments without changing the DNA hardware. Epigenetic modifications of DNA are more vulnerable to environmental factors than the DNA itself because there is no intracellular repair system for epigenetic errors similar to the system that repairs nucleotide copying errors in the DNA (Kubota et al., 2010). Genome plasticity, like brain plasticity, is therefore both good and bad according to the environments it is exposed to. Because epigenetic processes regulate gene expression according to what the organism does or ingests, the epigenetics of substance abuse is of major importance to criminologists who want a deeper understanding of this major crime correlate.

The epigenetic regulation of genetic activity is accomplished by two main processes: DNA methylation and acetylation (also called histone modification). Acetylation involves a groups of atoms called an acetyl group attaching itself to histones (see figures 1 and 2) which has the effect of “loosening” or “relaxing” them, which increases the likelihood of genetic expression. Conversely, deacetylation (the removal of the acetyl group) has the opposite effect (Lopez-Rangel & Lewis, 2006). DNA methylation occurs when a group of atoms called a methyl group are attached to a cytosine base which prevents the translation of DNA into mRNA, and hence the protein the gene codes for is not manufactured (Corwin, 2004). To apply a criminal justice metaphor to these processes, acetylation is a mechanism that aid and abets gene expression and methylation arrests it. Methylation can produce stable, even permanent changes in genetic functioning, but acetylation is labile and reversible (Powledge, 2009).

Epigenetic Mechanisms of Drug Addiction

Understanding how drugs alter brain chemistry helps to explain why addiction is so difficult to beat and of the importance of gene-environment interactions. Multiple genes, enzymes, and transcription factors are involved in drug addiction, with over 100 genes known to be changed with repeated cocaine exposure (Madras, 2006). There are two major models of the pathway from use to addiction, indicating that individual differences in susceptibility must be considered. Both models have in common the role played by DA signaling and point to weak executive functioning (low self-control), thus implicating the roles played by the PFC and the serotonergic system (Ahmed, Graupner & Gutkin, 2009).

We couch our discussion of epigenetic mechanisms in terms of cocaine addiction because it has the largest average heritability coefficient (.67) of all commonly abused substances (Bevilacqua & Goldman, 2009). However, only about 15-16% of users become addicted, just slightly more than the percentage of users of alcohol who become addicted to alcohol (Robinson & Berridge, 2003). The bare outline of what cocaine does is that it releases DA in the pleasure centers and then blocks its reuptake into the presynaptic knob. This blockage leaves DA signaling at DA receptors at the postsynaptic knob for much longer than the milliseconds it resides there in response to natural rewards. When DA stays in the synaptic gap and not taken back up for repackaging, it is eventually broken down by enzymes. The exposure and destruction of excess DA at the synapse leads to depletion of the neurons’ supply, leaving the abuser unable to feel much pleasure from natural rewards. This is an abnormal state of affairs for which the brain tries to compensate. Because these mechanisms of compensation (allostasis) that lead to the hell of addiction are complex, in the spirit of the old adage “A picture is worth a thousand words,” we present our discussion with reference to figures 1 and 2.

In the upper left-hand corner of figure 1 is a chromosome, which is a structure of protein and long chains of DNA. This combination of DNA and proteins is called chromatin. The primary protein components of chromatin are called histones, which are the spools shown in the figure around which the DNA is wound. Histones play an important role in gene regulation. As shown in figure 2, a nucleosome is DNA wrapped around histone protein cores. Figure 1 shows a methyl group attaching itself to the DNA, and the top portion of figure 2 illustrates what happens when it does. The initial process of reading the DNA code for a given substance is called transcription and is carried out in the cell nucleus by an enzyme called RNA polymerase (RNAP). When a protein needs to be manufactured, RNAP runs along the DNA strand “reading” the recipe for that protein and fashions a complementary strand of mRNA, which leaves the nucleus and enters the cell’s protein factory. When a methyl group attaches to a cytosine base (tagged as a “repressor complex” in figure 2) it prevents the code from being read—no transcription order, no protein.

--Figures 1 and 2 about here--

The opposite effect is illustrated in the bottom part of figure 2. Here we see RNAP doing its job in reading the recipe for “gene X” and clipping off the transcribed strand of mRNA. The right-hand insert of figure 1 shows how one of a family of enzymes called histone acetyltransferases (HATs) transfer an acetyl group of atoms that bind to lysine at the histone tail. This is thought to work by reducing lysine’s attraction to the negatively charged phosphate backbone of DNA. The reduced electrostatic charge loosens the chromatin enabling the RNAP to transcribe a gene (Rethal & Nesler, 2009). Conversely, another group of enzymes called histone deacetylases (HDACs) removes acetyl groups, thus reinstating the electrostatic attraction and repressing chromatin activity. Chronic cocaine use has been shown to induce histone acetylation in the nucleus accumbens by reducing HDAC functioning (Oh & Petronis,

2008). The optimal expression of genes is in large part a function of establishing a balance between the “on-off” functions of HATs and HDACs (Tsankova et al., 2007).

Cocaine and Allostatic Changes in the Nucleus Accumbens and Associated Areas

When cocaine is ingested it activates neurotransmitters that send their messages to the various brain areas associated with reward and addiction such as the nucleus accumbens (providing the pleasure and assigning salience), the PFC (providing the feedback), and the hippocampus (remembering how good it feels). In the process of neurotransmission, messages from multiple dendrites are assembled in the cell body of the receiving neurons and a “decision” is made whether or not to pass the message on. A molecule called cyclic adenosine monophosphate (cAMP) is synthesized from adenosine triphosphate (ATP), the source of energy in all cells, is a member of a group of intracellular molecules called “second messengers.” These second messengers convey the messages from neurotransmitters (the first messengers) from the cell’s membrane to its internal machinery. Chao & Nestler (2004, p. 103) state that: “one of the best established molecular mechanisms of addiction is the upregulation of the cAMP second messenger pathway.” It is through the actions of second messengers such as cAMP that long-term patterns of gene expression occur that change synaptic strength. Another way of putting it is that cAMP potentiates long-term memory, which is what addiction is all about.

The upregulation of cAMP results in the activation of a gene transcription factor (proteins that bind to genes and turn them on) called cAMP response element binding protein (CREB), which in turn recruits one of the family of HATs (CREB-binding protein--CBP) to facilitate gene expression. CREB promotes the transcription of a number of genes implicated in addiction through its role in chromatin remodeling, which many addiction researchers consider to be the molecular process that underlies to transition from casual use to addiction (Kalivas & O’Brien, 2008). Repeated exposure to cocaine (via the cAMP-CREB pathway) activates genes to produce a protein called dynorphin, which inhibits dopamine release in the ventral tegmental area (VTA) thus contributing strongly to certain aspects of tolerance (Madras, 2006).

Another transcription factor called delta FosB (Δ FosB) has effects opposite of CREB, leading to reverse tolerance; i.e., hypersensitivity to cocaine. This leads to many long-lasting structural changes in the reward circuitry of the nucleus accumbens that appear to promote the out flow of DA and other neurotransmitters. A single dose of cocaine will elevate chromatin acetylation for a short time, but with each intake of cocaine Δ FosB slowly accumulates in the brain and will remain active long (sometimes for many weeks) after the effects of CREB have faded. This buildup converts acute brain responses to cocaine use into stable, and perhaps permanent, allostatic adaptations that signal the transition from abuse to addiction.

Increasing levels of Δ FosB also change the neuroarchitecture by increasing brain-derived neurotrophic factor (BDNF). BDNF supports the survival of existing neurons, dendrites, and synapses and encourages the growth and differentiation of new ones. In response to increased Δ FosB, BDNF increases and sustains extra dendritic branches and spines (synaptic sites on the dendrites) on neurons in the nucleus accumbens and PFC, which results in increased sensitivity and drug-seeking behavior (Nestler, Barrot, & Self, 2001). Figure 3 illustrate the relevant reward brain areas for cocaine and other stimulants.

--Figure 3 about Here--

The Opponent Process Model

The interplay of CREB and Δ FosB is an example of the opponent process theory of motivation working at the molecular level. The theory maintains that emotions are oppositely paired and that experiencing one emotion will automatically engage its opponent (euphoria-dysphoria, fear-relief, and so on) after the termination of the stimulus that evoked the initial emotion is dissipated. The theory also avers that when one emotion is evoked the other is automatically suppressed. This opponent process is deemed necessary so that the body can return to emotionally neutral homeostasis. Solomon (1980, p. 693) provides an example of how the extreme fear experienced by novice parachutists automatically engages its opponent—extreme elation—at the end of the stimulus when they land safely: “they smile, chatter, and gesticulate, being very socially active and appearing to be elated.” However, repeated exposure to the stimulus will result in a lower level of the initial reaction and a stronger opposing reaction, and the individual will “crave” the next jump, not for the fear but for fear’s opponent—relief.

According to the opponent-process theory of drug addiction, addiction is the result of the emotional pairing of pleasure (euphoria) associated with the drug, and pain (dysphoria) associated with withdrawal. The addict initially experiences high levels of pleasure and low levels of dysphoria from withdrawal. Drugs are positive reinforcers at this point; that is, they are taken because they provide pleasure. The hedonic process is of rather short duration and over time CREB induced tolerance is reached and the addict requires increasing doses to achieve the same high. Not only is more of a substance required, the addict receives less and less pleasure from ingesting it (the transition from “better than expected” to “worse than expected”).

Addicts continue to use drugs when they are no longer positively reinforced because they are negatively reinforced instead (relieved from aversive stimuli). As the positive reinforcer (pleasure) decreases, withdrawal symptoms that accrue from not taking the drug increase, and this provides motivation to take the drug again. This negative process mediated by Δ FosB builds up strength slowly decays even more slowly and generates resistant to tolerance. Tolerance means that allostatic processes have changed the hedonic set point to a new and higher level, diminishing the effects of the drug. Once the set point has been established and addicts increase their cocaine consumption, the hedonic set point is pushed even further, leading to yet more consumption. Thus it is seeking negative reinforcement (more cocaine to deal with the pleasure center’s inability to deal with a hedonic set point that keeps escalating) rather than positive reinforcement that drives addiction. The capacity of drugs to alleviate some aspects of the dysphoria caused by the hedonic allostasis of the mesolimbic reward system is what sustains addictive behavior.

The Incentive-Sensitization Model

The incentive-sensitization model of addiction also maintains that addiction is caused by neuroadaptations resulting from long-term drug use, but focuses more on the brain’s sensitization to cocaine as opposed to the development of tolerance. The model also suggests that the adaptations underlying sensitization are stable, and possibly permanent. As the phrase *incentive sensitization* implies, hypersensitization (Δ FosB at work) makes the stimulus to which the brain has been sensitized highly salient, and thus the incentive to pursue it compulsively. All natural rewards have incentive salience, but sensitization of the reward system by cocaine results in the pathological enhancement of incentive salience so that drugs are sought often at the expense of ignoring the natural rewards of food, sex, and social relationships. The model shows how drug cues (a hypodermic needle, an old drug buddy, or even a “Just say no!” poster) can trigger compulsive drug seeking, drug taking, and relapse, even after many months of abstinence (Robinson & Berridge, 2008).

Robinson and Berridge (2008) distinguish between “liking” a drug and “wanting” a drug and show that the neural substrates for incentive-sensitization that attributes salience to wanting and liking are separate, although they may be strongly linked in the early stages of drug use. In other words, the pleasurable effects of a drug (“liking”) can be disassociated with the compulsive seeking of it (“wanting”), and that wanting, not liking, is the key to addiction. They further propose that the brain becomes more and more sensitized to drug wanting even as drug liking (it is no longer positively reinforcing) diminishes or even disappears. It is important to understand that “sensitization” refers to the increasing effects on the reward system that a drug has with repeated exposure. It does not mean that the initial effects become progressively stronger. Sensitization refers to hypersensitivity of the motivational system (BAS) to seek drugs (Robinson & Berridge, 2008). Sensitization increases the responsiveness of DA to activating stimuli in sensitized individuals above the level that was previously the case. However, this responsiveness does not translate into more pleasure for the individual; rather he or she experiences less pleasure due to allostatic reduction in DA receptors in response to previous DA receptor flooding. Administering the drug can alleviate some of the negative affective symptoms that accompany abstinence but it cannot reproduce its former pleasurable effects. This does not apply to casual users because infrequent use does not lead to allostatic adjustments.

Sociocultural Stress and Drug Abuse

Given that only a relatively few users of addictive substances become addicted to them, it is obvious that drugs per se do not cause addiction. Although it is true some individuals are “sitting ducks” for addiction for genetic reasons, there are numerous cultural, economic, and situational contexts implicated in the process whereby a sitting duck becomes a dead duck. Sitting ducks must be exposed to the drug, be induced to self-administer it, and be socially reinforced for doing so. It is not a case of a homicidal drug, but rather of an individual using it to play Russian roulette.

For the many reasons that adolescents turn to antisocial behavior and then desist with maturation, they also turn to and then desist from drugs. Adolescence is a particularly vulnerable time to be experimenting with drugs because major changes are occurring in the brain during that developmental period when it is most vulnerable to allostatic changes (Vaughn, 2009). Someone who starts taking drugs at age 16 or younger is two to three times more likely to become addicted than someone who starts at eighteen or older given the same level of genetic vulnerability (Koob & Le Moal, 2008). Yet this is the time when adolescents are most open to experimenting with all kinds of things, especially antisocial things. The pattern of drug use broken down by age is a mirror image of the age-crime curve. Although it is true that adolescents are more sensitive to the reinforcing properties of drugs and less sensitive to the negative properties (as they are to stimuli in general), drugs still have to be available before they can take them.

Psychosocial stress is also strongly related to both the onset of drug dependence and to relapse. Childhood stressors such as harsh and inconsistent parenting, rejection, physical, sexual, and emotional abuse have all been associated with increased vulnerability to addiction and relapse (Enoch, 2006). When we think about where abuse and addiction are most prevalent we find that they are in the same stress filled neighborhoods where child abuse/neglect, violence, and crime are also the most prevalent; that is, in the most run-down and deprived areas of our cities. These are the areas where the social ambience is dominated by the worst families in them, families that Anderson (1999) calls “street families” (as opposed to “decent families”). It is in these areas that oppositional cultures hostile to almost everything in mainstream culture flourish and in which living for kicks and for “the moment” is prevalent.

Stress is an inevitable part of life; it energizes and focuses us, and without it we would seriously be handicapped in our ability to successfully cope with life’s inevitable challenges, but toxic and protracted stress damages vital brain areas responsible for memory storage and behavioral regulation, such as the amygdala, hippocampus, and PFC (Narvaez & Vaydich, 2008). The stress response is mediated by the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, but we concentrate only on the HPA axis here. The HPA axis is activated in situations that call for a prolonged rumination rather than the visceral immediacy of the ANS’s preparation for fight or flight in the face of imminent threat, and is slower than the ANS response and lasts longer (Gunnar & Quevedo, 2007). The HPA axis response begins with the hypothalamus sending various chemical messages to the pituitary gland which leads to further chemical products that stimulate the adrenal glands to release the hormone cortisol. The brain is a major target for cortisol which, unlike the epinephrine which is part of ANS activity, is able to cross the blood/brain barrier (van Voorhees & Scarpa, 2004).

Cortisol is the fuel that energizes our coping mechanisms by increasing vigilance and activity, and is therefore functional within the normal range, but frequent HPA axis arousal may lead to upward or downward dysregulation. Upward dysregulation results in overproduction of cortisol, or hypercortisolism, and leads to anxiety and depressive disorders (van Voorhees & Scarpa, 2004). Hypercortisolism suggests a failure of the system to adjust to chronic environmental stressors and leads to internalizing problems such as chronic depression and post traumatic stress disorder.

Hypocortisolism, on the other hand, suggests an adaptive downward adjustment to chronic stress and leads to externalizing problems. It is adaptive because frequent stressful encounters habituate the organism to them, and as a consequence the organism does not react to further encounters as it had previously. Habituation means that both HPA axis and ANS response mechanisms have become blunted, and is more likely to be found in males than in females (van Goozen, et al. 2007). Blunted arousal means a low level of anxiety and fear, which is useful for those engaged in criminal activity.

Drugs can directly activate the HPA axis by releasing cortisol to act on the mesolimbic DA system mediating rewards (Goeders, 2002). Thus, and counter-intuitively, drugs of abuse can both stimulate the HPA axis to increase the perception of reward *and* at the same time function as self-medications to alleviate stress. People living in stressful environments may become locked into a complex vicious cycle of HPA axis activation (boosting the pleasure) leading to further substance abuse to alleviate the negative effects (fear, anxiety) of HPA axis activation, which again activates the HPA axis and keeps the whole process recycling. Such a vicious circle: “results in gross impairment of the normal stress response and other signaling mechanisms in the brain [certain subdivisions of the amygdala], results in a state of anxiety and internal stress” (Wand, 2008:119). Stressful criminogenic environments and drug abuse thus appear to have mutually reinforcing looping effects on one another in ways that go way beyond the modeling effects typically favored by social scientists. This is why Douglas Massey (2004, p. 22) in his Presidential address to the American Sociological Association made a plea for social scientists to stop ignoring the interaction of biological and social factors in their work:

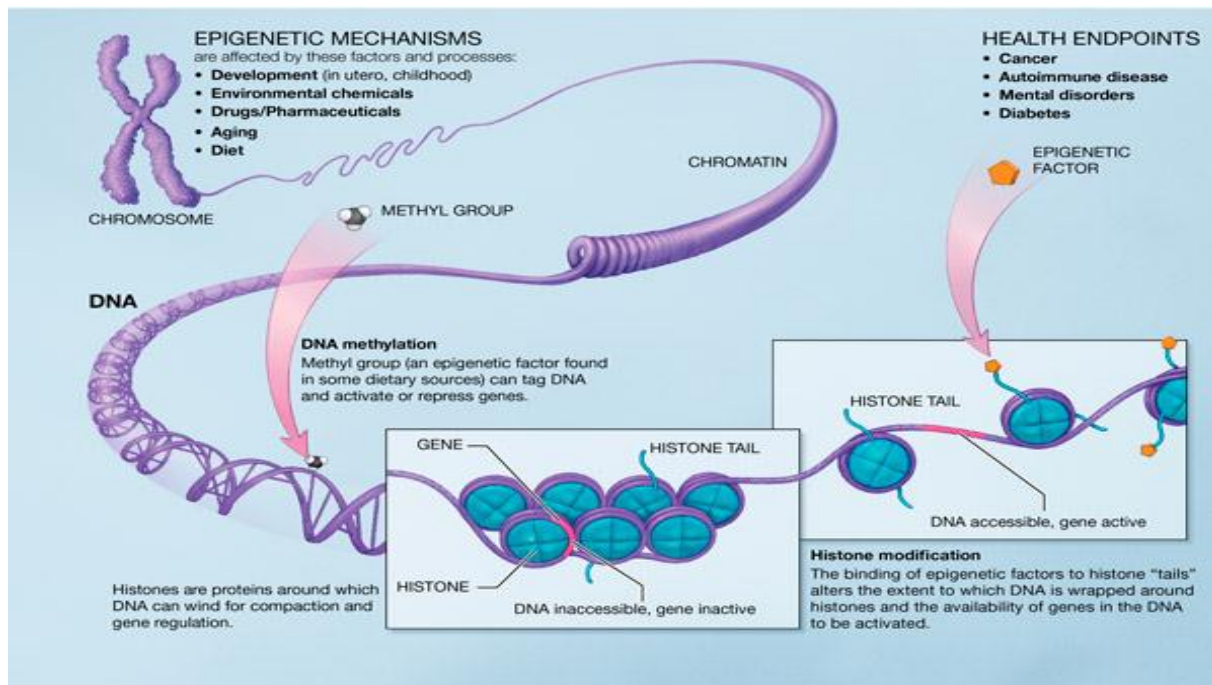
By understanding and modeling the interaction between social structure and allostasis, social scientists should be able to discredit explanations of racial differences in terms of pure heredity. In an era when scientific understanding is advancing rapidly through interdisciplinary efforts, social scientists in general—and sociologists in particular—must abandon the hostility to biological science and incorporate its knowledge and understanding into their work.

Conclusion

Drug abuse is common in our society and around the world, and is highly related to criminal behavior. Criminologists are well aware of the havoc in the lives of abusers and addicts, as well as the burden to society wrought by them, but they are less aware of the mechanisms of addiction. The processes of hedonic allostasis should be understood by criminologists so that they may appreciate the hell of addiction. We also need to recognize that although DNA is indeed the “molecule of life” and worthy of the reverence accorded it, like any other molecule it is subject to modifications which lead to different gene expression and thus to different phenotypes. Multiple lines of evidence have converged at the conclusion that addiction involves a genetic predisposition involving many genes coupled with these allostatic modifications in the brain resulting from substance abuse as the brain strives to accommodate itself to chemical invasion. There is also a need to understand the mechanisms of tolerance and relapse. Numerous chemical compounds both within and outside the neuron other than those we have identified play their roles in inducing addiction. We have only identified some of the most important ones in a truly complex epigenetic process.

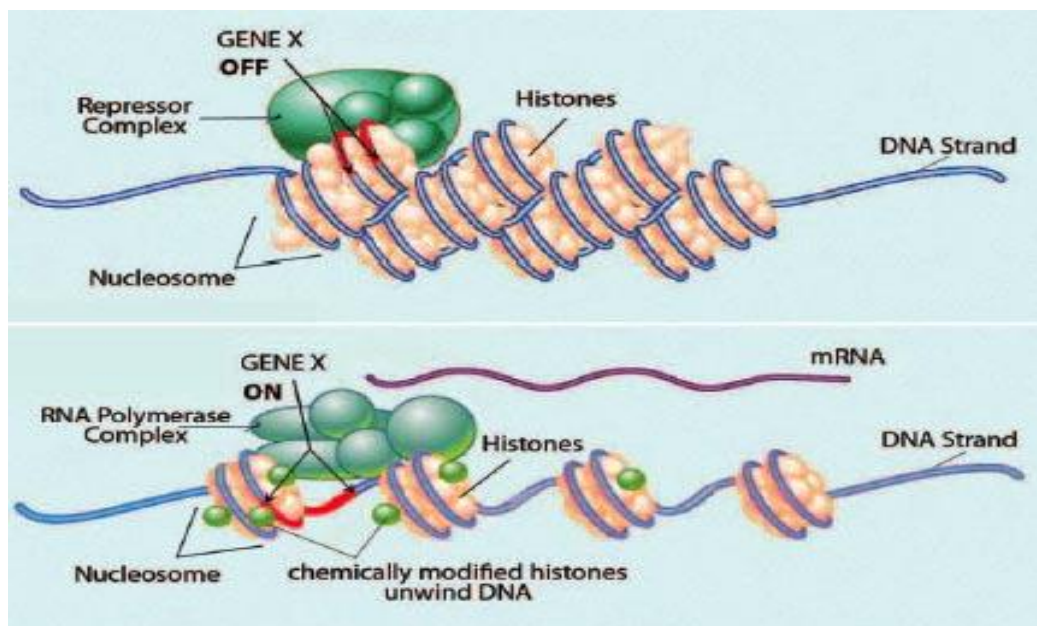
We have also shown once again that one should beware of looking at parts in isolation from the whole. While it is fascinating and necessary to explore molecular mechanisms, the sociocultural context in which they exist and play out cannot be ignored. Cultural norms and societal shifts most assuredly matter in the use and abuse of drugs, and in addiction to them. However, we should also be aware that although everyone shares (to varying degrees) in those cultural norms and societal shifts, they obviously do not affect everyone the same way. Very few people without genetic vulnerability (and it appears that it is the same genetic vulnerability to antisocial behavior in general) become addicted. But there are many biological pathways to addiction, and they all interact with environmental experiences captured by the incredible plastic brain.

Figure 1 DNA Methylation and Acetylation



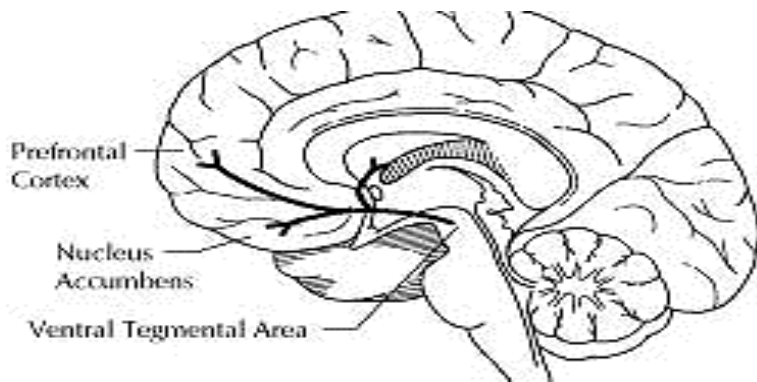
Source : <http://www.drugabuse.gov/NIDA-notes/NNvol121N4/gene.html>

Figure 2 Illustrating DNA Methylation (top) and Acetylation (bottom)



Source: <http://www.drugabuse.gov/NIDA-notes/NNvol121N4/gene.html>

Figure 3 The Brain's Reward System



Source: National Institute on Drug Abuse (1996). *The Brain's Drug Reward System* (NIDA Notes 11). Washington DC. Department of Health and Human Services.

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