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Epigenetics and Psychostimulant Addiction

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Chronic drug exposure alters gene expression in the brain and produces long-term changes in neural networks that underlie compulsive drug taking and seeking. Exactly how drug-induced changes in synaptic plasticity and subsequent gene expression are translated into persistent neuroadaptations remains unclear. Emerging evidence suggests that complex drug-induced neuroadaptations in the brain are mediated by highly synchronized and dynamic patterns of gene regulation. Recently, it has become clear that epigenetic mechanisms contribute to drug-induced structural, synaptic, and behavioral plasticity by regulating expression of gene networks. Here we review how alterations in histone modifications, DNA methylation, and microRNAs regulate gene expression and contribute to psychostimulant addiction with a focus on the epigenetic mechanisms that regulate brain-derived neurotrophic factor (BDNF) expression following chronic cocaine exposure. Identifying epigenetic signatures that define psychostimulant addiction may lead to novel, efficacious treatments for drug craving and relapse.

Drug addiction is a chronic, relapsing disorder that is characterized by compulsive drug seeking and taking despite adverse consequences (Mendelson and Mello 1996). The transition from recreational to chronic drug taking and the persistence of drug addiction are mediated, in part, by drug-induced alterations in gene expression profiles within the reward circuitry of the brain (Nestler 2001; Koob and Volkow 2010; Maze and Nestler 2011). Therefore, elucidating the molecular mechanisms by which chronic drug exposure promotes stable changes in gene expression and ultimately drug-seeking behavior may aid in the development of novel pharmacotherapies for drug addiction. Recent studies indicate that epigenetic mechanisms contribute to drug-induced structural, synaptic, and behavioral plasticity by orchestrating expression of gene networks in discrete brain nuclei (Renthal and Nestler 2008; Russo et al. 2010). In this article, we review how chromatin remodeling, DNA methylation, and microRNAs regulate gene networks and contribute to cocaine addiction. A particular emphasis is placed on the epigenetic mechanisms regulating expression of brain-derived neurotrophic factor

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(BDNF) in the mesocorticolimbic dopamine system following chronic cocaine exposure as a specific example of the general principles by which chromatin-dependent transcriptional regulation may contribute to drug addiction.

EPIGENETIC MECHANISMS OF CHROMATIN REGULATION

The definition of epigenetics has evolved to include not only heritable changes in gene expression but also stable changes in gene expression within mature, postmitotic neurons that do not include changes in DNA sequence (Bird 2007; Siegmund et al. 2007; Tsankova et al. 2007). Epigenetic mechanisms transduce environmental stimuli to promote stable alterations in chromatin structure that function to activate or repress gene transcription (Jaenisch and Bird 2003). Posttranslational modifications to histones and chromatin remodeling are dynamic epigenetic mechanisms that alter access of transcriptional machinery to promoter regions thereby regulating patterns of gene expression (Cheung et al. 2000; Strahl and Allis 2000; Berger 2007). A growing body of evidence indicates that chromatin remodeling, including stable enzymatic modifications to DNA and histone proteins, is associated with persistent changes in gene expression that may underlie drug addiction (Renthal and Nestler 2008; Maze and Nestler 2011).

Chromatin Structure, Histone Modifications, and Gene Transcription

Chromatin is a highly compact structure that consists of DNA wrapped around octamers of histone proteins. Access of transcription factors and basal transcriptional machinery to DNA sequences including promoter regions is regulated by chromatin structure (Berger 2007; Li et al. 2007a). Chromatin exists in two basic states that are characterized by different levels of condensation. In general, heterochromatin (condensed chromatin) is associated with inactive gene transcription owing to tight packaging of DNA around histone cores, whereas euchromatin (open chromatin) is associated with active gene transcription owing to a more relaxed chromatin structure and accessible DNA sequences (Berger 2007). Complex combinations of posttranslational modifications of histones alter the affinity of DNA sequences for histone proteins, thereby positively or negatively regulating gene transcription (Strahl and Allis 2000). Therefore, chromatin remodeling through covalent modifications of histone proteins is a requisite mechanism of gene transcription.

The amino-terminal tails of histones contain specific amino acid residues that are sites for several posttranslational modifications such as acetylation and methylation. In general, acetylation of lysine residues corresponds with transcriptionally active chromatin, whereas methylation of lysine and arginine residues is associated with transcriptional repression (Strahl and Allis 2000). Other histone modifications that increase gene transcription include phosphorylation and ubiquitination (Renthal and Nestler 2008). In addition, SUMOylation of histone residues has been shown to be associated with decreased gene transcription (Gareau and Lima 2010). Specific enzymes function to add or remove associated histone marks, indicating that these modifications are potentially reversible (Kouzarides 2007). The summation of dynamic histone signatures at single genes and across the genome forms a "Histone Code" that regulates gene expression (Strahl and Allis 2000). Thus, one epigenetic mechanism is the regulation of gene transcription by posttranslational modifications of histones that alter the affinity of DNA sequences for histone residues.

Histone Acetylation and Psychostimulant-Induced Changes in Gene Transcription

Acetylation of basic lysine residues in histone tails decreases the electrostatic interactions between histone proteins and negatively charged DNA (Kouzarides 2007). Hyperacetylation of promoter regions is associated with increased gene expression, whereas hypoacetylation is correlated with decreased gene expression (Kurdistani et al. 2004). Histone acetyltransferases (HATs) are enzymes that catalyze the addition

of acetyl moieties to histone proteins creating a more open chromatin configuration that is conducive to gene activation. In contrast, histone deacetylases (HDACs) function to remove acetyl moieties from histone proteins, thereby promoting condensation of chromatin and inactivation of gene transcription (Marks et al. 2003). It should also be noted that specific transcription factors have also been shown to have HAT activity (Doi et al. 2006). Together, HATs and HDACs function in concert to modify chromatin structure and regulate gene transcription.

Increased expression of the immediate early genes *Fos* and *Fosb* in the nucleus accumbens following acute cocaine administration is associated with increased histone H4 acetylation at their promoter regions (Kumar et al. 2005; Levine et al. 2005). In addition, global histone H4 acetylation and H3 phosphoacetylation are transiently increased in the striatum following acute cocaine exposure (Brami-Cherrier et al. 2005; Kumar et al. 2005). Furthermore, the time course of histone acetylation following acute cocaine is consistent with the induction kinetics of *Fos* and *Fosb* genes (Renthal and Nestler 2008). Chronic cocaine exposure also is associated with increased histone acetylation at distinct promoter regions. For example, repeated cocaine administration produces stable changes in *Cdk5* and *Bdnf* messenger RNA (mRNA) expression as well as increased histone H3 acetylation at their promoters (Kumar et al. 2005). Chronic cocaine exposure also decreases HDAC5 function in the accumbens promoting histone acetylation and increased expression of HDAC5 targeted genes (Renthal et al. 2007). Interestingly, chronic cocaine exposure induces differential epigenetic regulation of *Bdnf* transcription and these effects are region specific. Recent studies indicate that cocaine-induced increases in BDNF expression are associated with increased acetylation of histone H3 at the promoter encoding *Bdnf* exon I-containing transcripts in the accumbens (Cleck et al. 2008) and VTA (Schmidt et al. 2011). However, histone H3 acetylation at *Bdnf* promoter IV, but not promoter I, is preferentially increased in the medial prefrontal cortex (mPFC) following chronic cocaine (Sadri-Vakili et al. 2010). Cocaine-induced alterations in histone H3 acetylation and corresponding changes in gene expression are stable during periods of drug abstinence (Freeman et al. 2008), which suggests that cocaine-induced chromatin remodeling produces persistent changes in gene expression that may underlie drug craving and relapse.

Global histone H3 acetylation levels are significantly enhanced in mice that develop conditioned place preference following repeated methamphetamine administration (Shibasaki et al. 2011). Increased acetylation of histone H3 proteins is associated with genes that regulate synaptic plasticity in the forebrain (Shibasaki et al. 2011). Withdrawal from chronic amphetamine exposure also decreases transcription of the immediate early gene *Fos*, in part, through mechanisms that recruit HDAC1 to the *Fos* promoter (Renthal et al. 2008). Future studies are needed to determine the functional significance of amphetamine-induced changes in chromatin structure at gene promoters in the striatum and limbic forebrain.

Histone Acetylation and Psychostimulant-Induced Behavioral Responses

Histone acetylation and chromatin remodeling are functionally relevant as both pharmacological inhibition and genetic manipulation of HDACs alter behavioral responses to cocaine. Systemic and intraaccumbens administration of HDAC inhibitors significantly enhances cocaine-induced locomotor activity and conditioned place preference (Kumar et al. 2005; Renthal et al. 2007). Consistent with these results, viral-mediated overexpression of HDACs in the nucleus accumbens decreases histone acetylation and attenuates cocaine-induced conditioned place preference (Renthal et al. 2007). Mice deficient in the HAT cAMP response element binding (CREB) protein (CBP) have decreased histone H4 acetylation and display reduced sensitivity to cocaine (Levine et al. 2005). Taken together, these results indicate that cocaine-induced behavioral plasticity is mediated, in part, by increased acetylation of gene networks.

Recent studies indicate that the role of histone acetylation in cocaine-taking behavior is complex. Inhibition of HDACs promotes differential behavioral responses in animals self-administering cocaine and these effects are critically dependent on the timing of HDAC inhibitor administration. Systemic administration of an HDAC inhibitor before the initiation of daily cocaine self-administration sessions decreased the number of cocaine infusions self-administered, suggesting that histone acetylation decreases the reinforcing efficacy of cocaine (Romieu et al. 2008). In contrast, cocaine taking increases when animals that are stably self-administering cocaine are pretreated with a HDAC inhibitor, which suggests that histone acetylation in these animals, increases the reinforcing efficacy of cocaine (Sun et al. 2008). Administration of a HDAC inhibitor directly into the accumbens increases an animal's motivation to self-administer cocaine as measured by a progressive-ratio (PR) schedule of reinforcement and is associated with increased histone H3 acetylation in the accumbens (Wang et al. 2010). Furthermore, overexpressing HDAC4 in the nucleus accumbens shell decreases cocaine self-administration on a PR schedule (Wang et al. 2010). Although these results indicate that increased histone acetylation is one epigenetic mechanism that underlies cocaine-taking behavior, the exact temporal sequence of histone acetylation and gene transcription in relation to cocaine exposure and subsequent behavioral outcomes remains to be determined.

Histone acetylation also plays a critical role in the reinstatement of cocaine-seeking behavior. Administration of HDAC inhibitors facilitates extinction of cocaine-conditioned place preference and attenuates reinstatement of cocaine-seeking behavior (Malvaez et al. 2010; Romieu et al. 2011). These behavioral effects coincide with increased acetylation of histone H3 and suggest that chromatin remodeling and altered gene transcription during drug withdrawal may prevent drug craving and relapse (Malvaez et al. 2010).

Recent studies also show a role for histone acetylation in amphetamine-induced behavioral responses. Histone acetylation plays a critical role in behavioral sensitization to the locomotor-activating effects of amphetamine (Kalda et al. 2007; Shen et al. 2008). Chronic amphetamine exposure is associated with increased striatal histone H4 acetylation at the level of the *Fosb* promoter and increased phosphorylation of CREB (Shen et al. 2008). Furthermore, repeated methamphetamine administration increases histone H3 acetylation at unique gene promoters in the limbic forebrain (Shibasaki et al. 2011). Taken together, these results suggest that amphetamine-induced behavioral plasticity is regulated, in part, by changes in chromatin structure within the striatum that facilitate binding of transcription factors including CREB to promoter sequences to facilitate gene transcription.

Histone Methylation and Psychostimulant-Induced Changes in Gene Transcription

Addition of methyl groups to histone proteins does not change the charge of targeted amino acid residues and these modifications are relatively stable compared to histone acetylation (Rice and Allis 2001). Methylation of lysine and arginine residues on histone tails is complex and can occur in mono-(me), di-(me2), or trimethylated (me3) states with each methylation event having distinct, and often opposite, effects on gene transcription (Rice and Allis 2001). Histone methylation at gene promoters either promotes or represses gene transcription depending on the exact amino acid residues that are methylated and the valence of methylation at these residues (Maze and Nestler 2011); for example, di- and trimethylation of histone H3 lysine residues 9 (H3K9me2/3) and 27 (H3K27me2/3) recruit corepressor proteins that may function to increase chromatin condensation and thereby decrease gene transcription (Rice and Allis 2001). In contrast, trimethylation of histone H3 lysine residues 4 (H3K4me3) and 36 (H3K36me3) correlate with increased levels of gene transcription (Rice and Allis 2001).

Recent evidence indicates that psychostimulant exposure alters gene expression, in part,

through changes in histone methylation. Histone H3 methylation is decreased in the mPFC of adult rats that were exposed to cocaine during adolescence and these epigenetic marks coincide with altered gene expression in adulthood (Black et al. 2006). These findings suggest that cocaine exposure during adolescence produces long-lasting changes in gene expression that are mediated by chromatin remodeling. Repeated administration of cocaine in adult mice also reduces histone methylation in the brain and this epigenetic mechanism is associated with decreased expression of the methyltransferase G9a (Maze et al. 2010). Consistent with these findings, expression of G9a target genes is increased in the nucleus accumbens following repeated cocaine administration and viral-mediated knockdown of G9a expression, which mimics the effects of chronic cocaine exposure and facilitates cocaine-induced synaptic and behavioral plasticity (Maze et al. 2010). Moreover, repeated cocaine alters heterochromatic histone H3 methylation in the accumbens and produces long-lasting decreases in heterochromatin, which suggests that cocaine-induced alterations in histone methylation and heterochromatin formation are also an important mechanism in the long-term actions of cocaine (Maze et al. 2011). Amphetamine abstinence is also associated with changes in histone H3 methylation. Histone H3 methylation is increased at the *Fos* promoter in the striatum following repeated amphetamine exposure and is associated with decreased transcription of this immediate early gene (Renthal et al. 2008). Consistent with these results, expression of the histone H3 methyltransferase KMT1A is increased in the striatum following chronic amphetamine exposure (Renthal et al. 2008).

Histone Methylation and Psychostimulant-Induced Behavioral Responses

Adolescent rats exposed to chronic cocaine develop cognitive impairments in adulthood that are associated with altered histone methylation and gene transcription in the mPFC (Black et al. 2006). Chronic cocaine exposure in adult rats represses G9a expression thereby decreasing global histone methylation in the nucleus accumbens and enhancing cocaine-induced behavioral responses (Maze et al. 2010). The inability of G9a to regulate gene transcription following repeated cocaine results in aberrant synaptic plasticity in the accumbens (Maze et al. 2010) and may correlate with long-term psychostimulant-induced changes in structural plasticity (Robinson and Kolb 1997). G9a regulation of histone methylation in the accumbens also plays a critical role in drug-induced vulnerability to stress (Covington et al. 2011). Taken together, these results suggest that chronic cocaine exposure in adolescence and adulthood regulates expression of gene networks to alter structural plasticity in the brain that, in turn, may contribute to drug-induced behavioral plasticity. The role of histone methylation in regulating distinct gene networks to promote amphetamine-induced behavioral plasticity remains to be determined.

Histone Phosphorylation and Psychostimulant-Induced Changes in Gene Transcription

Histone phosphorylation is another posttranslational modification that is associated with increased gene transcription (Brami-Cherrier et al. 2009). Phosphorylation of serine 10 on histone H3 promotes HAT activity, phosphoacetylation of neighboring amino acid residues, and inhibits repressive methylation marks on H3 (Kouzarides 2007). Acute amphetamine administration transiently increases histone H3 phosphorylation (Rotllant and Armario 2012). Moreover, cocaine administration increases histone H3 phosphorylation and phosphoacetylation at the *Fos* promoter in the striatum, effects that are mediated by mitogen- and stress-activated protein kinase 1 (MSK1) (Brami-Cherrier et al. 2005; Brami-Cherrier et al. 2009). Constitutive knockdown of MSK1 blocks cocaine-induced increases in histone H3 phosphorylation and *Fos* expression and alters cocaine-induced behavioral plasticity (Brami-Cherrier et al. 2005). Although histone acetylation and phosphorylation are both associated with increased gene transcription, these epigenetic

mechanisms can act in concert or independently to regulate gene expression (Brami-Cherrier et al. 2007). The role of histone phosphorylation in psychostimulant-induced behavioral responses remains to be determined.

DNA Methylation and Psychostimulant-Induced Changes in Gene Transcription

In addition to posttranslational histone modifications, enzymatic modifications to DNA sequences also translate environmental stimuli such as drug exposure into altered patterns of gene expression and enduring behavioral phenotypes. DNA methylation involves the addition of methyl groups to cytosine-guanine dinucleotides (CpG) in the genome by DNA methyltransferases (DNMTs) (Suzuki and Bird 2008). Methylation of CpG islands interferes with transcription factor binding to target DNA sequences through the recruitment of corepressor complexes (Jaenisch and Bird 2003). Methyl-binding domain-containing proteins bind methylated DNA regions and recruit corepressors such as HDACs and methyltransferases to gene promoters. Therefore, it is important to note that DNA methylation and histone modifications are not mutually exclusive. Although originally thought to repress or inhibit gene transcription, DNA methylation is a dynamic process that functions to either promote or repress gene expression (Suzuki and Bird 2008).

Emerging evidence suggests that psychostimulant-induced changes in gene expression are regulated by DNA methylation. The hippocampi of rats exposed to cocaine in utero are characterized by altered global patterns of DNA methylation and corresponding changes in gene transcription (Novikova et al. 2008). Changes in gene expression following cocaine self-administration also correlate with increased expression of the methyl-CpG-binding protein MeCP2 (Host et al. 2011). Further evidence for a role of DNA methylation in cocaine-induced synaptic and behavioral plasticity comes from studies of DNMTs. Acute cocaine administration increases DNA methylation as well as the expression of DNMT3A and DNMT3B in the nucleus accumbens (Anier et al. 2010). Increased DNA methylation following acute cocaine is associated with enhanced binding of MeCP2 to specific gene promoters and corresponding decreases in gene transcription (Anier et al. 2010). Furthermore, pharmacological inhibition of DNMT decreases cocaine-induced DNA hypermethylation and attenuates drug-induced down-regulation of gene expression in the accumbens (Carouge et al. 2010). DNMT3a expression is increased during protracted periods of drug abstinence in cocaine-experienced animals (LaPlant et al. 2010). DNMT3a also plays a critical role in cocaine-induced increases in dendritic spine density, which suggests that DNA methylation is an important epigenetic mechanism in regulating cocaine-induced structural plasticity (LaPlant et al. 2010). Acute and subchronic methamphetamine administration has differential effects on DNMT1 mRNA expression that are brain region specific, suggesting that drug-induced changes in gene transcription are mediated, in part, by DNA methylation (Numachi et al. 2007). However, future studies are required to determine whether chronic methamphetamine increases DNMT1 protein and the functional significance of altered DNA methylation on drug-induced behavioral responses.

DNA Methylation and Psychostimulant-Induced Behavioral Responses

Dynamic changes in DNA methylation may underlie cocaine-induced behavioral responses. Sensitization to the locomotor-activating effects of cocaine is delayed in animals treated with a DNMT inhibitor and coincides with altered DNA methylation at gene promoters (Anier et al. 2010). Decreased DNMT3a function enhances the behavioral response to cocaine supporting the hypothesis that decreased DNA methylation promotes increased gene transcription following repeated cocaine exposure and contributes to drug-induced behavioral plasticity (LaPlant et al. 2010). Together, these results suggest that dynamic changes of DNA methylation may be an important epigenetic mechanism underlying cocaine-induced behavioral effects.

GENOME-WIDE STUDIES OF COCAINE-INDUCED CHANGES IN CHROMATIN REGULATION

Drug-induced histone modifications can be identified and characterized across the genome using microarrays and next-generation sequencing methods. Precise genomic loci that are associated with histones modified by drug exposure are identified using genome-wide promoter arrays (ChIP-chip) or massively parallel DNA sequencing platforms (ChIP-Seq) (Renthal et al. 2009; Maze et al. 2011; Zhou et al. 2011). These high-throughput methods characterize complex drug-induced signatures of epigenetic regulation including multifaceted histone modifications that regulate transcription of gene networks and may underlie drug-induced behavioral plasticity. ChIP-chip analyses of nucleus accumbens lysates reveals that chronic cocaine exposure regulates gene transcription by either increasing histone H3 or H4 acetylation (to elevate mRNA levels), or by increasing histone H3 dimethyl-K9/27 (to reduce mRNA expression) (Renthal et al. 2009). Chronic cocaine exposure also decreases repressive histone methylation (H3K9me3) in the accumbens and ChIP-Seq reveals that these histone marks are associated with intergenic genomic regions (Maze et al. 2011). These results suggest that cocaine-induced histone methylation produces heterochromatic derepression and increases expression of retrotransposable elements that in turn regulate gene transcription (Maze et al. 2011). A recent study used whole genome sequencing of mRNA transcripts (RNA-Seq) and ChIP-Seq to characterize histone methylation and gene expression in postmortem hippocampal tissue from cocaine-dependent subjects (Zhou et al. 2011). Interestingly, cocaine-induced changes in histone methylation did not correlate with corresponding changes in gene expression in the hippocampus, which suggests that complex epigenetic pathways act in concert to regulate gene transcription (Zhou et al. 2011). Taken together, these studies show that cocaine acts to alter patterns of gene expression in the nucleus accumbens and hippocampus through epigenetic mechanisms (i.e., histone acetylation and methylation) that promote stable, persistent changes in gene expression. Thus, genome-wide studies identify dynamic chromatin signatures following chronic cocaine exposure and reveal novel gene targets and molecular regulatory pathways that may play critical roles in drug taking and seeking. It is not clear whether other psychostimulants and drugs of abuse exert their behavioral effects through similar or divergent epigenetic regulation of gene networks.

MicroRNAs

Posttranscriptional regulation of gene expression following chronic drug exposure has also been shown to influence drug taking and seeking in laboratory animals (Pietrzykowski 2010; Li and van der Vaart 2011). Specifically, microRNAs (miRNAs) have emerged as a new class of epigenetic regulators that are capable of altering synaptic plasticity and behavior (Guarnieri and DiLeone 2008). miRNAs are a class of nonprotein coding RNA transcripts ($\sim$19–24 nucleotides) that regulate gene expression at the posttranscriptional level (Ambros 2004). It is predicted that there are $>$800 unique miRNA species in humans (Bentwich et al. 2005; Berezikov et al. 2006), many of which are highly expressed in the brain (Sempere et al. 2004; Lugli et al. 2008). More than 33% of the mammalian genome is subject to miRNA regulation and each miRNA targets on average 200 mRNA transcripts (Lewis et al. 2005; Friedman et al. 2009b). A growing literature indicates that miRNAs have diverse effects on gene expression including mRNA degradation, increased mRNA translation, chromatin remodeling, and DNA methylation.

Initially, miRNAs were thought to be located within intergenic clusters within the genome and regulated by their own promoter regions (Lagos-Quintana et al. 2001; Lau et al. 2001). However, it was determined recently that at least 50% of mammalian miRNAs are located within introns of protein-coding genes, which suggests that concurrent expression of miRNAs and their host genes is regulated by common promoter regions and transcriptional machinery (Rodriguez et al. 2004; Ason et al. 2006; Berezikov et al.

2007; Li et al. 2007b; Okamura et al. 2007; Saini et al. 2007). miRNA genes are transcribed by RNA polymerases to produce immature transcripts (Lee et al. 2002; Lee et al. 2004; Borchert et al. 2006). These immature transcripts are spliced, similar to mRNA, to produce double-stranded, hairpin-loop structures that are several hundred base pairs in length called primary miRNAs (pri-miRNAs) (Lee et al. 2002). Pri-miRNAs are further cleaved in the nucleus by the enzyme Drosha, as part of a protein complex called the microProcessor (Lee et al. 2003; Denli et al. 2004; Gregory et al. 2004; Yeom et al. 2006). The cleaved product is a double-stranded RNA fragment, called precursor miRNA (pre-miRNA), which is ~70 nucleotides in length and contains a two-nucleotide overhang at the 3′ end. The nuclear membrane protein Exportin 5 binds to the 3′ overhang of pre-miRNAs and transports them from the nucleus into the cytoplasm (Yi et al. 2003; Bohnsack et al. 2004; Lund et al. 2004). Following its translocation into the cytoplasm, pre-miRNA is cleaved by the enzyme Dicer to form an ~20–25 nucleotide duplex consisting of a mature miRNA strand and its opposite, complementary ("passenger") strand, miRNA* (Bernstein et al. 2001; Hutvagner et al. 2001). Dicer-mediated cleavage of pre-miRNAs is thought to coincide with unwinding of the duplex to produce single-stranded, active miRNAs (MacRae et al. 2008). Single-stranded miRNAs are preferentially loaded into the microRNA-induced silencing complex (miRISC) (Hutvagner and Zamore 2002). The main protein constituents associated with miRISC complexes are Argonaute (AGO) proteins that bind miRNAs and facilitate cleavage of targeted mRNA transcripts (Baumberger and Baulcombe 2005; Peters and Meister 2007). It is thought that one miRNA is sufficient to direct miRISC to target mRNAs to cleave or silence these transcripts.

miRNAs regulate gene expression by degrading mRNA transcripts, repressing mRNA translation, or both (Jackson and Standart 2007; Pillai et al. 2007). Target specificity is imparted through miRNA recognition and binding to complementary sequences (~2–7 nucleotides), or "seed regions," in the 3′-UTR (untranslated region) of mRNA (Lewis et al. 2003; Grimson et al. 2007; Bartel 2009). Originally thought to be nonfunctional by-products of pre-miRNA cleavage (Matranga et al. 2005), miRNA* strands also act at distinct binding sites to regulate gene expression (Tyler et al. 2008; Okamura et al. 2009; Ghildiyal et al. 2010). Emerging evidence indicates that molecular regulation of gene expression by miRNAs is more complex than originally thought. In addition to repressing protein synthesis and directing sequence-specific degradation of complementary mRNA, the miRNA/miRISC complex has also been shown to induce gene expression by activating mRNA translation (Vasudevan et al. 2007; Place et al. 2008; Steitz and Vasudevan 2009). miRNAs also remodel chromatin structure and increase DNA methylation thereby altering expression of target genes (Tan et al. 2009) and, in some cases, inducing gene activation (Place et al. 2008).

MicroRNAs and Psychostimulant Addiction

miRNAs coordinate the expression of networks of related genes involved in synaptic plasticity (Kosik 2006; Schratt et al. 2006). Furthermore, miRNAs have been identified in dendrites, which suggests that miRNAs function, in part, to rapidly translate cellular signals into regulation of local mRNA transcripts (Ashraf and Kunes 2006; Hobert 2008). Chronic drug exposure induces maladaptive changes in neural networks including aberrant synaptic plasticity in the mesocorticolimbic dopamine system (Kalivas et al. 2005; Kauer and Malenka 2007; Thomas et al. 2008; Russo et al. 2010). Given the potential role of drug-evoked synaptic plasticity in the development and persistence of compulsive drug-taking behavior (Hyman et al. 2006; Luscher and Malenka 2011; Mameli and Luscher 2011), it is not surprising that miRNAs play a critical role in drug addiction (Dreyer 2010; Pietrzykowski 2010; Li and van der Vaart 2011).

Recent studies indicate that compulsive cocaine consumption is mediated, in part, by miRNAs. Cocaine self-administration increases expression of miR-212 in the dorsal striatum (Hollander et al. 2010). Furthermore, increased

miR-212 expression in the striatum is associated with decreased cocaine self-administration and suggests that up-regulation of striatal miR-212 is a compensatory mechanism that decrease's the motivational properties of cocaine (Hollander et al. 2010). In contrast, the transcriptional repressor MeCP2 plays a critical role in regulating increased cocaine consumption (Im et al. 2010). MeCP2 attenuates cocaine-induced up-regulation of miR-212 expression in the striatum, whereas miR-212 inhibits MeCP2 expression (Im et al. 2010). Thus, a pivotal balance between MeCP2 and miR-212 levels in the striatum regulates compulsive drug-taking behavior.

Chronic cocaine exposure also increases expression of miR-181a and decreases expression of miR-124 and let-7d in the mesocorticolimbic dopamine system (Chandrasekar and Dreyer 2009). Although increased expression of miR-124 and let-7d in the nucleus accumbens attenuates cocaine-induced conditioned place preference (CPP), increased expression of miR-181a in the accumbens enhances cocaine CPP (Chandrasekar and Dreyer 2011). Differential behavioral effects of miR-124, let-7d, and miR-181a are associated with distinct changes in gene expression in the nucleus accumbens (Chandrasekar and Dreyer 2011). Taken together, these results suggest that complex miRNA regulatory pathways modulate cocaine-induced behavioral plasticity by directing expression of gene networks. It remains to be determined whether other psychostimulants exert similar effects on miRNA expression.

Thus, miRNAs are epigenetic regulators that play a critical role in translating drug-induced changes in synaptic plasticity into persistent neuroadaptations associated with drug addiction. By targeting hundreds of mRNA transcripts, a single miRNA coordinates expression of gene networks that regulate neuronal plasticity and behavior. Although miRNAs may represent promising new targets in the development of novel therapies to treat drug craving and relapse, future studies are needed to determine the precise role of miRNAs and their targets in the molecular mechanisms underlying drug addiction.

BDNF AND COCAINE ADDICTION

BDNF is a member of the neurotrophin family that includes nerve growth factor, neurotrophin-3, and neurotrophin 4/5 (Thoenen 1995). BDNF is synthesized as a propeptide (32 KDa) that is proteolytically processed into a smaller (13 KDa), mature form that binds to and activates tropomyosin receptor kinase B (TrkB) receptors (Bibel and Barde 2000). TrkB stimulation results in receptor dimerization and tyrosine phosphorylation that provides docking sites for adapter molecules, internalization, and intracellular signaling leading to changes in gene expression and synaptic plasticity (Sommerfeld et al. 2000; Patapoutian and Reichardt 2001; Lu 2003; Nagappan and Lu 2005). Stimuli that induce neuronal activity in a calcium-dependent manner increase *Bdnf* mRNA and BDNF protein expression (Shieh et al. 1998). Following transcription, *Bdnf* mRNA is trafficked to active synapses (Tongiorgi et al. 1997) where long 3′ UTR mRNA transcripts are preferentially localized and translated (An et al. 2008). Synaptic secretion of BDNF and subsequent TrkB receptor activation are associated with increased glutamatergic activity (Jovanovic et al. 2000; Hartmann et al. 2001; Balkowiec and Katz 2002). Furthermore, BDNF promotes both early and late-phase long-term potentiation (LTP), dendritic protein synthesis, and dendritic spine formation (Bramham et al. 1996). BDNF regulates dendritic spine formation and synaptic plasticity by inhibiting miR-134, a miRNA that negatively regulates dendritic spine development and maturation (Schratt et al. 2006). BDNF-mediated inhibition of miR-134 promotes translation of Lim kinase 1, an enzyme that regulates actin filament activity and synaptic plasticity (Schratt et al. 2006).

Many cocaine-induced neuroadaptations that are thought to underlie cocaine seeking are manifested by alterations in the plasticity of mesocorticolimbic circuitry (Schmidt and Pierce 2010). *Bdnf* mRNA is expressed abundantly in cortical as well as midbrain dopamine neurons and at much lower levels in striatal neurons (Altar et al. 1997; Lipska et al. 2001). In fact, cortical pyramidal neurons are thought

to supply ~80% and dopamine neurons ~20% of BDNF protein within the striatum (Altar et al. 1997). Endogenous *Bdnf* mRNA and protein are differentially regulated in mesolimbic and cortical neurons in response to acute and repeated administration of psychostimulants or during extended periods of drug abstinence (Meredith et al. 2002; Le Foll et al. 2005; Filip et al. 2006; Liu et al. 2006; Fumagalli et al. 2007; Saylor and McGinty 2008; Fumagalli et al. 2009). In addition, a persistent BDNF protein response develops in mesolimbic, striatal, and cortical structures and lasts for extended durations during abstinence from cocaine self-administration (Grimm et al. 2003; Im et al. 2010; McGinty et al. 2010). Altered expression of BDNF in this network of reciprocally interconnected structures following cocaine exposure and/or drug abstinence suggests that BDNF may constitute a critical component of cocaine-induced plasticity.

The effects of exogenous BDNF infusion on cocaine seeking are brain region specific and time dependent. Infusion of BDNF into subcortical structures, like the nucleus accumbens and VTA, enhances cocaine-seeking behavior (Lu et al. 2004; Graham et al. 2007). These studies implicate VTA and nucleus accumbens BDNF activity in long-term modulation of cocaine-induced behavior. In contrast, BDNF infusion into the dorsomedial PFC immediately following a final session of cocaine self-administration attenuates the reinstatement of cocaine seeking by normalizing cocaine-induced alterations in phospho-ERK and phospho-CREB expression in the PFC and glutamate transmission in the nucleus accumbens (Berglind et al. 2007; Berglind et al. 2009; Whitfield et al. 2011). In support of the cocaine-suppressing effects of BDNF, knockdown of BDNF in the mPFC augments the intake of cocaine in rats self-administering cocaine (Sadri-Vakili et al. 2010). In contrast, overexpression of BDNF in the dorsal striatum has been implicated in the acceleration of, and loss of control over, compulsive cocaine taking (Im et al. 2010). Moreover, suppression of endogenous BDNF signaling, by infusing a neutralizing antibody to BDNF in the dorsal striatum, decreases cocaine intake (Im et al. 2010). Thus, exogenous infusion or manipulation of endogenous BDNF levels has a selective functional impact in different target areas that are critical to mediating or preventing cocaine-induced dysfunctional neuroadaptations.

EPIGENETIC REGULATION OF BDNF EXPRESSION IN RESPONSE TO COCAINE

A growing body of evidence suggests that epigenetic mechanisms of regulation are important for the modulation of drug-induced *Bdnf* transcription (Fig. 1). The *Bdnf* gene is comprised of nine exons with at least eight alternative promoters that are differentially responsive to cocaine-activated signaling cascades (Liu et al. 2006; Aid et al. 2007). Cocaine-induced increases in *Bdnf* transcription are associated with increased histone acetylation at several *Bdnf* promoters (Kumar et al. 2005; Schroeder et al. 2008; Sadri-Vakili et al. 2010; Schmidt et al. 2011). Histone acetylation at specific *Bdnf* promoters is associated with binding of the histone acetyltransferase CBP (Schmidt et al. 2011), and the histone deacetylases HDAC1 and HDAC2 (Guan et al. 2009) to these promoter regions.

Reduced DNA methylation of various regions across the *Bdnf* locus has been detected following many stimuli that increase BDNF expression (Lubin et al. 2008; Ma et al. 2009). However, it remains to be determined whether cocaine modulates DNA methylation of the *Bdnf* gene. Induction of *Bdnf* transcription in the PFC is correlated with the dissociation of MeCP2 from BDNF promoter IV, consistent with a potential reduction in DNA methylation under these conditions (Sadri-Vakili et al. 2010). Evidence for the functional importance of DNA methylation in the regulation of *Bdnf* transcription comes largely from studies in which MeCP2 expression has been disrupted. Although MeCP2 is bound widely to DNA across the genome (Skene et al. 2010), decreased MeCP2 expression is associated with surprisingly subtle changes in the expression of a subset of genes (Tudor et al. 2002; Chahrour et al. 2008; Skene et al. 2010). Nonetheless, levels of *Bdnf* are consistently reduced in the brains of *Mecp2* knockout mice (Chang et al. 2006; Fyffe et al.

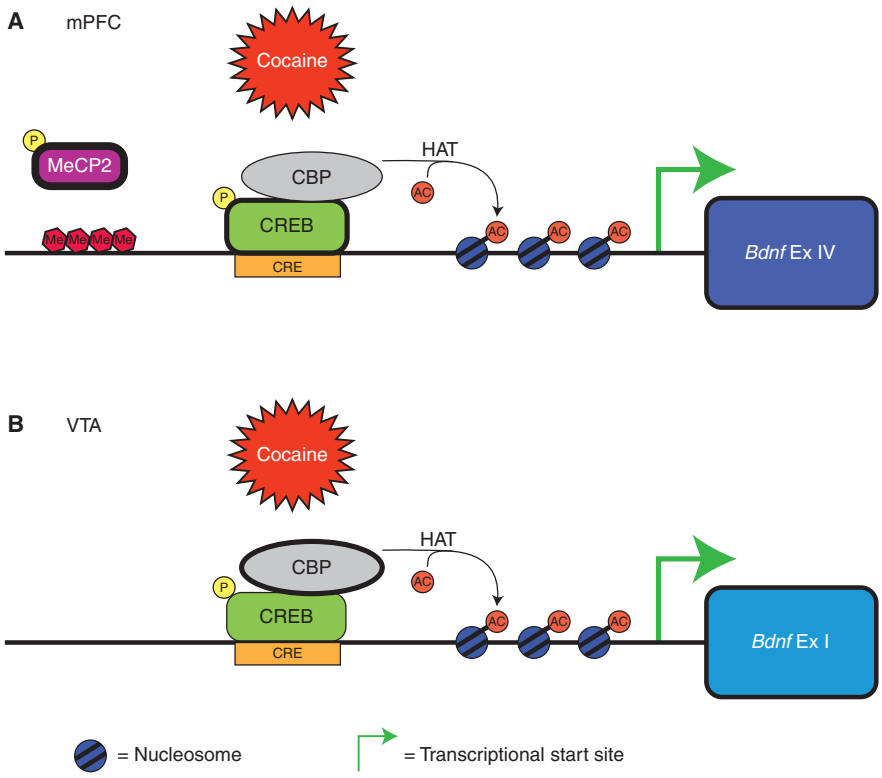

Figure 1. Differential cocaine-induced effects at specific *Bdnf* promoters are mediated by distinct epigenetic mechanisms in the mPFC and VTA. (*A*) Cocaine selectively increases *Bdnf* exon IV–containing transcript levels in the mPFC. Cocaine-induced increases in mPFC *Bdnf* transcription are associated with increased CREB phosphorylation and histone H3 acetylation at *Bdnf* exon IV promoters. Furthermore, MeCP2 binding to *Bdnf* exon IV promoter regions is decreased following cocaine self-administration. (*B*) In contrast, cocaine selectively increases *Bdnf* exon I–containing transcript levels in the VTA. Cocaine-induced increases in VTA *Bdnf* transcription are associated with recruitment of CBP, an enzyme that catalyzes the addition of acetyl groups to histone proteins, and increased histone H3 acetylation at exon I–containing promoter regions. AC, acetyl group; *Bdnf*, brain-derived neurotrophic factor; CBP, CREB-binding protein; CRE, cAMP response element; CREB, cAMP response element binding protein; Ex IV, exon IV; Ex I, exon I; HAT, histone acetyltransferase; Me, methyl group; MeCP2: methyl-CpG-binding protein 2; P, phosphate group.

2008). Interestingly, MeCP2 is a target of regulation by psychostimulant-activated signaling cascades (Deng et al. 2010; Im et al. 2010). Phosphorylation of MeCP2 at Ser421 is induced rapidly and robustly by acute and repeated administration of cocaine or amphetamine, and this phosphorylation is selective for specific populations of neurons in the PFC and nucleus accumbens (Deng et al. 2010). Although the consequences of Ser421 phosphorylation for MeCP2 function are not known, this regulation suggests a mechanism to couple MeCP2-dependent transcription of *Bdnf* and other genes with psychostimulant exposure. In addition, expression of MeCP2 is up-regulated following chronic cocaine self-administration in the dorsal striatum of rats where knockdown of MeCP2 expression is associated with impaired cocaine-dependent up-regulation of BDNF protein (Im et al. 2010; Host et al. 2011). However, it is unclear whether increased MeCP2 expression is directly acting under these conditions to alter transcriptional regulation of *Bdnf*.

miRNAs represent a third epigenetic mechanism that may contribute to psychostimulant-induced expression of BDNF. Although a

number of miRNAs can bind directly to the 3′-UTR of *Bdnf* (Mellios et al. 2008; Friedman et al. 2009a; Muinos-Gimeno et al. 2011), the relevance of this epigenetic mechanism for the in vivo regulation of BDNF levels remains to be determined. However, miRNAs may impact cocaine-induced BDNF expression indirectly via regulation of MeCP2 expression and CREB activation. Cocaine self-administration is associated with increased expression of miR-132 and miR-212 in the dorsal striatum, both of which can repress the expression of MeCP2 (Klein et al. 2007; Hollander et al. 2010; Im et al. 2010). MeCP2 appears to exert a complementary repression of miR-132 and miR-212, suggesting that these transcriptional regulators are engaged in a homeostatic feedback loop (Klein et al. 2007; Im et al. 2010). Overexpression of miR-212 in the dorsal striatum attenuates cocaine-induced up-regulation of MeCP2 expression and inhibits cocaine-induced up-regulation of BDNF protein (Im et al. 2010). Interestingly, in addition to its effects on MeCP2 expression, miR-212 has been shown to amplify CREB signaling and to increase cocaine-induced expression of CREB-target genes including *Fos* (Hollander et al. 2010; Im et al. 2010). *Bdnf* transcription is also regulated by CREB as well as MeCP2 (Shieh et al. 1998; Tao et al. 1998) and it remains to be determined why the effects of miR-212 overexpression on MeCP2 appear to dominate with respect to BDNF regulation over the effects on CREB. These observations highlight the challenges of interpreting the effects of disrupting single regulatory factors within the context of an interconnected transcriptional network, and suggest that there is a rich world of complexity contributing to the tight spatial and temporal control of BDNF expression that remains to be explored.

CONCLUDING REMARKS

Increasing evidence suggests that epigenetic mechanisms including histone modifications, DNA methylation, and miRNAs regulate psychostimulant-induced gene expression profiles in discrete brain regions. Many changes in chromatin regulation following chronic psychostimulant exposure correlate in time with the expression of maladaptive behaviors including drug taking and seeking. However, molecular genetic studies have also implicated some of the transcriptional regulatory factors discussed in this review (i.e., miR-212, MeCP2, HDAC5, and BDNF in the mPFC) in the induction of adaptive forms of neuroplasticity that appear to repress or inhibit drug self-administration. Further characterizing the molecular substrates that regulate chromatin remodeling and gene transcription following chronic drug exposure may identify novel drug targets for drug craving and relapse. Given the evidence that BDNF expression in different brain regions has both essential and distinct effects on drug-taking behavior, understanding the transcriptional regulation of this single gene offers an opportunity to discover insights into the role of epigenetic mechanisms of chromatin regulation in drug addiction. However, future studies that more broadly elucidate the epigenetic processes that mediate long-lasting changes in gene expression networks throughout the brain will substantially enhance our understanding of how persistent changes in gene transcription contribute to the development and expression of compulsive drug-taking behaviors.

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